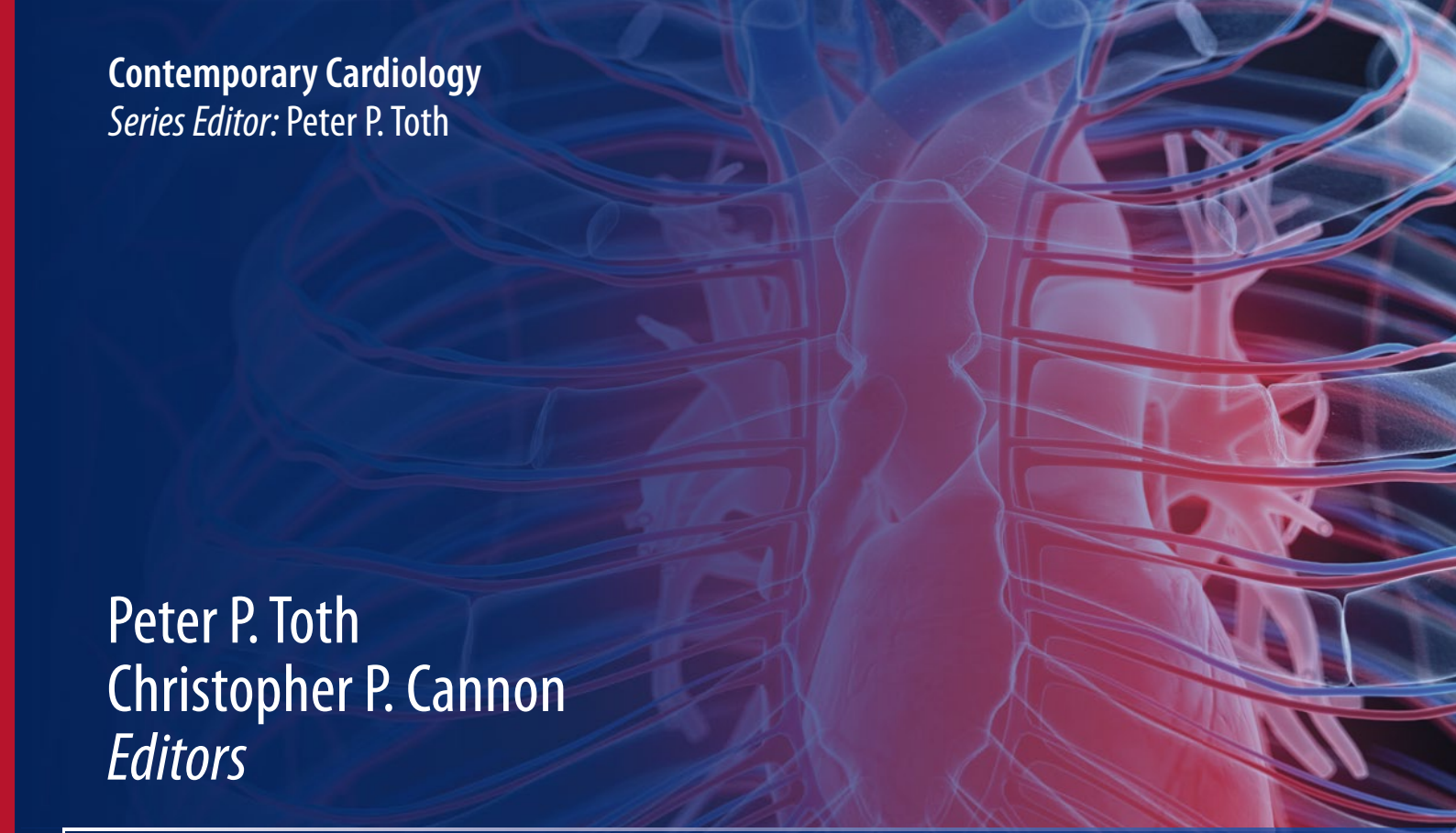

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Comprehensive Cardiovascular Medicine in the Primary Care Setting

Second Edition

Humana Press

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Peter P. Toth • Christopher P. Cannon
Editors

Comprehensive Cardiovascular Medicine in the Primary Care Setting

Second Edition

Humana Press

Editors
Peter P. Toth
Ciccarone Center for the Prevention of Cardiovascular Disease
Johns Hopkins University School of Medicine
Baltimore
Maryland
USA

Christopher P. Cannon
Cardiovascular Division
Harvard Medical School Brigham & Women's Hospital
Boston
MA
USA

ISSN 2196-8969 ISSN 2196-8977 (electronic)
Contemporary Cardiology
ISBN 978-3-319-97621-1 ISBN 978-3-319-97622-8 (eBook)
https://doi.org/10.1007/978-3-319-97622-8

Library of Congress Control Number: 2018965194

This Humana Press imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

To our wives Karen and Sophie, for their patience, understanding, and kindness.

Preface

It has been 8 years since the publication of the first edition of *Comprehensive Cardiovascular Medicine in the Primary Care Setting*. Our goals and objectives for this second edition have not changed. Once again, we have attempted to craft a volume that will help to guide the busy primary care provider in their delivery of state-of-the-art cardiovascular medicine. Every chapter contained herein has been updated. Cardiovascular disease is burgeoning and continues to be the number one cause of morbidity and mortality worldwide. It has never been more crucial for primary care providers to actively treat patients with cardiovascular disease in both the primary and secondary prevention settings so as to prevent both the development and progression of disease and to reduce risk for acute cardiovascular events.

The guidelines for virtually every cardiovascular disease as well as for relevant metabolic disorders have evolved and are more nuanced. Numerous new pharmacologic therapies, diagnostic technologies, and nonsurgical interventions have been introduced. Never before have we had so many tools at our disposal for improving cardiovascular medicine. It is our most sincere hope that within these pages our colleagues will discover clear, easy to apply guidance on managing both acute and chronic issues in cardiovascular medicine with confidence.

Baltimore, Maryland, USA — Peter P. Toth, MD, PhD
Boston, MA, USA — Christopher P. Cannon, MD

Preface to the First Edition

Cardiovascular disease is highly prevalent throughout the world. The American Heart Association estimates that in the year 2009, the direct and indirect costs of cardiovascular disease in the United States will approximate one-half trillion dollars. Despite a staggering series of discoveries and innovations over the last five decades, cardiovascular disease remains the leading cause of morbidity, disability, and mortality among men and women. The pace of progress in the field of cardiology is rapid and keeping up with medical, surgical, and diagnostic breakthroughs is quite challenging. Our ability to beneficially impact cardiovascular disease has grown exponentially. Clinical trials and novel insights from basic scientific and clinical investigation continually transform what, when, and how we have come to do things in cardiovascular medicine. The frequency with which national guidelines and recommendations of best practice are promulgated for a variety of cardiovascular disease states is accelerating and their complexity is growing. Unfortunately, adherence to national guidelines and levels of patient goal attainment nationwide tend to be relatively low. Many proven, highly efficacious therapies and interventions remain underutilized.

Primary care clinicians must play a larger role in the prevention, diagnosis, and management of cardiovascular diseases. A high clinical priority in contemporary medicine is the prevention of disease. It has now become routine to screen patients for such disorders as dyslipidemia, hypertension, metabolic syndrome, diabetes mellitus, heightened systemic inflammation, and albuminuria, all of which impact risk for atherosclerosis. Early identification of established disease is also critical so as to prevent progression and long-term adverse clinical sequelae, such as myocardial infarction, stroke, heart and renal failure, claudication and lower extremity amputation, and thromboembolic phenomena. In addition to laboratory measures of genetic and metabolic background, it is important to cultivate clinical skills and proficiency in using imaging modalities to characterize such anatomical abnormalities such as coronary artery and peripheral arterial disease, aortic aneurysms, and cardiac valvular disease. A critical feature of long-term care is ensuring that specific disease states remain optimally treated through lifestyle modification and pharmacologic intervention and that patients remain compliant with these therapies lifelong. Primary care clinicians play critical roles in all of these areas.

Comprehensive Cardiovascular Medicine in the Primary Care Setting was written for the busy, practicing clinician. There are numerous exceptional texts in cardiovascular medicine of encyclopedic scope, which are for the most part targeted toward specialist audiences. Given the high prevalence of cardiovascular diseases, we have developed a text in cardiovascular medicine that addresses the needs and gaps in knowledge of primary care clinicians. More and more cardiovascular diseases are being identified and managed by primary care clinicians in its subclinical, acute, and chronic stages. Our principal aim in this book is to provide comprehensive coverage of cardiovascular disease in an authoritative and easy to apply manner. Concept is intricately balanced with practical utility. The pathophysiology of specific cardiovascular diseases is explained. Algorithms, case studies, and recommendations on evidence-based best practice are presented in every chapter. There is appropriate emphasis on optimal approaches to pharmacologic management. Each chapter begins with a bulleted list of the 10–12 most important points for each disease state addressed. This volume is not intended to

be encyclopedic; rather, it is designed to help the busy practitioner perform assessments, initiate and guide efficacious therapy, and know when referral to a cardiologist or cardiovascular surgeon is indicated. The book is divided into five main sections: cardiovascular disease risk factors, coronary artery disease, peripheral forms of venous and arterial disease, cardiac disease, and cardiac imaging. Improving the quality of patient care and expanding scope of practice are our ultimate goals. We sincerely hope this book also helps foster greater cooperation and synergy between primary care clinicians, cardiologists, and cardiovascular surgeons.

Baltimore, Maryland, USA — Peter P. Toth, MD, PhD
Boston, MA, USA — Christopher P. Cannon, MD

Contents

Contributors

Nikolaos Alexopoulos, MD Cardiovascular Imaging Unit, Radiology Department, Euroclinic Athens, SA, Athens, Greece

Sary F. Aranki, MD Division of Cardiac Surgery, Brigham and Women's Hospital, Boston, MA, USA

Eric R. Bates, MD Division of Cardiovascular Medicine, University of Michigan Medical Center, Ann Arbor, MI, USA

Nicole M. Bhave, MD Division of Cardiovascular Medicine, University of Michigan Medical School, Ann Arbor, MI, USA

George D. Dangas, MD, PhD Cardiovascular Innovation, Mount Sinai Medical Center, New York, NY, USA

Fernando Ramirez Del Val, MD, MPH Division of Cardiac Surgery, Brigham and Women's Hospital, Boston, MA, USA

Mary R. Dicklin, PhD Midwest Biomedical Research/Center for Metabolic and Cardiovascular Health, Glen Ellyn, IL, USA

Daniel Duprez, MD, PhD Cardiovascular Division, Department of Medicine, University of Minnesota, Minneapolis, MN, USA

Kim A. Eagle, MD Division of Cardiovascular Medicine, Cardiovascular Center, University of Michigan Medical School, Ann Arbor, MI, USA

Michela Faggioni, MD Mount Sinai Heart, Mount Sinai Medical Center, New York, NY, USA

Cardiothoracic Department, Division of Cardiology, University Hospital of Pisa, Pisa, Italy

Borek Foldyna, MD Department of Radiology, Massachusetts General Hospital - Harvard Medical School, Boston, MA, USA

Blair Foreman, MD Cardiovascular Medicine, Midwest Cardiovascular Research Foundation, Davenport, IA, USA

Jordan Fulcher NHMRC Clinical Trials Centre, University of Sydney, Camperdown, Sydney, Australia

Eli V. Gelfand, MD Cardiovascular Division, Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA

Jay Giri, MD, MPH Cardiovascular Division, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Eric A. Heller, MD Columbia University Medical Center, New York, NY, USA

Udo Hoffmann, MD Department of Radiology, Massachusetts General Hospital - Harvard Medical School, Boston, MA, USA

Eric M. Isselbacher, MD, MSc Cardiology Division and Department of Medicine, Massachusetts General Hospital, Boston, MA, USA

Andrzej S. Januszewski NHMRC Clinical Trials Centre, University of Sydney, Camperdown, Sydney, Australia

University of Melbourne, Department of Medicine, Melbourne, VIC, Australia

Alicia J. Jenkins NHMRC Clinical Trials Centre, University of Sydney, Camperdown, Sydney, Australia

University of Melbourne, Department of Medicine, Melbourne, VIC, Australia

Department of Diabetes and Endocrinology, St. Vincent's Hospital, Fitzroy, Melbourne, Australia

Steven R. Jones Department of Medicine, Division of Cardiology, Johns Hopkins Hospital, Baltimore, MD, USA

Tsuyoshi Kaneko, MD Division of Cardiac Surgery, Brigham and Women's Hospital, Boston, MA, USA

Andreas Kastrup, MD Departments of Neurology, Klinikum Bremen-Ost and Klinikum Bremen-Mitte, Bremen, Germany

Aslam M. Khaja, MD Neurology, Northwest Neurology, Ltd., South Barrington, IL, USA

Sumeet A. Khetarpal, PhD Departments of Medicine and Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Gary Kilov University of Melbourne, Department of General Practice, Melbourne, VIC, Australia

Robert A. Kloner, MD, PhD Huntington Medical Research Institutes, Pasadena, CA, USA

Taisei Kobayashi, MD Cardiovascular Division, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Ahmed A. Kolkailah, MD Division of Cardiac Surgery, Brigham and Women's Hospital, Boston, MA, USA

William E. Kraus, MD Division of Cardiology, Department of Internal Medicine, Duke University School of Medicine, Durham, NC, USA

Robert F. Kushner, MD Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Raymond Y. Kwong, MD, MPH Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA

Jay I. Lakkis, MD Division of Nephrology, University of Maryland Medical System, Baltimore, MD, USA

Thorsten M. Leucker Department of Medicine, Division of Cardiology, Johns Hopkins Hospital, Baltimore, MD, USA

Leonard S. Lilly, MD Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Michael Lu, MD Department of Radiology, Massachusetts General Hospital - Harvard Medical School, Boston, MA, USA

Kevin C. Maki, PhD Midwest Biomedical Research/Center for Metabolic and Cardiovascular Health, Glen Ellyn, IL, USA

DePaul University, Chicago, IL, USA

Seth S. Martin Department of Medicine, Division of Cardiology, Johns Hopkins Hospital, Baltimore, MD, USA

Robert W. McGarrah, MD Division of Cardiology, Department of Internal Medicine, Duke University School of Medicine, Durham, NC, USA

P. Elliott Miller Division of Cardiovascular Medicine, Yale University School of Medicine, New Haven, CT, USA

Emile R. Mohler III, MD Department of Vascular Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Róisín Morgan, MD Brigham and Women's Hospital, Boston, MA, USA

Kiran Musunuru, MD, PhD, MPH Departments of Medicine and Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Brahmajee K. Nallamothu, MD Division of Cardiovascular Medicine, University of Michigan Medical Center, Ann Arbor, MI, USA

Stephen J. Nicholls, MD Department of Cardiovascular Medicine, Center for Cardiovascular Diagnostics and Prevention, Heart and Vascular Institute, Cleveland Clinic Foundation, Cleveland, OH, USA

Kristin M. Nieman, PhD Midwest Biomedical Research/Center for Metabolic and Cardiovascular Health, Glen Ellyn, IL, USA

Patrick T. O'Gara, MD Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Paolo Raggi, MD Mazankowski Alberta Heart Institute, Division of Cardiology, University of Alberta, Edmonton, AB, Canada

Thorsten Reffelmann, MD Medizinische Klinik II, Klinikum Idar-Oberstein, Idar-Oberstein, Germany

Jeremy Robbins, MD Cardiovascular Division, Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA

Fidencio Saldana, MD Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Emma Scott NHMRC Clinical Trials Centre, University of Sydney, Camperdown, Sydney, Australia

Nicolas W. Shammas, MD Midwest Cardiovascular Research Foundation, Davenport, IA, USA

Garrick C. Stewart, MD Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Yee-Ping Sun, MD Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Peter P. Toth, MD, PhD, FCCP, FAHA, FESC, FACC Ciccarone Center for the Prevention of Cardiovascular Disease, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Matthew Weir, MD Division of Nephrology, University of Maryland Medical System, Baltimore, MD, USA

Part I

Cardiovascular Disease Risk Factors

Epidemiologic Characterization of Risk for Cardiovascular Diseases

1

Kevin C. Maki, Mary R. Dicklin, and Kristin M. Nieman

Key Points

- Over 80 million people in the United States exhibit one or more forms of cardiovascular disease (CVD), and atherosclerotic CVD (mainly coronary heart disease and stroke) is, by far, the leading cause of death among men and women. In 2013, for the first time since 1983, more men died from CVD in the United States than women. However, more women than men continue to die of stroke each year (58% of all stroke deaths in the United States).
- Atherosclerotic CVD has become a worldwide pandemic. While CVD mortality has declined over the last several decades in developed countries, incidence and prevalence of atherosclerotic CVD are increasing in the developing world.
- Potentially modifiable factors account for a large percentage of the variation between and within populations in CVD risk, with population attributable risk fractions estimated at 90% or higher worldwide.
- Traditional CVD risk factors include dyslipidemia, elevated blood pressure, cigarette smoking, and diabetes mellitus. Lifestyle factors are very important in the atherothrombotic disease process. Therapeutic lifestyle changes include smoking cessation, regular physical activity, weight loss if overweight or obese, and consumption of a healthy dietary pattern. A healthy dietary pattern emphasizes whole grains, nuts, seeds and legumes, fruits and vegetables, seafood and lean meats, and nontropical vegetable oils and limits intakes of saturated fat, trans fat, sodium, processed meats, sweets, and sugar-sweetened beverages.
- Numerous novel and emerging risk factors are under study. Improved understanding of the roles of these factors in the atherothrombotic disease process may aid in risk stratification and/or in identifying and testing novel targets for therapy.
- Presently, the greatest utility of nontraditional risk indicators, such as high-sensitivity C-reactive protein, lipoprotein (a), and measures of subclinical CVD, including coronary artery calcium, is for risk refinement when there is uncertainty about an individual's risk category and the value of initiating or intensifying pharmacotherapy.

1.1 The Burden of Atherosclerotic Cardiovascular Disease in the United States

Atherosclerotic cardiovascular disease (CVD) encompasses a range of conditions resulting from atherosclerotic plaques in arterial beds including those in the heart (coronary heart disease [CHD]), legs (peripheral arterial disease), aorta, and carotid, cerebral, and renal arteries. In the United States, lifetime risk for CVD (atherosclerotic and nonatherosclerotic) among men and women free from CVD at 50 years of age in the Framingham Heart Study was estimated to be 51.7% for men and 39.2% for women [1, 2]. According to the US National Center for Health Statistics, the leading causes of

K. C. Maki (✉)
Midwest Biomedical Research/Center for Metabolic and Cardiovascular Health, Glen Ellyn, IL, USA

DePaul University, Chicago, IL, USA
e-mail: KMAKI@MBCLINICALRESEARCH.COM

M. R. Dicklin · K. M. Nieman
Midwest Biomedical Research/Center for Metabolic and Cardiovascular Health, Glen Ellyn, IL, USA

P. P. Toth, C. P. Cannon (eds.), *Comprehensive Cardiovascular Medicine in the Primary Care Setting*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-319-97622-8_1

death were (i) diseases of the heart (primarily CHD, 23.5%), (ii) cancer (22.5%), (iii) chronic lower respiratory diseases (5.7%), (iv) accidents (5.0%), and (v) cerebrovascular diseases (5.0%) [3].

Based on data from 2012, it was estimated that more than 85,000,000 people in the United States exhibited one or more forms of CVD, including CHD, high blood pressure (a major risk factor for atherosclerosis), history of stroke, heart failure, or congenital CVD [4]. Although surveys show that a majority of women feel more vulnerable to breast cancer [5], CVD is by far the leading cause of death among women: 1 in 31.6 deaths of females is attributable to breast cancer, whereas 1 in 8.0 female deaths is attributable to CHD [4]. According to the 2012 National Health and Nutrition Examination Survey data, the prevalence of CVD among adult females is 33.7% and in adult males is 36.4%; using the 2013 Centers for Disease Control and Prevention data, CVD mortality among females is 49.7% compared to 50.3% among males [4].

1.2 Cardiovascular Epidemiology and the Investigation of Risk Factors

Epidemiology is the study of the distributions and determinants of diseases in human populations and the application of that knowledge to improve disease prevention and management. By studying characteristics of individuals who do and do not develop the disease or condition under study, epidemiologists are able to generate hypotheses about possible causal relationships, some of which may subsequently undergo evaluation in clinical intervention trials. Before the middle of the twentieth century, epidemiological methods had been employed mainly in the study of infectious disease outbreaks or "epidemics." In the latter half of the twentieth century, epidemiological methods were extended to the study of chronic diseases such as atherosclerotic CVD. These studies provided the foundation for the concept of CVD risk factors and ultimately led to large, randomized trials to evaluate strategies for primary and secondary CVD prevention.

Early studies compared CVD mortality rates between countries. For example, in the 1950s, Ancel Keys and colleagues documented that annual mortality from CVD per population unit (e.g., per 100,000 persons) varied by as much as tenfold between countries [6, 7]. Autopsy studies showed that among individuals who died from accidents or in wars, those from countries with high CVD mortality rates had more fatty streaks and atherosclerotic lesions in their coronary arteries [8]. Other investigations showed that various factors were associated with higher CVD mortality rates, such as higher average levels of blood cholesterol and blood pressure and greater prevalence of cigarette smoking [9, 10].

Immigration studies showed that people who migrated from countries with low CVD mortality rates to countries with high CVD mortality rates and adopted the lifestyle patterns of their new home showed changes in levels of blood cholesterol and blood pressure. For example, the Japan–Honolulu–San Francisco Study showed that people who migrated from Japan (where CVD mortality was low) to the United States (where CVD mortality was high) had increases in blood pressure and cholesterol levels [11]. Furthermore, the degree to which these changes occurred and the subsequent risk for a CVD event depended on the degree to which the immigrants had adopted dietary and other lifestyle habits similar to those common in the United States [12].

1.3 The Framingham Heart Study

The Framingham Heart Study, initiated in 1948, was one of the earliest large-scale investigations in cardiovascular epidemiology, and its findings helped to provide the foundation for the idea that variation in CHD rates within a population could be predicted by several "risk factors." The investigators measured characteristics of a group of roughly 5000 residents in the town of Framingham, MA, and followed them (and eventually their offspring and the offspring of the offspring) over decades to determine what characteristics were associated with CVD events later in life. The Framingham study showed that many factors were associated with higher or lower CVD incidence and that these were often identifiable years or decades before clinical events, suggesting the potential for prevention through risk factor modification. The enormous success of the Framingham Heart Study paved the way for later studies in the United States and throughout the world that have confirmed and expanded their findings. More information about the history of cardiovascular epidemiology may be found at www.epi.umn.edu/cvdepi, including brief descriptions of many of the major population and intervention studies undertaken during the 1940s through the 1970s in the United States and elsewhere.

1.4 Atherosclerotic CVD Is a Worldwide Pandemic

A pandemic is a condition that occurs throughout a wide geographic area and affects a high proportion of the population. Despite extraordinary advances in options for prevention and treatment, CVD remains the leading cause of death worldwide. In fact, while mortality due to CVD has declined in developed countries, the rate of CVD-related mortality in developing countries has accelerated, likely due to increased urbanization and rising rates of obesity

and other lifestyle-related risk factors [13]. The rising rates of CVD incidence and mortality in the developing world partly reflect declines in competing causes of death that shorten life expectancy. However, results from studies within and across populations strongly support the view that atherosclerotic CVD is largely a disease that is attributable to potentially modifiable lifestyle factors that promote biological changes (e.g., dyslipidemia, hypertension, obesity), which are injurious to the arterial system.

Data from the Nurses' Health Study (84,129 women) show that among female nurses living in the United States, those who demonstrate a "low-risk" profile, as indicated by abstinence from smoking, maintenance of a desirable body weight, regular exercise, healthy dietary habits, and moderate alcohol consumption, have a CHD event risk more than 80% lower than the remainder of the cohort who do not fit this "low-risk" profile [14]. In cohorts from the Multiple Risk Factor Intervention Trial and a large population study in Chicago, together comprising more than 366,000 men and women, a low risk factor burden, defined as blood pressure ≤120/80 mm Hg, total cholesterol <200 mg/dL, absence of smoking, diabetes mellitus, and major electrocardiographic abnormalities, was associated with a 73–85% lower CVD mortality [15].

1.5 Development and Evolution of the Atherothrombotic Process

Population and laboratory studies have provided a framework for understanding the evolution of atherothrombotic disease. A detailed description of this process is beyond the scope of this chapter but will be described briefly (Fig. 1.1). The earliest stage of atherosclerosis is the fatty streak, which can often be found in the coronary arteries of children, particularly in countries with high CVD event rates. Fatty streak formation involves a process through which lipoproteins enter the arterial wall, undergo modification (e.g., oxidation), and are taken up by macrophages in an unregulated fashion, creating foam cells. Foam cells coalesce to form fatty streaks. The fatty streak can grow over time into a raised lesion with a connective tissue cap and a lipid-filled core. If sufficiently large, such lesions may impede blood flow and cause ischemia (e.g., exertional angina or claudication) (Fig. 1.1).

An acute clinical event (myocardial infarction or ischemic stroke) generally occurs when a plaque becomes unstable. Inflammatory processes are important in the development of plaque instability because inflammation can produce thinning of the connective tissue cap, enhancing the probability of fissure formation or frank rupture. Exposure of subendothelial connective tissue and other plaque components in a ruptured plaque activates platelets and can trigger the formation of an occlusive thrombus, disrupting blood flow to the affected organ. This process can be exacerbated by endothelial dysfunction because disruption of the normal endothelium increases vasoconstriction and platelet activation. Myocardial ischemia and infarction can trigger ventricular arrhythmia, which is often the proximal cause of sudden cardiac death.

Thus, the atherothrombotic process can be thought of as a "response to injury" and can be induced or accelerated by factors that enhance the entry of atherogenic lipoproteins into the arterial wall. Such factors include increased concentrations of cholesterol-containing atherogenic lipoproteins, exposures that disrupt normal endothelial function such as elevated blood pressure and hyperglycemia, processes that enhance inflammation such as damage induced by toxic substances contained in cigarettes and inflammatory cytokines produced by expended adipocytes, and an altered balance between thrombosis and fibrinolysis such as increased blood viscosity and endothelial dysfunction. In addition, the susceptibility of the myocardium to electrical instability during an ischemic event can be influenced by sympathetic tone and myocardial fatty acid concentrations.

1.6 Prediction Versus Causation

Early studies identified CVD risk factors that were strongly related to event risk, including dyslipidemia (elevated total cholesterol), hypertension, smoking, and diabetes mellitus. However, causation cannot be established solely on the basis of associations in observational studies. Noncausal associations can arise due to chance, bias, or confounding. An example of a discrepancy between observational study findings and clinical trial results is for the relationship between high-density lipoprotein (HDL) cholesterol and reduced CHD risk. Despite observational results supporting this association, to date, randomized controlled trials of cholesteryl ester transfer protein inhibitors that raise HDL cholesterol have not been shown to decrease risk for CHD [16]. A risk factor may be associated with a disease because it reflects a process that is involved in the causal pathway, but is not itself causal. For example, an elevated level of C-reactive protein (CRP), a marker for peripheral inflammation, is associated with an increased risk for CVD events. However, a study of polymorphisms associated with increased CRP, but not with inflammation, showed that such polymorphisms were not associated with increased ischemic CVD risk [17]. Thus, while CRP is a risk factor that is strongly associated with CVD events, it appears unlikely that the CRP molecule itself is involved in atherothrombosis. Instead, an elevated level of CRP likely reflects a response to inflammatory processes that are in the causal pathways. Accordingly, there is a low probability that development of a pharmacological agent that

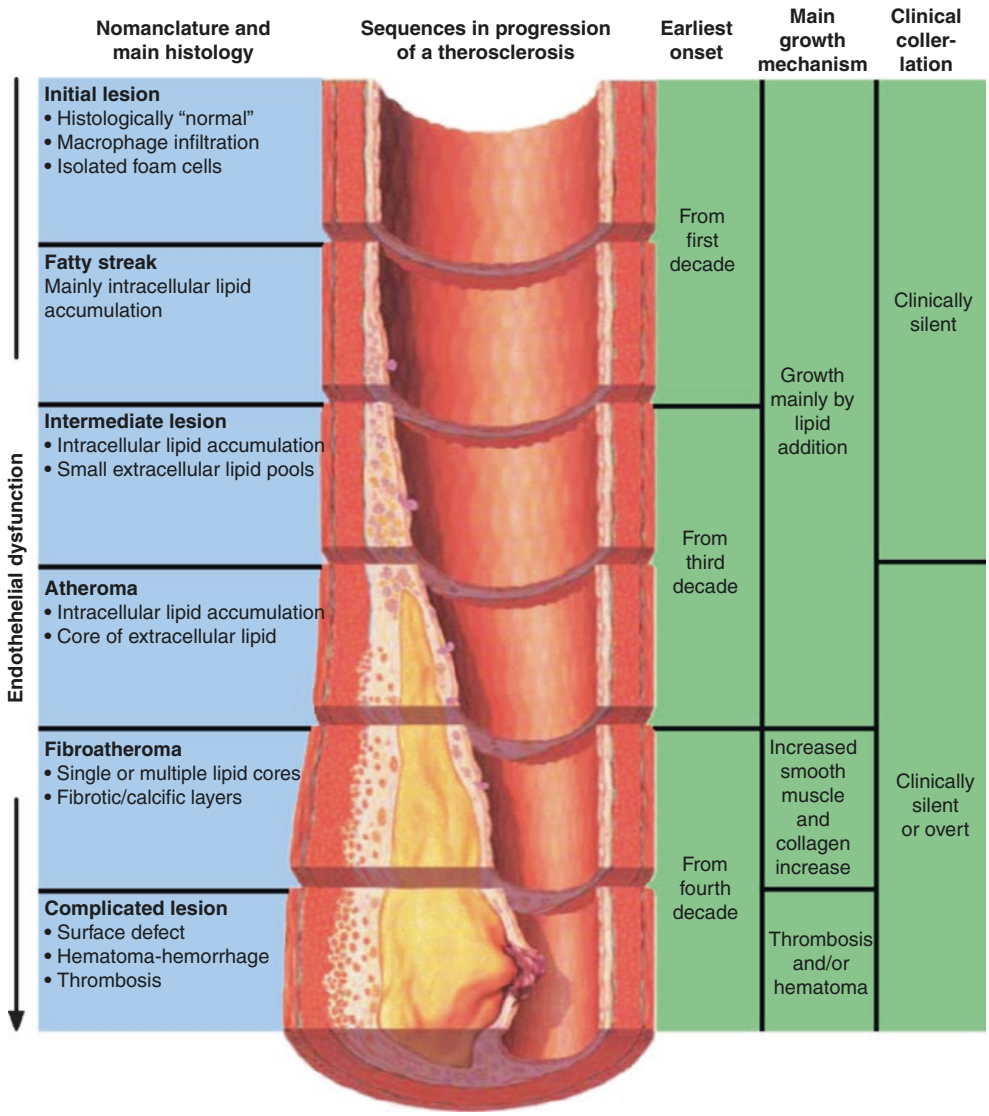

Fig. 1.1 Progression of the atherosclerotic lesion (Note: This figure was released under the GNU Free Documentation License. The GNU Free Documentation License is a copy license for free documentation, designed by the Free Software Foundation (FSF) for the GNU Project. It is similar to the GNU General Public License, giving readers the rights to copy, redistribute, and modify a work and requires all copies and derivatives to be available under the same license. The GFDL was designed for manuals, textbooks, other reference and instructional materials, and documentation that often accompanies GNU software)

blocks the biological actions of CRP will be effective for lowering CVD event risk [18]. In contrast, interventions that reduce inflammation in the vascular wall are promising targets for therapy.

Sir Austin Bradford Hill proposed nine criteria for judging causality, mainly from observational data [19]. The probability that a relationship between a risk factor and a disease is causal must be inferred from the totality of the evidence, including the strength and consistency of the relationship across studies and populations, dose–response, a biologically plausible mechanism to explain the association, appropriateness of the temporal relationship between the risk factor and the disease (i.e., the risk factor precedes the disease), and availability of confirmatory evidence from laboratory and clinical intervention studies. Epidemiological investigations have helped to establish the physiologic links between lifestyle patterns and biological changes (e.g., increases in blood pressure and circulating lipoproteins) pointing toward testable hypotheses regarding causal pathways and, therefore, targets for intervention. Using hypercholesterolemia as an example, population studies showed a strong relationship between elevated blood cholesterol and CVD event and mortality rates. Dietary intervention studies demonstrated that high intakes of saturated fats and cholesterol produced elevations in blood cholesterol. Animal studies indicated that raising the blood cholesterol level by feeding a diet high in saturated fat and cholesterol produced atherosclerosis. These observational and laboratory studies thus laid the foundation for clinical trials that have since demonstrated that lowering an elevated level of cholesterol carried by atherogenic lipoproteins reduces CVD event risk [20, 21].

An area with growing promise for the investigation of predictors of CVD is the use of Mendelian randomization

[22]. Mendelian randomization is the random assortment of genes inherited by offspring from parents during meiosis. Investigations using this approach are useful because the causal nature of "exposures" is less susceptible to the bias and confounding that are problematic in the interpretation of results from other types of observational studies. In addition, this approach incorporates the temporal relationship between the exposure and the outcome [23]. The Mendelian randomization approach has been used to examine the potential causality of low HDL cholesterol levels in the reduction of CHD risk, which lead to the identification of single nucleotide polymorphisms that increased HDL cholesterol (without changing triglyceride or low-density lipoprotein [LDL] cholesterol levels) but were not associated with risk for myocardial infarction. Genetic studies of individuals with mutations in proprotein convertase subtilisin/kexin type 9 and Niemann–Pick C1-Like 1, both of which result in lower levels of LDL cholesterol throughout life, showed associations with lower CVD risk [24, 25]. Similarly, genetic variants in lipoprotein lipase, apolipoprotein C3, and apolipoprotein A5 that result in decreased triglyceride and triglyceride-rich lipoprotein cholesterol levels have also been shown to be associated with reduced atherosclerotic CVD risk [26].

Although atherosclerotic CVD can be thought of as a disease that results largely from behaviors that increase risk, it does not follow that efforts at prevention should be limited to lifestyle interventions. Some risk factors, once established, are resistant to modification through lifestyle changes. Moreover, some pharmacologic interventions to modify risk factors have been shown to be effective in the absence of substantial lifestyle changes and should not be denied to individuals who are unwilling to change their habits regarding diet, exercise, and/or smoking. On the other hand, clinicians often underestimate the importance of lifestyle in producing an adverse CVD risk factor profile and the potential for lifestyle changes to reduce the risk factor burden.

1.7 Population Attributable Risk Fraction

The impact of a risk factor on the incidence of a disease in a population depends on two features: (i) the strength of the relationship between the risk factor and the disease (assuming a causal relationship) and (ii) the prevalence of the risk factor. Thus, a causal factor that has a strong association with the disease outcome might, nevertheless, have only a minor influence on the population attributable risk fraction if it has a low prevalence. Conversely, a causal factor that produces a modest increase in risk can have a high population attributable risk fraction if it is very common. In the United States, the major established modifiable risk factors (dyslipidemia, hypertension, and smoking) have high population attributable risk fractions because they are both common and strongly related to CVD risk [27]. The six major, established CVD risk factors are shown in Table 1.1.

The estimation of population attributable risk fraction is complicated by the fact that risk factors are often correlated with one another. For example, diabetes mellitus is a strong CVD risk factor, but it is also associated with other risk factors such as obesity; elevated triglycerides; depressed HDL cholesterol; small, dense LDL particles; increased levels of inflammatory markers; and elevated blood pressure. Modification of some of the associated risk factors, particularly dyslipidemia and hypertension, is effective for reducing CVD event risk in patients with diabetes [29]. In contrast, aggressive glycemic control appears to reduce risks of microvascular complications, but has not proven consistently effective for preventing CVD events, suggesting that the increased CVD event risk associated with diabetes is largely attributable to other risk factors and that the relationship to hyperglycemia per se is less certain [30]. Recent clinical trials have shown that glucose-lowering agents (i.e., a sodium-glucose cotransporter-2 inhibitor, two glucagon-like peptide-1 agonists, and a thiazolidinedione) can reduce cardiovascular events in patients with diabetes, but it is not clear that the decrease is attributable to improved glycemic control or to other mechanisms [31].

CVD risk quantification methods recommended for clinical practice generally do not include factors such as obesity, physical inactivity, and poor diet, not because they lack predictive value but because they are more distal in the causal pathway, exerting their influence mainly through changes in

Table 1.1 Major atherosclerotic cardiovascular disease risk factors – excluding atherogenic lipoprotein cholesterol levels[a]

Current cigarette smoking
Hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or use of antihypertensive medication for lowering blood pressure)
Family history of premature CHD
CHD[b] in a male first-degree relative[c] <55 years of age
CHD[b] in a female first-degree relative[c] <65 years of age
Age
≥45 years of age for men
≥55 years of age for women
Low HDL cholesterol
<40 mg/dL for men
<50 mg/dL for women

Adapted from the National Lipid Association (NLA) recommendations for the patient-centered management of dyslipidemia [28]

[a]Atherogenic lipoprotein cholesterol levels (LDL cholesterol and non-HDL cholesterol) are not included among the risk factors because they are used to assess risk category and treatment goals for atherogenic lipoprotein cholesterol levels. Diabetes mellitus is not listed because it is considered a high- or very high-risk condition (depending on the presence of additional risk factors) for CVD risk assessment purposes

[b]CHD is defined as myocardial infarction, coronary death, or a coronary revascularization procedure

[c]First-degree relatives include parents, siblings, and children

other risk factors that are used in the risk calculations. Nevertheless, these risk factors remain important targets for therapy [32] (Fig. 1.2).

Despite continued uncertainty and controversy about the relative importance of specific risk markers, it is clear that potentially modifiable factors account for a large percentage of the variation between and within populations in CVD risk. For example, results from INTERHEART [9], a study of risk factors for acute myocardial infarction across 52 countries, suggest that more than 90% of the population attributable risk for CHD in men and women can be explained by potentially modifiable risk factors. These results, together with those from many other investigations, strongly support the view that substantial potential exists for preventive efforts, both on a population basis and in clinical settings, although it should be emphasized that, at present, clinical outcomes data from randomized clinical trials are only available for a limited number of preventive strategies, most notably treatment of dyslipidemia, treatment of hypertension, and the use of aspirin.

Some of the interventions recommended in current guidelines, such as smoking cessation or increased physical activity, are unlikely to ever be tested in large-scale CVD event trials due to practical or ethical considerations. In such cases, observational studies and studies on the effects of the intervention on accepted risk factors (e.g., lipoprotein lipids, blood pressure) will remain the best guide to clinical practice. The science of CVD prevention is evolving rapidly, and the reader is referred to the frequently updated list of Scientific Statements and Practice Guidelines from the American Heart Association (AHA) for current recommendations (http://professional.heart.org/professional/GuidelinesStatements/UCM_316885_Guidelines-Statements.jsp), as well as recommendations and statements from the National Lipid Association (https://www.lipid.org/practicetools/guidelines).

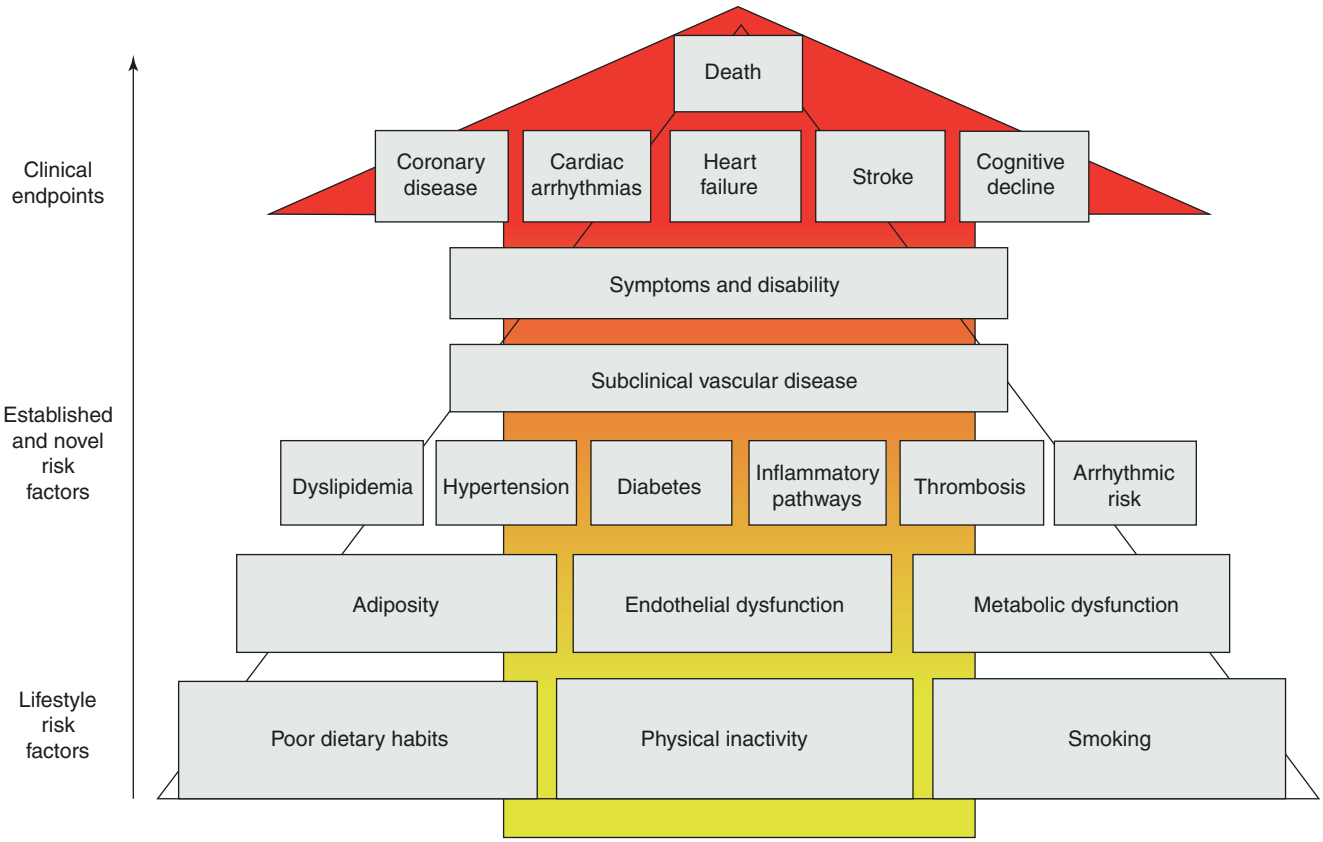

Fig. 1.2 The relations of lifestyle, established and novel risk factors, and cardiovascular disease. Assessment and treatment of dyslipidemia, hypertension, and diabetes are major foci of clinical care, practice guidelines, performance measures, and scientific research. These established cardiovascular risk factors are strongly influenced by lifestyle, including dietary behaviors, physical inactivity, smoking, and excess adiposity. Excess adiposity itself results partially from poor diet and inactivity. Lifestyle risk factors also influence disease risk via effects on other novel risk factors such as endothelial function, inflammation/oxidative stress, thrombosis/coagulation, arrhythmia, and other pathways. These basic lifestyle habits – poor diet, physical inactivity, and smoking – are thus the most proximal risk factors for cardiovascular disease [32]

The remainder of this chapter will provide an overview of traditional and emerging risk factors for atherosclerotic CVD and explore some areas where controversies persist. The reader should also note that there is some variation with regard to the relationships between individual risk factors and the different manifestations of atherosclerotic CVD. For instance, hypertension is a stronger risk factor for stroke than for CHD, while cigarette smoking and diabetes are particularly strong correlates of peripheral arterial disease. The focus herein will be on risk factors for atherosclerotic CVD in general, and we will not attempt to differentiate the importance of individual risk factors for predicting specific clinical outcomes.

1.8 Dyslipidemia

Because atherosclerotic plaques contain a lipid core, hypercholesterolemia was investigated early on as a possible CVD precursor. High levels of cholesterol were found to be associated with increased risk, although later studies showed that this relationship was more complicated than was appreciated at first. Higher levels of cholesterol carried by HDL particles seemed to be protective. Furthermore, the circulating triglyceride was also found to correlate directly with risk, particularly in women.

Cholesterol and triglycerides are not water soluble; thus, they are carried in the blood in lipoprotein particles. The three main classes of circulating lipoproteins in the fasting state are:

- Very low-density lipoproteins (VLDL)
- LDL
- HDL

The triglyceride concentration in plasma correlates very strongly with the VLDL cholesterol concentration, which is the basis for the Friedewald equation that is used for calculation of LDL cholesterol (LDL cholesterol = total cholesterol – HDL cholesterol – triglycerides/5).

1.8.1 Measures of Atherogenic Lipoprotein Burden

Although previous treatment guidelines focused on an elevated level of LDL cholesterol as the primary target for therapy, results from population and clinical intervention studies have shown that non-HDL cholesterol is a better predictor of risk, leading to some recommendations emphasizing non-HDL cholesterol as a target of therapy [28, 33, 34]. Non-HDL cholesterol is calculated as the difference between the total and HDL cholesterol concentrations and comprises the cholesterol carried by all potentially atherogenic particles, including LDL, intermediate density lipoprotein, VLDL and VLDL remnants, chylomicron particles and chylomicron remnants, and lipoprotein (a). Apolipoprotein B is another important predictor of CVD. The apolipoprotein B concentration reflects the total number of circulating atherogenic particles because each VLDL and LDL particle contains one molecule of apolipoprotein B. Unless the individual has very high triglycerides, nearly all of the apolipoprotein B is carried by VLDL and LDL particles in the fasting state, and < 1% is carried by chylomicron remnants of intestinal origin that contain a truncated 48 amino acid form of apolipoprotein B rather than the 100 amino acid form of hepatic origin.

Apolipoprotein B and non-HDL cholesterol are each better predictors of event risk than LDL cholesterol [35, 36] and are highly correlated with one another. While apolipoprotein B may be a slightly better predictor of CVD events than non-HDL cholesterol, it appears unlikely that the modest increase in predictive ability will justify the incremental expense and complexity of running an additional test. Non-HDL cholesterol can be easily calculated from the standard laboratory lipoprotein profile, and fasting is not required to obtain an accurate non-HDL cholesterol concentration. Until recently, it was not widely recognized that each 1 mg/dL increment in VLDL cholesterol is associated with roughly the same increase in CHD event risk as a 1 mg/dL increment in LDL cholesterol, whether or not triglycerides are elevated, accounting for the superior predictive value of non-HDL cholesterol over LDL cholesterol [37] (Fig. 1.3). LDL and non-HDL particle concentrations are also measures of atherogenic lipoprotein burden that can be used as alternatives

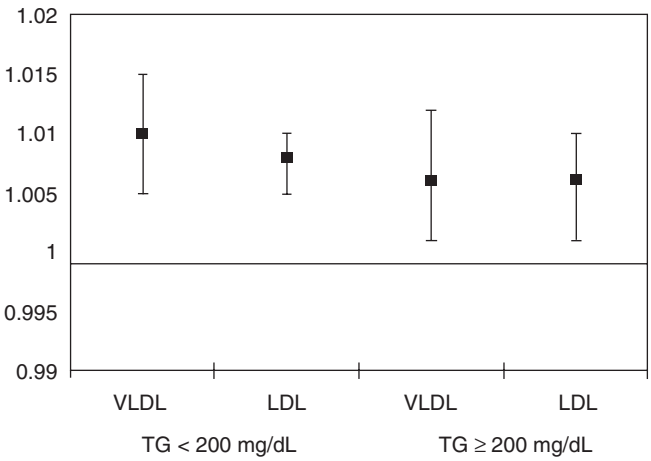

Fig. 1.3 Risk of coronary heart disease incidence for very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) cholesterol, as continuous variables, by triglyceride (TG) levels, adjusted for age, gender, study, smoking status, systolic blood pressure, and prevalent diabetes (at baseline) [37]

to apolipoprotein B, both as indicators of CVD risk and responses to therapy [38, 39].

Data from clinical trials indicate that lowering an elevated non-HDL cholesterol level by 1% produces a reduction in CHD event risk of 1.0–1.5% over 5–6 years or roughly half the reduction that might be expected based on results from population studies [40]. While not conclusive, findings from observational studies, such as those of individuals with genetic mutations that result in lower LDL and non-HDL cholesterol throughout life, suggest that maintaining a low burden of atherogenic lipoproteins over an extended period may reduce risk to a greater extent than has been demonstrated to date in clinical trials, with CHD risk reduction estimates of 2.5–3.0% per 1% reduction, similar to the relationships from population studies [24].

1.8.2 Measures of Antiatherogenic Lipoproteins

Low HDL cholesterol is strongly linked with increased CVD risk. Each 1% decrement in HDL cholesterol is associated with a 2–3% increase in CHD risk [41]. Moreover, as was the case for atherogenic lipoproteins (i.e., apolipoprotein B), the concentration of apolipoprotein AI, a surrogate for the number of HDL particles, is a stronger predictor of CHD risk than the HDL cholesterol concentration [42]. HDL cholesterol concentration may also play an important role in the difference between men and women in CVD risk. Before puberty, boys and girls have similar levels of HDL cholesterol, but the level drops in boys as testosterone level increases. The mean difference between men and women in HDL cholesterol concentration (~10 mg/dL lower in men) could account for a large fraction of the difference between the sexes in CVD risk, although it is uncertain whether the relationship between HDL-cholesterol level and CHD risk is causal.

Some evidence supports the view that increases in HDL cholesterol or apolipoprotein AI levels contribute to the reduction in risk associated with lipid-altering therapies [43]. However, to date, clinical trials on therapies that raise HDL cholesterol, including niacin and cholesteryl ester transfer protein inhibitors, have failed to demonstrate a reduction in CVD risk associated with their use. Because changes in HDL cholesterol in clinical intervention studies are nearly always associated with changes in other lipid and non-lipid risk factors (e.g., LDL cholesterol, triglycerides, body weight), the quantitative role of changes in HDL cholesterol or particle number in risk reduction has not been fully defined. In addition, HDL cholesterol can be raised through a variety of mechanisms, and it is not certain that all would produce the same benefit with regard to CVD event risk. For this reason, HDL cholesterol is not a target of therapy, and current guidelines do not assign specific treatment goals for the HDL cholesterol level, although it is recognized that HDL cholesterol is often raised as a result of lifestyle and drug therapies aimed at reducing levels of atherogenic cholesterol.

1.8.3 Ratios of Atherogenic to Antiatherogenic Lipoproteins

Because atherogenic and antiatherogenic lipoproteins are both strong predictors of CVD risk, it is not surprising that their ratios, such as total/HDL cholesterol and apolipoprotein B/apolipoprotein AI, are better predictors than their components. The main objection to the use of such a ratio in clinical practice is that it is not certain that changes in the numerator and denominator that produce equivalent changes in the ratio will produce equivalent changes in CVD risk.

1.8.4 Triglycerides and LDL Particle Size

An elevated level of triglycerides is associated with increased CVD risk, particularly in women. However, an increased triglyceride concentration is also associated with higher concentrations of triglyceride-rich lipoproteins (VLDL and chylomicron remnants), lower levels of HDL cholesterol, and increased levels of small, dense LDL particles. It remains a matter of controversy as to whether lowering triglycerides will have any benefits beyond those derived from changing the levels of atherogenic (chylomicron remnants, VLDL, LDL) and antiatherogenic (HDL) particle numbers.

One argument in favor of a potential benefit from lowering triglyceride level beyond that reflected by changes in non-HDL cholesterol level is that the triglyceride level is an important determinant of LDL particle size. Individuals seem to have a threshold for triglyceride level below which they will exhibit a predominance of large, buoyant LDL particles (pattern A) and above which they will exhibit a predominance of small, dense particles (pattern B) [44]. This threshold varies between individuals but falls in the range of 100–250 mg/dL for most of the population. Thus, lowering the triglyceride level from 600 to 250 mg/dL will have no effect on LDL size for most people because the threshold for conversion from pattern B to pattern A will not be breached. However, lowering the triglyceride concentration from 250 to 100 mg/dL will cause most individuals to convert to pattern A.

Small, dense LDL particles may be more atherogenic than larger LDL and VLDL particles for a variety of reasons, including greater ease of entry into the subendothelial space, enhanced interaction with subendothelial proteoglycans, and greater susceptibility to oxidation [45]. According to this model, a gradient of atherogenicity exists with large VLDL at one end, followed by small VLDL particles, then

large LDL particles, and finally small LDL particles at the most atherogenic end of the spectrum. At present the existence and/or steepness of this gradient remains uncertain, so the emphasis remains on LDL and non-HDL cholesterol lowering. Triglyceride (except when very high, ≥ 500 mg/dL) and HDL cholesterol concentrations are not targets of therapy.

1.8.5 Lipoprotein (a)

Lipoprotein (a) is a subspecies of LDL particles that contain a protein [apoprotein (a)] that varies in length depending on the number of repeating segments (kringles) that are expressed. Apoprotein (a) is similar in structure to plasminogen, and, as a result, increased levels of lipoprotein (a) in circulation may interfere with the function of plasminogen [46].

Many studies have suggested that an elevated level of lipoprotein (a) is a risk factor for CVD. Current US guidelines and recommendations do not indicate routine screening for lipoprotein (a). However, elevated lipoprotein (a), defined as ≥ 50 mg/dL (protein) using an isoform insensitive assay, is recommended for use as an additional atherosclerotic CVD risk indicator to consider for risk refinement in identifying individuals with at least moderate risk to determine if they should be moved to a higher risk category. Lipoprotein (a) is highly heritable, and identification of a value ≥ 50 mg/dL, which represents approximately the 80th percentile in the general population, may warrant more aggressive management of other risk factors, especially reducing levels of atherogenic lipoproteins, as well as screening of relatives for lipoprotein (a) elevation.

1.9 Hypertension

The Seventh Joint National Committee on Prevention, Evaluation, and Treatment of High Blood Pressure defined hypertension as a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg or current use of antihypertensive medication. Persons with blood pressures <120 (systolic) and <80 (diastolic) mm Hg are considered normal, whereas those with blood pressures between these categories are considered to have "prehypertension" [47]. These definitions were not changed in the 2014 Eighth Joint National Committee guidelines [48] that focused on treatment guidance.

Intervention trials have shown that lowering blood pressure reduces risk for CHD and stroke. Beginning at a blood pressure of 115/75 mm Hg, the risk for CVD doubles with each increment of 20 mm Hg for systolic blood pressure and 10 mm Hg for diastolic blood pressure. Treating hypertension to a goal of <140/90 mm Hg (or <130/80 mm Hg for those with diabetes or renal disease) has been shown to reduce CVD morbidity and mortality. Each 5 mm Hg reduction in systolic blood pressure is associated with reductions of 14% for mortality from stroke and 9% for mortality from CHD [49]. Recently, results from the Systolic Blood Pressure Intervention Trial demonstrated that among patients at high risk for cardiovascular events (but without diabetes), achieving a systolic blood pressure <120 mm Hg, compared with <140 mm Hg, resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause, although these results have been controversial, in part because the method of measurement used tends to produce lower values than blood pressures assessed in routine clinical practice [50–52].

Evidence of end-organ damage such as left ventricular hypertrophy, glomerular filtration rate <60 mL/min, or microalbuminuria are associated with greater CVD morbidity and mortality at any level of blood pressure (Fig. 1.4). Left ventricular hypertrophy has been shown to regress with aggressive blood pressure management and lifestyle interventions such as sodium restriction, weight loss, and increased physical activity enhance regression. Although not conclusive, the balance of the available data supports the view that greater left ventricular hypertrophy regression is associated with improved outcomes [53].

1.10 Smoking

Cigarette smoking is the last of the "big three" major modifiable CVD risk factors: dyslipidemia, hypertension, and cigarette smoking. Cigarette smoking (and to a lesser extent, pipe and cigar smoking) has a number of adverse effects on the vascular system that promote the atherothrombotic process. Toxins from cigarette smoke damage the endothelium and enhance platelet aggregation, making thrombosis more likely. Smoking also induces insulin resistance, raises the triglyceride concentration, and lowers the HDL cholesterol level [32].

Many investigations show a dose-dependent increase in risk associated with cigarette smoking, and being a current smoker of 20 cigarettes per day increases CVD event risk by two- to threefold relative to a never smoker. Although randomized trials of smoking cessation and CVD events are not feasible for ethical reasons, prospective investigations have shown lower CVD morbidity and mortality for former smokers compared with continuing smokers. A reduction in risk is evident within months after smoking cessation, and increasing intervals since quitting are associated with progressively lower CVD morbidity and mortality. Benefits from quitting are observed in former smokers even after many years of heavy smoking.

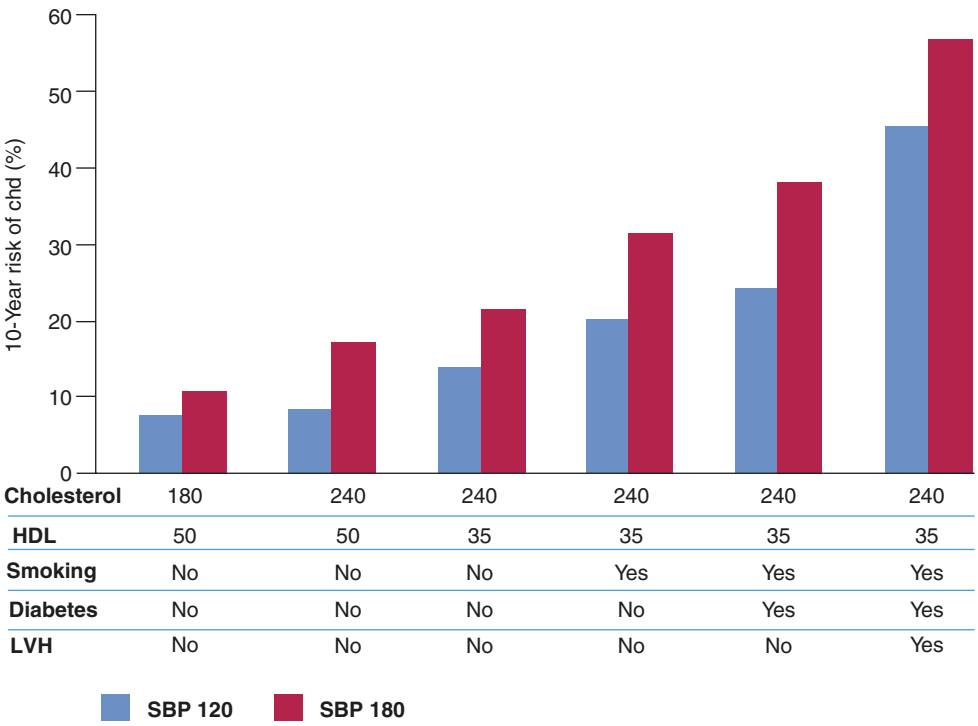

Fig. 1.4 Ten-year risk for coronary heart disease by systolic blood pressure and the presence of other risk factors [47]. Abbreviations: CHD coronary heart disease, HDL high-density lipoprotein cholesterol, LVH left ventricular hypertrophy, SBP systolic blood pressure

1.11 Overweight, Obesity, and Body Fat Distribution

Overweight and obesity are very common in the United States and other developed countries. Data from the National Health and Examination Survey and the National Health Interview Survey indicate that in 2009–2010, the prevalence of overweight (body mass index 25.0–29.9 kg/m^2) or obesity (body mass index ≥30.0 kg/m^2) in the United States was 68.8% among adults 20 years of age or older [54, 55]. Within this group, 33.1% were overweight and 35.7% obese.

Excess adiposity is associated with greater morbidity and mortality from CVD and also increases the probability of developing other risk factors such as dyslipidemia, hypertension, and diabetes. This is particularly true when increased adiposity is centrally distributed. Expanded visceral adipose depots (in the abdominal cavity – mainly omental and mesenteric) have increased fatty acid turnover and contribute disproportionately to the fatty acids released into the portal circulation [56]. Thus, the impact of increased adiposity on the metabolic profile is partly dependent on the location of the expanded fat cells. Visceral adiposity is most metabolically harmful, upper body subcutaneous adiposity has an intermediate influence, and lower body subcutaneous fat has only a modest metabolic effect. Waist circumference is an indicator of both total and abdominal adiposities with >90% of the variance in waist girth explained by differences in total fat mass and visceral adipose tissue area [57], whereas waist/hip ratio is an indication of the propensity of an individual to store body fat centrally.

Increased hepatic free fatty acid flux stimulates synthesis and secretion of triglyceride-rich VLDL particles. A rise in circulating VLDL triglyceride enhances exchange of triglyceride for cholesterol between VLDL and HDL particles, contributing to a decline in HDL cholesterol. Furthermore, since VLDL is the precursor to LDL, an increase in VLDL secretion can also lead to elevation in the LDL cholesterol concentration. When the circulating free fatty acid level is chronically elevated, resistance develops to the ability of insulin to stimulate glucose uptake in skeletal muscle, leading to the need for compensatory hyperinsulinemia to maintain normal glucose tolerance [56]. Hyperinsulinemia enhances renal sodium reabsorption and sympathetic activation, increasing fluid volume, heart rate, and cardiac output, thereby increasing risk for hypertension. Over time, chronic insulin resistance can lead to pancreatic beta-cell dysfunction and, consequently, glucose intolerance and diabetes mellitus.

Obesity has both environmental and genetic determinants. An individual with two obese parents has greater than an 80% probability of being obese in young adulthood. However, even among those with a genetic predisposition,

obesity may not become manifest in the absence of an obesity-promoting lifestyle. For example, Pima Indians living in Arizona in the Gila River basin have a famously high prevalence of obesity, with more than 85% of male Pimas classified as obese by age 35 years [58]. However, Pima Indians living in mountainous areas in Mexico, who live a traditional lifestyle characterized by high levels of physical activity and little consumption of processed foods, have very little obesity [58].

1.12 Metabolic Syndrome and Diabetes Mellitus

Type 2 diabetes mellitus and atherosclerotic CVD share a number of common risk factors. Several of these cluster together more often than would be predicted by chance, suggesting that they are metabolically linked. Over the years, this group of interrelated risk factors has been referred to variously as syndrome X, the deadly quartet, the insulin resistance syndrome, and the cardiometabolic risk syndrome. The National Cholesterol Education Program Adult Treatment Panel III coined the term metabolic syndrome and proposed a set of criteria for its diagnosis [59]. A joint statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity proposed the definition of the metabolic syndrome shown in Table 1.2 that is universally accepted and was upheld by the NLA in their recommendations for the patient-centered management of dyslipidemia [28, 60].

Risks for both diabetes mellitus and atherosclerotic CVD increase progressively as the number of metabolic syndrome components increases. The underlying link between these conditions is thought to be resistance to the ability of insulin to promote glucose uptake and suppress free fatty acid release from adipose tissue. While increased adiposity is the most common cause of insulin resistance, it can occur in the absence of obesity, and such "metabolically obese" individuals may have the metabolic syndrome without increased body mass index or waist circumference. The primary aim of creating a diagnostic category for the metabolic syndrome was to assist in targeting this group for more aggressive preventive measures, including therapeutic lifestyle changes (weight loss and increased physical activity), as well as other therapies as needed to manage the individual risk factors. In the Diabetes Prevention Program, a lifestyle intervention aimed at reducing body weight by 7% and increasing physical activity to 150 min/week reduced new-onset diabetes by 58% over an average follow-up period of 3.3 years among individuals with impaired glucose tolerance [61].

Table 1.2 Criteria for clinical diagnosis of metabolic syndrome [59]

Any three or more components	Cut points
Elevated waist circumference[a,b]	≥40 in. (102 cm) in men ≥35 in. (88 cm) in women
Elevated triglycerides	≥150 mg/dL (1.7 mmol/L) *Or* Drug treatment with a triglyceride-lowering agent[co]
Reduced HDL-cholesterol	<40 mg/dL (0.9 mmol/L) in men <50 mg/dL (1.1 mmol/L) in women
Elevated blood pressure	Systolic ≥130 mm Hg and/or diastolic ≥85 mm Hg *Or* Antihypertensive drug treatment in a patient with a history of hypertension
Elevated fasting glucose	≥100 mg/dL (5.6 mmol/L) *Or* Drug treatment of elevated glucose

[a]To measure waist circumference, locate top of right iliac crest. Place a measuring tape in a horizontal plane around the abdomen at the level of iliac crest. Before reading the tape measure, ensure that tape is snug but does not compress the skin and is parallel to the floor. Measurement is made at the end of a normal expiration

[b]AHA/National Heart, Lung, and Blood Institute guidelines for metabolic syndrome suggest waist circumference thresholds of ≥37 in. (≥94 cm) in men and ≥32 in. (≥80 cm) in women as optional cut points for individuals or populations with increased insulin resistance including those of Asian descent (alternate values have been published for other groups)

[c]Fibrates, nicotinic acid, and high-dose long-chain omega-3 fatty acids are the most commonly used drugs for elevated triglycerides. Patients taking one of these drugs are presumed to have elevated triglycerides

Although diabetes mellitus is a major independent risk factor for CVD, it should be noted that prediabetes is also associated with ~20% increased CVD risk compared with risk in normoglycemic individuals [62, 63]. However, it is uncertain to what degree glucose elevation per se contributes to the enhanced CVD risk. Prediabetes is usually diagnosed on the basis of at least two fasting glucose concentrations in the range of 100–125 mg/dL or a glycated hemoglobin level of 5.7–6.4% [64]. Lifestyle (weight loss, increased physical activity, Mediterranean diet) and pharmaceutical (metformin, alpha glucosidase inhibition, thiazolidinedione therapy, and intestinal lipase inhibition) have been shown to prevent or delay the onset of diabetes mellitus in those with prediabetes [65].

1.12.1 Diabetes Mellitus

Diabetes mellitus (type 1 or 2) is an important non-lipid ASCVD risk factor. CVD event rates among individuals who have had diabetes for 8–10 years are similar to those of people with a prior CHD event. The presence of diabetes

increases risk for a CVD event by two- to eightfold, and mortality is higher among those with diabetes after a CVD event [29, 66]. The increase in relative risk for CVD associated with diabetes is larger for women than men [14]. According to the 2015 NLA recommendations, patients with diabetes and 0–1 other major atherosclerotic CVD risk factors and no evidence of end-organ damage are considered to be at high risk, and individuals with diabetes and at least two other major atherosclerotic CVD risk factors or evidence of end-organ damage are considered to be at very high risk [28]. Diabetes is also an important consideration in the 2013 ACC/AHA cholesterol guidelines, which state that individuals with diabetes aged 40–75 years of age and with LDL cholesterol 70–189 mg/dL, but without clinical atherosclerotic CVD, comprise one of four "statin-benefit" groups for whom atherosclerotic CVD risk reduction clearly outweighs the risk of adverse events [67].

The National Health and Nutrition Examination Survey 2007–2010 showed that the prevalence of diabetes was 18.5% among obese adults, 8.2% in overweight adults, and 5.4% in normal weight adults [68]. Data from clinical trials show that intensive glycemic control is effective for reducing microvascular complications (e.g., retinopathy, neuropathy, nephropathy) in patients with type 1 or 2 diabetes mellitus [30]. Aggressive glycemic control has not been consistently demonstrated to reduce macrovascular complications in type 2 diabetes. Although recent clinical trials have shown that glucose-lowering agents can reduce cardiovascular events in patients with diabetes, it is not clear whether the decrease is due to improved glycemic control or perhaps attributable to other mechanisms [30, 31]. Other preventive measures (lipid management, blood pressure control, and use of aspirin) have proven effective for reducing CVD events in patients with diabetes [69–72]. Thus, while adequate glycemic control remains an important goal of therapy, aggressive CVD risk factor management is central to efforts to reduce CVD morbidity and mortality in those with diabetes.

1.13 Diet and Physical Activity

Throughout this chapter, emphasis has been placed on the importance of lifestyle in driving adverse changes in risk factors that, in turn, promote the atherothrombotic process. Lifestyle modification plays a critical role in preventive efforts, and favorable changes in diet and physical activity habits simultaneously improve multiple risk factors [73]. Table 1.3 summarizes the lifestyle recommendations from the 2013 AHA/American College of Cardiology (ACC) Guideline on Lifestyle Management to Reduce Cardiovascular Risk [74].

Table 1.3 2013 AHA/ACC recommendations for lifestyle management [74]

Recommendations
Diet
Consume a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils, and nuts; and limits intake of sweets, sugar-sweetened beverages, and red meats
• Adapt dietary pattern to appropriate calorie requirements, personal and cultural food preferences, and nutrition therapy for other medical conditions
• Achieve this pattern by following plans such as DASH, USDA, or AHA Diets
Specific advice for LDL cholesterol lowering:
• Aim for dietary pattern which includes no more than 5–6% calories from saturated fat
• Reduce percent of calories from saturated fat
• Reduce percent of calories from trans fat
Specific advice for blood pressure lowering:
• Lower sodium intake
Physical activity
Engage in aerobic physical activity to reduce LDL cholesterol, non-HDL cholesterol, and blood pressure: 3–4 sessions/week lasting on average 40 min per session, involving moderate- to vigorous-intensity physical activity

Abbreviations: *DASH* dietary approaches to stop hypertension, *USDA* US Department of Agriculture

1.13.1 Dietary Factors

The Dietary Guidelines Advisory Committee, as well as the 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk and the NLA recommendations for the patient-centered management of dyslipidemia support the dietary recommendations outlined in Table 1.3 [74–76]. In addition to maintenance of a healthy body weight, these recommendations emphasize consumption of fruits, vegetables, nuts, legumes, and whole grains. Population studies show that higher intakes of these foods are associated with reduced CVD risk, although the mechanisms responsible for these relationships are not fully understood and are under active investigation [73]. The recommendations also include consumption of oily varieties of fish, which contain the long-chain omega-3 fatty acids eicosapentaenoic and docosahexaenoic acid. Both population studies and clinical trials have shown that greater intakes of these fatty acids are associated with reduced CVD mortality [77]. The benefits of omega-3 fatty acids may derive, at least in part, from incorporation of these fatty acids into myocardial membranes, which appears to reduce susceptibility to arrhythmias, particularly those triggered by ischemia [78]. Reducing added sugars and salt helps with maintenance of normal body weight and blood pressure, and lowering intakes of saturated fats, trans fats, and cholesterol to levels below those in the typical American diet helps to maintain normal levels of cholesterol and atherogenic lipoproteins.

1.13.2 Alcohol Consumption

A consistent association has been observed between moderate alcohol consumption and reduced CVD morbidity and mortality in many populations, and this relationship holds true for both wine and other types of alcoholic beverages [79]. Alcohol raises HDL cholesterol in a dose–response manner and has effects on platelet function and inflammatory markers that may help to explain this association [80]. At higher intakes, alcohol has a number of adverse effects, including raising levels of triglycerides and blood pressure. Beyond moderate levels of alcohol intake, increases in morbidity and mortality from other causes offset any cardiovascular benefits [79]. Alcohol is not recommended for CVD prevention because it is potentially addictive; but for patients who choose to consume alcohol, the recommendation is to limit intake to not more than two drinks per day for men and one drink per day for women (a drink is 12 oz. of beer, 5 oz. of wine, 1.5 oz. of spirits).

1.13.3 Physical Activity

Regular physical activity is associated with lower risks for CVD, obesity, diabetes, hypertension, osteoporosis, and cancers of the breast and colon [73]. Regular activity, particularly if at least some of it is vigorous, has been demonstrated to improve levels of blood pressure, blood lipids (triglyceride and HDL cholesterol levels), insulin resistance, adiposity, as well as biomarkers of inflammation and hemostasis [81].

Among adults ≥18 years of age who responded to the 2015 National Health Interview Survey, ~49% did not meet the 2008 federal guidelines for aerobic activity, which included performing at least 150 min/week of moderate-intensity aerobic physical activity or 75 min/week of vigorous-intensity aerobic physical activity or an equivalent combination of moderate- and vigorous-intensity aerobic activity [82]. A greater amount of physical activity is necessary to reduce LDL cholesterol and body weight – generally 200–300 min/week of moderate- or higher-intensity physical activity [75]. The prevalence of sedentary lifestyle increases with age, is higher in women than men, and is especially high in minority (African American and Hispanic/Latino) subsets of the population [82].

1.14 Inflammatory Markers

As described earlier, the atherothrombotic process is essentially a "response to injury" in the arterial wall in which inflammation plays a central role. Given the central role of inflammation in atherothrombosis, it is not surprising that various biological markers for inflammation are associated with increased CVD event risk. For a number of reasons, many of these are poorly suited for use in clinical practice, but some do have potential clinical applications, particularly CRP. General screening for elevations in inflammatory markers is not recommended. The greatest utility of these markers in clinical practice is for identifying those individuals with at least moderate risk for a CVD event for whom the clinician is not certain whether more aggressive therapy, particularly lipid-altering therapy, is warranted [28, 67, 83].

Because of significant intraindividual variation, the measurement of high-sensitivity CRP (hs-CRP) should be completed on at least two separate occasions and the results averaged. Results may be categorized as follows based on population tertiles:

- Low: <1.0 mg/L
- Average: 1.0–3.0 mg/L
- High: >3.0 mg/L

A value of 2.0 mg/L, representing the midpoint of the "average" population tertile, can be used as a risk indicator for risk refinement in conjunction with major atherosclerotic CVD risk factors, to reclassify an individual into a higher risk category [28]. The high tertile for hs-CRP is associated with a relative risk for a CVD event that is roughly twofold that of the lowest tertile and does appear to add predictive value beyond that of traditional risk markers [84, 85]. It should be noted that noncardiovascular causes can produce hs-CRP elevation, and other causes such as infection or trauma should be considered if the value is >10 mg/L.

The Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study evaluated whether rosuvastatin (20 mg/day), compared with placebo, would decrease the rate of occurrence of first major cardiovascular events in otherwise healthy individuals with elevated hs-CRP (≥2.0 mg/L) and LDL cholesterol <130 mg/dL [86]. Rosuvastatin therapy reduced LDL cholesterol by 50% and hs-CRP by 37%. The trial was stopped early because the rosuvastatin group showed reductions of ~50% in several cardiovascular endpoints relative to the placebo group. The JUPITER results provide clear evidence that those with elevated hs-CRP are at increased CHD risk and that rosuvastatin therapy lowers this risk. However, JUPITER did not answer the question of whether hs-CRP reduction per se should be a target of therapy. An additional outstanding question is the mechanisms that account for the increased risk associated with elevated hs-CRP. Is hs-CRP elevation reflecting vascular inflammation, dysregulation of adipose tissue resulting in the release of proinflammatory cytokines and greater hepatic sensitivity to inflammatory stimuli, or does hs-CRP itself promote some aspect of the

atherothrombotic process? Results from genetic studies indicate that polymorphisms associated with elevated hs-CRP are not themselves predictive of CVD risk, suggesting that hs-CRP itself is not raising risk, but instead that acquired hs-CRP elevation is a marker for some process that is proatherogenic and/or prothrombotic [17, 18].

To date, hs-CRP is the most promising measure of vascular inflammation for use clinically. However, other inflammatory biomarkers are important for research purposes, including cytokines (e.g., interleukin [IL]-6 and tumor necrosis factor-alpha), chemokines (e.g., IL-8 and monocyte chemoattractant protein-1), oxidized LDL, cell adhesion molecules (e.g., intercellular adhesion molecule-1, vascular cell adhesion molecule-1, E-selectin, and P-selectin), and matrix metalloproteinases [87].

1.15 Measures of Subclinical CVD

Like testing for inflammatory markers, tests for subclinical atherosclerotic CVD have the greatest utility for patients at moderate risk and can help the clinician to decide whether more aggressive risk factor intervention is warranted. In various studies, a positive test for subclinical atherosclerosis has been shown to provide predictive information above and beyond that available from traditional global risk scoring [88]. The cost associated with many tests for subclinical disease such as electron beam computed tomography for coronary calcium scoring, carotid intima-media thickness, or screening graded exercise testing is high. Summarizing the various recommendations for their application in clinical practice is beyond the scope of this chapter, although the use of calcium scoring to assess coronary plaque burden and ankle-brachial index as an indicator of peripheral arterial disease will be discussed briefly.

1.15.1 Coronary Calcium

In 2010, an ACC Foundation/AHA Clinical Expert Consensus document included recommendation for use of coronary artery calcium scoring in CVD risk assessment [89]. In an analysis of pooled data from 6 studies of 27,622 asymptomatic patients, the rate of CHD events (CHD deaths or myocardial infarction) was 0.4% over the subsequent 3–5 years among patients with coronary artery calcium scores of 0 Agatston units, whereas a score between 100 and 400 indicated a relative risk of 4.3, a score of 400–1000 indicated a relative risk of 7.2, and a score >1000 indicated a relative risk of 10.8 [89]. The consensus document recommendations were that coronary artery calcium scores between 100 and 300 Agatston units are associated with a high rate of incident CHD events over the ensuing 3–5 years, so that persons with scores in this range are suitable for therapies. More recently, the 2013 ACC/AHA guidelines and the 2015 NLA recommendations for the patient-centered management of dyslipidemia have utilized a coronary artery calcium score ≥300 Agatston units (or 75th percentile for age, sex, and ethnicity [according to the Coronary Artery Calcium Score Reference Values web tool available at http://www.mesa-nhlbi.org/CACReference.aspx]) [28, 67]. This cut point was selected based on data from the Multi-Ethnic Study of Atherosclerosis which showed that a score of >300 Agatston units, compared to a score of 0, was predictive of risk for myocardial infarction or CHD death among asymptomatic individuals with coronary risk factors (i.e., at moderate risk). Later follow-up studies have provided further support for the use of coronary artery calcium testing in CVD risk assessment. Over 10.4 year median follow-up of 6814 men and women free of baseline CVD in the Multi-Ethnic Study of Atherosclerosis, coronary artery calcium was the strongest predictor of incident CHD [90]. The event rates for coronary artery calcium =0, >0, and >100 were 0.9/1000, 5.7/1000, and 11.0/1000 person-years, respectively. There is also a novel risk score, derived from the Multi-Ethnic Study of Atherosclerosis, to estimate 10-year CHD risk using coronary artery calcium and traditional risk factors [91]. Validation studies of this risk calculator show that coronary artery calcium adds significant information to traditional risk factors for risk prediction. Coronary artery calcium has been reported to be an independent predictor of mortality after accounting for other CVD risk factors [92] and a strong predictor of CVD event risk across racial and ethnic subgroups [93].

1.15.2 Ankle-Brachial Index

The use of the ankle-brachial index to assess suspected peripheral arterial disease is simple and inexpensive to perform. A value <0.90 is diagnostic of lower extremity arterial disease and fulfills a criterion for classification of ASCVD according to US guidelines and recommendations [27, 28, 67]. Intensive risk factor modification is warranted in such patients.

1.16 Hemostatic Variables

A number of variables associated with the balance between thrombosis and fibrinolysis are associated with CVD event risk including fibrinogen, plasminogen activator inhibitor-1, tissue plasminogen activator, and others. At present, these generally remain research tools and are not recommended for clinical risk assessment [94].

1.17 Chronic Kidney Disease

There are many links between the cardiovascular and renal systems that lead to a complex interrelationship between CVD and chronic kidney disease [95]. Patients with chronic kidney disease often have a clustering of several traditional CVD risk factors (e.g., hypertension, dyslipidemia, and diabetes) as well as nontraditional risk factors specific to chronic kidney disease (e.g., anemia, volume overload, abnormal mineral metabolism, proteinuria, malnutrition, oxidative stress, and inflammation). Patients with chronic kidney disease stage 3B (defined as estimated glomerular filtration rate [eGFR] 30–44 mL/min/1.73 m^2) or stage 4 (eGFR 15–29 mL/min/1.73 m^2) are considered to be at high risk for atherosclerotic CVD, and patients with stage 5 chronic kidney disease (or on hemodialysis) are at very high risk [28].

1.18 Nonmodifiable Risk Factors

A number of factors that cannot be modified are associated with increased CVD event risk including age, family history of CVD, and race/ethnicity. Although age and family history cannot be altered, they are important for risk stratification. In addition, a strong family history of premature CVD may prompt investigation for nontraditional risk markers such as elevated levels of lipoprotein (a). The prevalence of some risk factors varies by race/ethnicity, and the clinician should be aware of these differences. For example, hypertension and elevated lipoprotein (a) are particularly common among African Americans. Dyslipidemia is less prevalent, and type 2 diabetes mellitus, obesity, and metabolic syndrome are more common among Americans of Hispanic/Latino ethnicity, compared with non-Hispanic white Americans [75]. Individuals of South Asian descent also have increased prevalence of insulin resistance and metabolic syndrome, compared to non-Hispanic white Americans. Clinicians should also be aware that individuals of Asian descent have different waist circumference cut points of defining overweight/obesity for the definition of the metabolic syndrome, compared with those recommended for non-Hispanic whites (≥37 in. [≥94 cm] for men and ≥32 in. [≥80 cm] for women). However, despite these differences, the available evidence suggests that the relationships between risk factors and CVD event risk do not vary markedly by race/ethnicity.

1.19 Psychosocial Factors

A number of psychosocial factors have been associated with increased risk for CVD, including low social support, depression, personality traits (e.g., type A personality, locus of control), perceived stress, life change events, and others [96]. This is a promising area for research aimed at identification of high-risk individuals and has generated a number of testable hypotheses; however, methods for identification and management have generally not been incorporated into guidelines for prevention of CVD. In addition, low educational attainment and low socioeconomic status have also been shown to predict higher CVD risk. The available data suggest that the higher risk in these subgroups can be largely accounted for by greater prevalence and severity of established risk CVD factors [97, 98].

1.20 Sleep Apnea and Sleep Quantity and Quality

It has been known for some time that sleep apnea is associated with increased CVD risk. Central or obstructive sleep apnea is strongly associated with a number of conditions that are CVD risk factors such as obesity, diabetes, and hypertension [99]. The AHA/ACC Foundation released a Scientific Statement on sleep apnea and CVD [100].

Even in the absence of apnea, lower sleep quantity and quality have been found to correlate with a number of risk factors, including obesity, insulin resistance, hypertension, and inflammation [100]. An analysis from the Coronary Artery Risk Development in Young Adults study showed that incident coronary calcification over an average follow-up period of 5 years was associated with low sleep duration [101]. Each additional hour of sleep per night measured by actigraphy was associated with a 33% reduction in the incidence of new coronary calcium. While the clinical implications of these findings are unclear at present, they represent an important area for additional research since sleep quantity and quality are potentially modifiable risk factors.

1.21 Conclusions: Translating Risk Factor Identification into Prevention

Application of epidemiological methods of investigation has contributed tremendously to the understanding of atherosclerotic CVD etiology and led to the identification and testing of numerous preventive measures. Population studies continue to play an important role in advancing the field of preventive cardiology. Investigation of risk factors and interactions between risk factors remains a source of intense scientific inquiry.

New techniques for evaluating genetic determinants of risk as well as investigation of new potential targets for therapy such as vascular inflammation and sleep quality suggest that the coming decades will provide more effective means through which the scourge of atherosclerotic CVD can be brought under control.

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Arterial Hypertension

2

Daniel Duprez

2.1 Introduction

High blood pressure (BP) is a very important (CV) risk factor and is often considered as the silent killer, because arterial hypertension will lead to serious cardiovascular (CV) events such as ischemic heart disease, myocardial infarction, stroke, heart failure, and peripheral arterial disease [1, 2]. Moreover uncontrolled essential hypertension will also lead to renal insufficiency, which will accelerate the process of blood pressure elevation. There is a shift regarding diagnosis and treatment of arterial hypertension. With aging systolic hypertension is becoming a more important risk factor than diastolic hypertension and is more difficult to control (Fig. 2.1).

2.2 Definition of Arterial Hypertension

For decades arterial hypertension was defined if systolic blood pressure was equal or greater than 140 mmHg and/or diastolic blood pressure was equal or greater than 90 mmHg. In November 2017 the American Heart Association/American College of Cardiology in collaboration with nine other scientific organizations announced the new guidelines for diagnosis and treatment of hypertension [3, 4]. Despite increasing BP levels being a continuous cardiovascular (CV) risk factor, the new BP guidelines considered four different categories (Table 2.1). Normal blood pressure is now defined as a SBP below 120 mmHg and a DBP below 80 mmHg. Elevated hypertension is now defined as a SBP in a BP range between 120 mmHg and 129 mmHg and DBP below 80 mmHg. Another new classification in the 2017 BP ACC/AHA guidelines is that the SBP range of 130–139 mmHg or the DBP range of 80–89 mmHg is considered as stage I hypertension and SBP equal or greater than 140 mmHg or DBP equal or greater than 90 mmHg is considered as stage 2 hypertension. The other difference with the previous guidelines is that there are no different target goals anymore for patients with diabetes mellitus (DM) and chronic kidney disease (CKD). The evidence for the new reclassification of hypertension was based on the observational findings regarding SBP and/or DBP level and CVD risk, the beneficial effects of lifestyle modification on BP lowering, and the evidence obtained from the randomized clinical trials with antihypertensive drugs and the CVD risk reduction [1, 2, 5–8]. Another rationale to lower the threshold for SBP and DBP was that with aging a high normal level at younger age was accelerating the development of hypertension and consequently increasing the CVD risk at a later age [9, 10].

2.3 Epidemiology of Hypertension

Hypertension is considered the most common reversible or treatable CV risk factor [11].

In 2010, high BP was the leading cause of death and disability-adjusted life years worldwide [12, 13]. The population attributable risk due to elevated BP is large and present in all ethnic groups and regions of the world. It is not then surprising that hypertension has been identified as a condition, which accounts for a substantial portion of total global disease burden. From a clinical perspective, there is one generally accepted cardinal principle that describes the hypertensive state and which has served to define the importance of hypertension to world health. The presence of an elevated uncontrolled BP overtime will lead to progression in the severity or stage of hypertension, the development, or wors-

D. Duprez
Cardiovascular Division, Department of Medicine, University of Minnesota, Minneapolis, MN, USA
e-mail: dupre007@umn.edu

P. P. Toth, C. P. Cannon (eds.), *Comprehensive Cardiovascular Medicine in the Primary Care Setting*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-319-97622-8_2

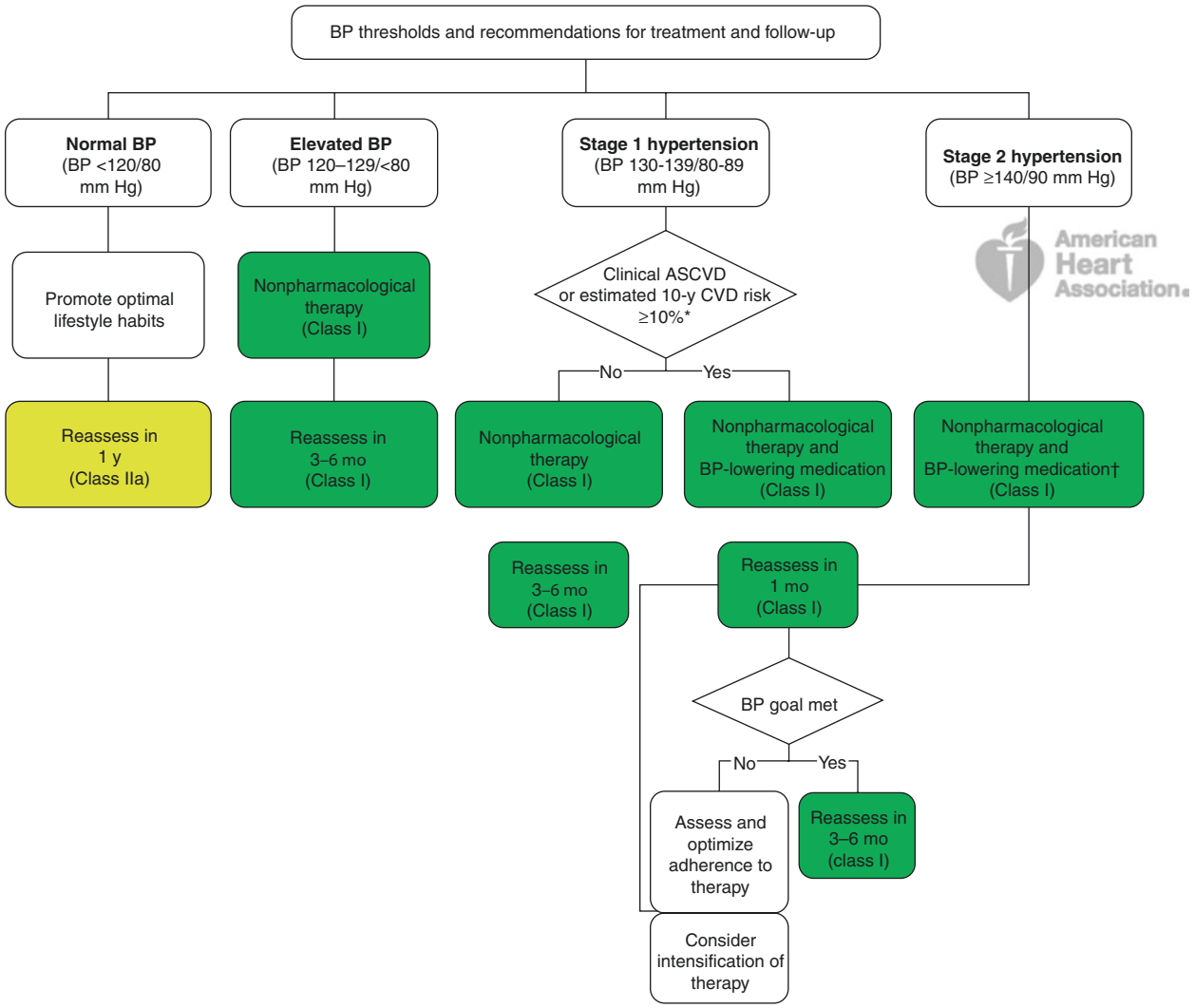

Fig. 2.1 Blood pressure (BP) thresholds and recommendations for treatment and follow-up. (Copy Fig. 4 from Whelton et al. [3])

Table 2.1 Categories of BP in adults[a]

BP category	SBP		DBP
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120–129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	130–139 mm Hg	or	80–89 mm Hg
Stage 2	≥140 mm Hg	or	≥90 mm Hg

Copy Table 6 from Whelton et al. [3]
BP indicates blood pressure (based on an average of ≥2 careful readings obtained on ≥2 occasions, as detailed in Sect. 2.4), *DBP* diastolic blood pressure, *SBP* systolic blood pressure
[a]Individuals with SBP and DBP in two categories should be designated to the higher BP category

ening of target organ damage and to increased CV morbidity and mortality. Given the relationship of hypertension to stroke, myocardial infarction, heart failure, and other vascular disease, the control of high BP will have a profound impact on individual well-being and national healthcare costs. Elevated BP demonstrates a consistent, strong, and graded relationship with multiple CV events including CV death, myocardial infarction, stroke, heart failure, and renal dysfunction. The risk of CV mortality has been observed to double with each 20/10 mmHg increase in BP from 115/75 mmHg in adults aged from 40 to 69 years of age. Unfortunately, a gap continues to exist between hypertension and awareness and control [14].

2.4 Mechanisms of Hypertension

The pathogenesis of essential hypertension is a heterogeneous process, and several physiological systems result in a change of the cardiovascular hemodynamics. Arterial blood

pressure is the product of cardiac output (stroke volume × heart rate) × total peripheral vascular resistance.

2.4.1 Hemodynamics

The blood pressure required to supply the different organs and tissues with blood through the circulatory bed is provided by the pumping action of the heart (cardiac output) and arterial tone (total peripheral vascular resistance). Each of these primary components is determined by the interaction of a complex series of factors. Arterial hypertension has been attributed to abnormalities in nearly every one of these factors [15, 16]. During the last decade, there has been more attention to pulse pressure, which is the difference between SBP and DBP and is a simple parameter to have some information about arterial stiffness and also an independent predictor for cardiovascular disease events [17]. There is growing information that the arterial blood pressure waveform provides more information for CV risk than the SBP and DBP value, because two BP values are only the two extreme points of the whole BP waveform [18–20].

An increase in arterial tone has traditionally been viewed as the hallmark for an elevated BP. Although some have suggested that an increase in cardiac output with a normal vascular resistance is the initial hemodynamic abnormality in patients with hypertension, the chronic hypertensive state usually is associated with an increase in total systemic vascular resistance [21]. This increase in resistance is generally attributed to an increase in vascular tone. Multiple mechanisms possibly contribute to this increase in systemic vascular resistance: activation of the sympathetic nervous system [22], the renin–angiotensin–aldosterone system (RAAS) [23], endothelial dysfunction [24], and inflammation [25].

2.4.2 Renal

The relationship between the development or pathogenesis of hypertension and the kidney is complex [26]. The kidney through a variety of distinct renal mechanisms can cause or contribute to the development or to the progression of hypertension [27]. On the other hand, hypertension per se can contribute to progressive renal structural and vascular damage, which in turn may contribute to a worsening or perpetuation of the hypertensive state. Renal functional and structural changes can promote sodium retention. Excessive sodium reabsorption can lead to plasma volume expansion, an increase in cardiac output, and ultimately an increase in total peripheral resistance and BP [28]. These mechanisms most certainly contribute to the BP elevation, which accompanies CKD and some cases of primary hypertension. Several other renal factors have received attention as potential contributors to this vicious cycle that is characterized by development of hypertension and progressive renal damage. Inappropriate or excessive activation of the RAAS in relationship to the sodium/volume balance may contribute to BP elevation, especially in the setting of renal parenchymal disease.

2.4.3 Neurohumoral Factors

Many factors are now implicated in the development of hypertensive vascular disease, and the RAAS appears to be one of the most significant. Angiotensin II, the principal effector peptide of the RAAS, has far-reaching effects on vascular structure, growth, and fibrosis and is a key regulator of vascular remodeling and inflammation. The RAAS is an important contributor to the regulation of BP, water and salt balance, and tissue growth. It functions both as a circulating endocrine system and as a tissue paracrine/autocrine system, most notably in the heart, brain, kidney, and vasculature. Aldosterone is the major mineralocorticoid hormone secreted by the adrenal cortex and plays an important role in resistant hypertension [29]. Identification of mineralocorticoid receptors in the heart, vasculature, and brain has raised speculation that aldosterone may directly mediate its detrimental effects in these target organs, independent of angiotensin II and the regulatory role of aldosterone in kidney function and BP [30].

2.4.4 Baroreflexes

The arterial baroreflex is known to represent a mechanism of fundamental importance for short-term BP homeostasis in daily life. Reduced baroreflex sensitivity appears to characterize not only patients with established hypertension but also normotensive offspring of hypertensive parents [31].

2.4.5 Aging

Available evidence suggests that the incidence of systolic hypertension is increasing in individuals over 50 years of age. There are multiple mechanisms involved [32]. These include an altered vascular resistance, the classical hallmark of high BP, as well as changes in arterial stiffness and wave reflection, which occur in the conduit arteries, mainly the aorta and its principal branches.

2.5 Etiology of Hypertension

The specific set of events that lead to progressive elevation of BP and the development of hypertension remains unknown. Depending on the clinical setting, 90% of hypertensives had no known cause for their hypertension. For that reason, most hypertension states were originally classified as essential hypertension. Primary hypertension is another terminology, which is used to compare and contrast with the secondary hypertension. In case of secondary hypertension, a cause is found, and the therapeutic strategy will be guided by the cause.

2.5.1 Primary or Essential Hypertension

Although the pathogenesis of primary hypertension is uncertain, as previously noted, specific mechanisms appear to be involved in the development of primary hypertension: altered regulation of sympathetic nervous system, cell membrane defects, renin secretion, salt sensitivity, as well as other vascular and hormonal factors. In addition to these multiple physiologic abnormalities, diet, environment, other lifestyle factors, and most certainly genetics frequently play a role in the development of hypertension.

Patients with primary hypertension are generally asymptomatic. Although some patients report symptoms related to hypertension such as headache, dizziness, fatigue, palpitations, and chest discomfort, these symptoms and their level of intensity generally do not correlate well with BP level. Thus, primary hypertension has no consistent symptoms or signs, except for the elevated BP itself. A specific type of headache has, however, been reported to occur with elevated BP. Hypertensive headache is a clinical entity, which has been described as a diffuse morning headache, and is generally associated with more severe stages of hypertension; in some circumstances these headaches may actually be associated with sleep apnea complicating arterial hypertension, rather than the BP itself.

2.5.2 Genetics

Hypertension is a complex polygenic disorder in which many genes or gene combinations influence BP. There is tremendous research going on in the field of genetics, epigenetics, transcriptomics, and proteomics which try to link the genotypes with the underlying mechanisms [33]. There are some rare monogenic forms of hypertension such as glucocorticoid-remediable aldosteronism, Liddle's syndrome, Gordon's syndrome, and others in which single-gene mutations fully explain the pathophysiology of hypertension [34].

2.5.3 Lifestyle Risk Factors

Lifestyle plays a major role in cardiovascular health and has an important effect on blood pressure control. One of the most well-known is salt intake.

2.5.3.1 Salt

The association between salt intake and BP increase has been well established. This finding has been derived from large epidemiological studies [35]. Sodium intake is associated with age-related increase for BP. Moreover excessive salt intake is associated with a higher risk for CVD and stroke [36, 37]. African–Americans, older hypertensive subjects, patients with chronic kidney disease (CKD), diabetes patients, and patients with cardiometabolic syndrome have a higher salt sensitivity. Race and genetics play an important role in salt-sensitive hypertension. Salt sensitivity is especially common in blacks, older adults, and those with a higher level of BP or comorbidities such as CKD, diabetes mellitus, or the metabolic syndrome.

2.5.3.2 Potassium

Prospective studies have demonstrated that potassium intake is inversely related with BP level [38]. The investigators postulated that an increase potassium intake to the recommended level of 90 mmol/day may have the potential to reduce the incidence of hypertension. A meta-analysis of several prospective studies regarding potassium intake showed that higher dietary potassium intake is associated with lower rates of stroke and might also reduce the risk of coronary heart disease and total CVD [39]. These results support recommendations for higher consumption of potassium-rich foods to prevent vascular diseases.

2.5.3.3 Smoking

Smoking will lead to BP rise acutely mainly due to increase of heart rate due to sympathetic activation. A Mendelian randomization meta-analysis was performed by the CARTA consortium including 141,317 participants (62,666 never, 40,669 former, 37,982 current smokers) from 23 population-based studies. They concluded that was a causal association of smoking heaviness with higher level of resting heart rate, but not with blood pressure [40]. These findings suggest that part of the cardiovascular risk of smoking may operate through increasing resting heart rate but not with blood pressure.

2.5.3.4 Alcohol

Several systematic reviews and meta-analyses have shown that alcohol consumption and hypertension are linked in a dose-dependent fashion [41–43]. Alcohol overconsumption is responsible for 36% of the cases of reversible hypertension.

The potential threshold, the dose–response relationship, is not linear over the full range of alcohol consumption, but for both sexes there is a monotonic dose–response relationship for higher levels of consumption, and thus hazardous/harmful drinking and AUDs are closely associated with elevated BP and/or hypertension. The above-described association between hazardous/harmful alcohol consumption and hypertension means that a logical intervention to reduce BP is to reduce alcohol consumption.

2.5.3.5 Obesity

There is an indirect relationship between body mass index and BP with no evidence of a threshold [44, 45]. The relationship with BP is even stronger for waist-to-hip ratio. The relationship between obesity at a young age and change in obesity status over time is strongly related to future risk of hypertension. Becoming normal weight reduced the risk of developing hypertension to a level similar to those who had never been obese [46].

2.5.3.6 Physical Fitness

Epidemiological studies have an inverse relationship between physical activity and physical fitness and level of BP and hypertension [47].

2.5.4 Secondary Hypertension

Secondary causes of hypertension are uncommon and account for 10% of all cases of high BP in an unselected hypertensive population. Although infrequent, secondary forms of hypertension account for many cases of drug-resistant hypertension. Because of this finding, higher prevalence rates of secondary hypertension have been noted in specialized hypertension clinics. Secondary hypertension is usually associated with a specific organ and/or vascular abnormalities, a metabolic abnormality, or endocrine disorder. The diagnosis of these specific hypertensive conditions is important because of the potential for a permanent cure or improvement in control of hypertension. If left undiagnosed, secondary hypertension may lead to progressive target organ damage, as well as CV and renal complications.

In secondary hypertension, the elevated BP may be the major presenting manifestation of an underlying process, or elevated BP may simply be one component of a complex group of signs and symptoms in a patient with a systemic disease. Secondary causes of hypertension are often nonspecific in their presentation, and laboratory test and/or imaging studies are required for screening and confirmation of the diagnosis. Nevertheless, there are some well-recognized clinical presentations and clinical clues which deserve mention and which should raise a clinician's suspicion of a secondary cause of hypertension. The documented early (less than age 30 years) or late (more than age 50 years) onset of hypertension is thought to raise the possibility of secondary form of hypertension. In pediatric populations, congenital renal or endocrine causes of secondary hypertension are more likely to result in elevated BP. Fibromuscular dysplasia of the renal artery(s) characteristically occurs in young white women, generally without a strong family history of hypertension. The most common cause of secondary hypertension in older patients, with associated vascular disease, is atherosclerotic renal artery stenosis. In obese patients, obstructive sleep apnea and Cushing's disease may be considered as potential causes of secondary hypertension. A thorough search for secondary causes of hypertension is not considered cost-effective in most patients with hypertension. Expended work-ups should be considered with compelling clinical or laboratory evidence for a specific secondary cause or when a patient presents with drug-resistant or refractory hypertension or hypertensive crisis and should be referred to a hypertension-specialized clinic. Causes of secondary hypertension are listed in Table 2.2.

Table 2.2 Secondary causes of hypertension

Chronic kidney disease (renal parenchymal disease)
Atherosclerotic renovascular hypertension
Fibromuscular dysplasia
Renal artery aneurysm
Page kidney
Systemic vasculitis
Renin-secreting tumor
Primary hyperaldosteronism
Aldosterone-producing adenoma
Idiopathic hyperaldosteronism
Glucocorticoid-remediable hyperaldosteronism
Pheochromocytoma
Cushing's disease/syndrome
Coarctation of the aorta
Hypothyroidism
Sleep apnea

2.5.5 Chronic Kidney Disease (CKD): Renal Parenchymal Hypertension

CKD or renal parenchymal disease is the most common form of secondary hypertension. Hypertension occurs in more than 80% of patients with chronic renal failure and is a major factor causing their increased CV morbidity and mortality seen in CKD [48]. Any type of CKD, including acute or chronic glomerulonephriti*s*, may be associated with hypertension. Hypertension is frequently the presenting feature of adult polycystic kidney disease. Clinically, affected patients may experience abdominal pain and hematuria, and the renal or associated hepatic cysts may be palpable on physical examination.

CKD should be suspected when the estimated glomerular filtration rate (eGFR) is less than or equal to 60 mL/min/1.73m^2 or when 1+ or greater proteinuria and/or specific urinary sediment abnormalities are noted on urine analysis. The diagnosis can be confirmed either by the direct measurement of glomerular filtration rate (GFR) or collection for a creatinine clearance showing a value of less than 60 mL/min. Proteinuria should be confirmed by a 24-h urine, which should demonstrate a total protein excretion of more than 150 mg or by a spot urine specimen showing microalbuminuria defined as a urine albumin-to-urine creatinine ratio between 30 mg/g and 300 mg/g. In patients with mild or moderate renal insufficiency, stringent BP control is imperative to reduce the progression to end-stage renal disease and reduce the excessive CV risk associated with CKD.

2.5.6 Renovascular Hypertension

Renovascular hypertension may be the most common form of potentially curable hypertension [49]. Current estimates indicate that this is seen in 1–2% of a hypertensive population in general medical practice. There are two major causes, atheromatous disease and fibromuscular dysplasia, of the renal artery, and each is associated with a distinct clinical presentation. Renovascular hypertension frequently is associated with resistance to a multiple drug antihypertensive regimen. It is not surprising, therefore, that up to 30% of patients referred to some specialized hypertension clinics are found to have renovascular hypertension. Several clinical clues occurring alone or in combination may point to the diagnosis of renovascular hypertension:

- New onset or drug-resistant hypertension, before age 30 or after age 50
- Accelerated or malignant hypertension
- Lateralizing epigastric or upper quadrant systolic–diastolic abdominal bruit noted in a hypertensive patient
- Progressive worsening of renal function in response to ACE-I
- Diffuse atherosclerotic vascular disease in the setting of severe hypertension
- Unexplained pulmonary edema (flash pulmonary edema) generally associated with progressive renal insufficiency and occurring during antihypertensive therapy of a renin-dependent hypertension

Other mechanisms can also contribute to the development of progressive hypertension in the setting of renovascular hypertension. Long-standing or accelerated hypertension can promote the development of structural changes such as arteriolar nephrosclerosis in a contralateral kidney in the case of unilateral renal artery stenosis. Associated renal parenchymal damage may also contribute further to BP elevation and renal impairment. The most common cause of renovascular hypertension is atherosclerotic renal artery stenosis, which generally affects the proximal renal arteries. Atherosclerotic renal artery stenosis is progressive and may lead to worsening hypertension, renal artery occlusion, ischemic nephropathy, and renal failure. The majority of these cases with atherosclerotic renal artery disease occur in the setting of other coronary, cerebrovascular, or peripheral vascular disease. Fibromuscular dysplasia of the renal arteries is the most frequent cause of renovascular hypertension in young women (those under 50 years old). This disease occurs rarely in males but may on occasion be seen in males with strong family histories of fibromuscular dysplasia. The clinical suspicion and even the confirmed diagnosis of renovascular hypertension will frequently present clinicians with difficult diagnostic and therapeutic dilemmas. Individualized treatment decisions are currently required for the effective management and treatment of renovascular hypertension. The diagnostic evaluation and therapeutic strategy for patients with suspected renovascular hypertension are predicated on several factors including the severity of hypertension, the presence of associated renal failure or insufficiency, the type of renal artery lesion, the location of the stenotic lesion, the presence of concomitant CVD, a patient's general health status, and the ability of a patient to tolerate multiple antihypertensive medications.

Patients with clinical presentations suggestive of renovascular hypertension can be screened with noninvasive studies (ultrasound), and, if results are positive, confirmation of the diagnosis can be made with renal arteriography. If the index of suspicion for renovascular hypertension is high, renal arteriography can be performed in the absence of noninvasive tests. Noninvasive testing is frequently employed to diagnose or confirm the anatomical site of a renal artery lesion or to examine the functional significance of a renal artery stenosis. Intensive medical therapy for renovascular hypertension is generally required for BP control and involves the use of ACE-Is, in conjunction with multiple other medications. Treatment frequently involves the use of a calcium channel blocker (CCB), judicious use of diuretics, and occasionally the use of a sympathetic inhibitor. Renal

function and serum potassium should be monitored regularly, as they can deteriorate with ACE-I or BP reduction alone. ACE-I should be withdrawn with moderate deterioration (>30%) in renal function and/or if a patient becomes hyperkalemic. Angiotensin receptor blockers (ARBs) should be substituted in those patients who develop an ACE-I cough or those who develop mild hyperkalemia with ACE-I.

Medical management of renovascular hypertension includes intensive treatment of associated CV risk factors, with concomitant aggressive lipid lowering, smoking cessation, and the use of low-dose aspirin. Percutaneous transluminal renal artery angioplasty (PTRA) and stenting or surgical revascularization of the renal arteries should be considered in the setting of drug-resistant and worsening hypertension, in patients who develop progressive renal failure in response to medical therapy, and finally in those with high-grade bilateral renal artery stenosis. Preservation of renal function is currently the leading cited indication for intervention in patients with renal artery stenosis and renovascular hypertension. BP can frequently now be controlled with potent multidrug antihypertensive regimens. Revascularization, however, may prevent renal artery occlusion, progressive ischemic nephropathy, and renal atrophy. Percutaneous and surgical procedures are not without risk. Patient selection and timing may be crucial to limit complications and maximize outcomes.

Several randomized controlled trials (RCT) studied the role of endovascular management of atherosclerotic renal artery stenosis and arterial hypertension, which failed to demonstrate the benefit of stenting. In the largest RCT to date, the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) study did not find benefit of revascularization compared to medical therapy alone [50]. The current ACC/AHA recommendations for RAS management are supported by many level II evidence cohort studies which consistently found the benefit of revascularization in groups with the highest likelihood of clinically significant RAS [51].

2.5.7 Primary Hyperaldosteronism

Primary hyperaldosteronism or Conn's syndrome is characterized by hypokalemia, hypertension, very low plasma or suppressed renin activity (PRA), and excessive aldosterone secretion [52]. Aldosterone binds with the mineralocorticoid receptor in the distal nephron and contributes to salt and water homeostasis and maintenance of plasma volume through this interaction. Excessive production of the hormone promotes an exaggerated renal Na + –K+ exchange, which usually results in hypokalemia. The diagnosis of primary hyperaldosteronism should be considered in any patient with severe refractory hypertension. Traditionally, it was thought that 1–2% of patients with hypertension had primary hyperaldosteronism. The syndrome has been reported to be more common in females and may present with mild, moderate, or resistant hypertension. Patients are generally asymptomatic, though symptoms such as muscle cramps, weakness, and paresthesias attributable to hypokalemia may predominate. Polyuria and polydipsia have also been reported. Many patients with primary hyperaldosteronism will present with severe, persistent, or refractory diuretic-induced hypokalemia. The best clinical clues to the diagnosis in patients with hypertension is either unprovoked hypokalemia with a serum K+ less than 3.5 mg/dl in the absence of diuretic therapy or the development of more profound hypokalemia during diuretic therapy with a serum K+ less than 3.0 mg/dL. Laboratory testing is frequently required to differentiate between secondary hyperaldosteronism associated with diuretic use, renovascular hypertension, and renin-secreting tumors. The most utilized confirmatory test is the urine aldosterone excretion rate, which involves the 24-h collection of urine, under conditions of a high-salt load. Adrenal computed tomography (CT) scans with 3 mm cuts should be used to localize adenomas or neoplasm. Control of BP and hypokalemia can be obtained with antihypertensive regimens based on spironolactone and eplerenone or, on occasion, with amiloride. Multiple medications will be frequently required. Unilateral adrenalectomy is highly effective for reversing the metabolic consequences of hyperaldosteronism in patients with aldosterone-producing adenoma.

Brown et al. [53] investigated whether a spectrum of subclinical renin-independent aldosteronism increases the risk for hypertension in normotensive persons. They found that suppression of renin and higher aldosterone concentrations in the context of this renin suppression are associated with an increased risk for hypertension and possibly also with increased mineralocorticoid receptor activity. These findings suggest a clinically relevant spectrum of subclinical primary aldosteronism (renin-independent aldosteronism) in normotension.

2.5.8 Pheochromocytoma

Pheochromocytomas are rare catecholamine-producing tumors that originate from chromaffin cells of the adrenergic system. Majority of these tumors are benign and are located in the adrenal gland, but others can develop as functioning paraganglioma in a variety of extra-adrenal sites [54]. Pheochromocytomas generally secrete both norepinephrine and epinephrine, though norepinephrine is usually the predominant amine.

Pheochromocytoma has a reported incidence of 0.05% in the general population with peak incidence occurring in the 30s and 40s. The rule of 10s has been used to characterize the clinical presentation of the tumor: approximately 10% of pheochromocytomas are extra-adrenal, 10% are malignant, 10% are familial, 10% occur in children, 10% are bilateral and affect both adrenals, and 10% are multiple. A family history or an early onset of pheochromocytoma may suggest an

underlying genetic disorder such as multiple endocrine neoplasia type II, Von Hippel–Lindau disease, or neurofibromatosis type I. Classic clinical presentations are characterized by hypertension, palpitations, headache, and hyperhidrosis. The hypertension can be severe and sustained (55%) or paroxysmal (45%). Pounding headaches, palpitations, and diaphoresis are prominent features of the syndrome and may occur together in a paroxysmal attack. Postural hypotension may occasionally be present as a result of low or constricted plasma volume. Hypertension associated with panic attack as well as other causes of neurogenic hypertension, including the BP elevations sometimes seen with sympathomimetic agents, and obstructive sleep apnea can be confused with pheochromocytoma.

Plasma-free metanephrines, if available, are a preferred screening test for excluding or confirming the diagnosis of pheochromocytoma. Twenty-four-hour urine collections for metanephrine (100% sensitive) are also useful for screening for the tumor. The accuracy of the 24-h urine metanephrine may be improved by indexing urinary metanephrine levels by urine creatinine levels. A positive screening test should be reconfirmed if there is a suspicion of drug interference or a false-positive test [55]. Patients with a suspicion of pheocromocytoma should be referred to a specialized center and to emergency in case of a hypertensive crisis.

Table 2.3 Causes of resistant hypertension

Poor adherence to medical regimen
Poor adherence to lifestyle changes
Obesity and weight gain
Heavy alcohol intake
Improper BP measurement
Improper cuff size
Stress or office hypertension
Pseudoresistance in the elderly
Volume overload
Excess sodium intake
Inadequate diuretic therapy
Pseudotolerance
Alpha methyldopa
Direct acting vasodilators
Progressive CKD
Drug-induced or other causes
Inadequate doses of antihypertensive medication
Inappropriate combinations of antihypertensive medications
Drug interactions
Nonsteroidal anti-inflammatory drugs
Cocaine, amphetamines, other illicit drugs
Sympathomimetics (decongestants, anorectics)
Oral contraceptives and adrenal steroids
Cyclosporine and tacrolimus
Erythropoietin
Licorice ingestion
Unsuspected secondary hypertension
Obstructive sleep apnea

2.6 Complicated Management Problems in Hypertension

2.6.1 Resistant Hypertension

Resistant hypertension is becoming an increasingly common problem with the national guidelines focusing on lower goal BPs [56]. The diagnosis of resistant hypertension is made when a patient takes three antihypertensive medications with complementary mechanisms of action (a diuretic should be one of the antihypertensive drugs) but does not achieve control or when BP control is achieved but requires at least four or more medications [57]. With the new definition of hypertension (target BP <130/80 mmHg), one may expect a higher incidence of resistant hypertension.

True drug-resistant hypertension is relatively rare, but treatment failure is relatively common, frequently being secondary to nonadherence, socioeconomic factors, and lifestyle issues. Before embarking on an expanded work-up to determine the cause of drug-resistant hypertension, clinicians should be careful to rule out "pseudoresistance" secondary to BP measurement artifacts or errors and "white-coat" hypertension and antihypertensive medication compliance. Out-of-office measurements, including home BPs, or 24-h ambulatory BP monitoring (ABPM) may be required to establish a patient's actual BP. The absence of target organ damage in the setting of prolonged resistant or refractory hypertension should raise a clinician's suspicion regarding pseudoresistance.

Refractory hypertension is an extreme phenotype of antihypertensive treatment failure, defined as uncontrolled blood pressure (systolic/diastolic, ≥140/90 mm Hg) on ≥5 antihypertensive drug classes [58]. Participants with resistant hypertension are older and commonly present with obesity, unrestricted or excessive dietary salt intake, and the clinical syndrome of sleep apnea. Causes of resistant hypertension are summarized in Table 2.3.

Current approaches to correction of drug resistance focus on evaluation and correction of potential contributing causes, the development of a more effective drug regimen, and identification of any unrecognized secondary causes of hypertension.

Volume expansion plays a key role in drug resistance, and it cannot be adequately assessed with a clinical exam. Treatment should include a strong emphasis on lifestyle changes including weight loss, exercise, dietary, and salt restriction, all of which should be monitored. New multidrug antihypertensive regimens should incorporate the more potent vasodilator antihypertensive agents such a CCBs or direct acting vasodilators with adequate diuretic therapy, especially if intense vasoconstriction is suspected as the physiologic cause or culprit. Recent data indicate that

aldosterone antagonists may be effective when added to existing antihypertensive regimens even in the absence of primary aldosteronism [59]. Consultation with a hypertension specialist should be considered if target BP cannot be achieved.

2.6.2 Hypertensive Emergencies and Urgencies

Hypertensive emergencies are defined as severe elevations in BP (>180/120 mm Hg) associated with evidence of new or worsening target organ damage. It is very important that in case of hypertensive emergencies, one starts to lower immediately the SBP and DBP. Hypertensive urgencies are situations associated with severe BP elevation in otherwise stable patients without acute or impending change in target organ damage or dysfunction. Following the 2017 ACC/AHA new hypertension guidelines, in adults with a compelling condition (i.e., aortic dissection, severe preeclampsia or eclampsia, or pheochromocytoma crisis), SBP should be reduced to less than 140 mm Hg during the first hour and to less than 120 mm Hg in aortic dissection ([3]; see original Fig. 11).

For adults without a compelling condition, SBP should be reduced by no more than 25% within the first hour and then, if stable, to 160/100 mm Hg within the next 2–6 h and then cautiously to normal during the following 24–48 h [3].

The presence of severe hypertension alone is not sufficient to make the diagnosis of hypertensive emergency. The diagnosis of hypertensive emergencies ultimately depends on the clinical presentation rather than on the absolute level of the BP. Thus, these cases usually present with severe hypertension complicated by some cardiac, renal, neurologic, hemorrhagic, or obstetric manifestation. Hypertensive encephalopathy, acute aortic dissection, and pheochromocytoma crisis are well-recognized hypertensive emergencies. Some cases of accelerated or malignant hypertension, acute left ventricular failure, cerebral infarction, head injury, scleroderma, and acute myocardial infarction interaction can also present as hypertensive emergencies. Other causes for an acute symptomatic rise in BP include medications, noncompliance, and poorly controlled chronic hypertension.

The clinical history and physical examination should be highly focused in an attempt to determine the cause of a patient's severe hypertension and should attempt to exclude other clinical presentations which may mimic hypertensive emergencies or urgencies such as panic attack or postictal hypertension.

There is no randomized controlled trial (RCT) evidence that antihypertensive drugs reduce morbidity or mortality in patients with hypertensive emergencies. There is also no high-quality RCT evidence to inform clinicians as to which first-line antihypertensive drug class provides more benefit than harm in hypertensive emergencies. This lack of evidence is related to the small size of trials, the lack of long-term follow-up, and failure to report outcomes. Several antihypertensive agents in various pharmacological classes are available for the treatment of hypertensive emergencies.

2.7 Blood Pressure Measurement

2.7.1 Office Blood Pressure Measurement

The most common reason for an outpatient physician visit is for the diagnosis and treatment of hypertension. Standardized BP measurement is the basis for the diagnosis, management, treatment, epidemiology, and research of hypertension, and the decisions affecting these aspects of hypertension will be influenced, for better or worse, by the accuracy of measurement [60]. Accurate BP measurement is well described in the new hypertension guidelines [3]. All of these guidelines are a synthesis of the methodology used in all the important epidemiologic and treatment trials of hypertension. Factors important in this methodology include (i) resting for 5 min, (ii) sitting with back supported and feet on the floor, (iii) arm supported at heart level, (iv) appropriate size cuff applied, (v) use of the Korotkoff Phase I sound for SBP and Phase V for DBP, and (vi) using the mean of two or more BP measurements as the patient's BP. Failure to conform to all of these recommendations can result in significant errors in ausculted BP and misdiagnosis and mistreatment of the hypertensive patient. Certain groups of people merit special consideration for BP measurement.

These include children; the elderly, who often have isolated systolic hypertension or autonomic failure with postural hypotension; obese people in whom the inflatable bladder may be too small for the arm size, leading to "cuff hypertension"; patients with arrhythmias in whom BP measurement may be difficult and the mean of a number of measurements may have to be estimated; pregnant women in whom the disappearance of sounds (Phase V) is the most accurate measurement of diastolic pressure, except when sounds persist to zero, when the fourth phase of muffling of sounds should be used; and any individual during exercise.

Bilateral measurements should be made on first consultation, and, if persistent differences greater than 20 mmHg for systolic or 10 mmHg for diastolic pressure are present on consecutive readings, the patient should be referred to a CV center for further evaluation with simultaneous bilateral measurement and the exclusion of arterial disease.

The second option for accurate BP measurement is the use of validated automated BP devices. The automated BP-measuring devices use a proprietary oscillometric method. Each of these devices needs to be independently validated and then calibrated to each patient. Rarely, they do

not sense BP accurately but, more commonly, fail if the cardiac rhythm is very irregular (e.g., atrial fibrillation). It is interesting to note that even with auscultatory BP measurement in elderly patients with atrial fibrillation, considerable observer variability is seen. It is critically important that if an automated BP-measuring device is used, it must have passed a recognized validation protocol.

2.7.2 Home BP Measurement

Home BP monitoring has become popular in clinical practice, and several automated devices for home BP measurement are now recommendable. Out-of-office BP measurements are recommended to confirm the diagnosis of hypertension and for titration of BP-lowering medication, in conjunction with telehealth counseling or clinical interventions. Home BP is generally lower than clinic BP and similar to daytime ambulatory BP. Home BP measurement eliminates the white-coat effect and provides a high number of readings, and it is considered more accurate and reproducible than clinic BP. It can improve the sensitivity and statistical power of clinical drug trials and may have a higher prognostic value than clinic BP. Home monitoring may improve compliance and BP control and reduce costs of hypertension management. Diagnostic thresholds and treatment target values for home BP remain to be established by longitudinal studies. Out-of-office BP measurements are recommended to confirm the diagnosis of hypertension and for titration of BP-lowering medication, in conjunction with telehealth counseling or clinical interventions [61]. Until then, home BP monitoring is to be considered a supplement. Home BP provides an opportunity for additional monitoring of BP levels and its variability.

Some advantages of self-measured BP are raising patient awareness of how their BP responds to medication or dietary changes, decreasing physician inertia to adjust medication when the office-measured BP is high, and decreasing office visits for BP management. Adequate self-measurement of BP is more associated with target organ damage than office-based BP, and its prognostic value is comparable with ambulatory BP recording based on observational studies.

2.7.3 Ambulatory BP

Ambulatory blood pressure (ABPM) provides automated measurements of brachial artery blood pressure over a 24-h period, while patients are engaging in their usual activities. This method has been used for more than 30 years in clinical research on hypertension [62–64]. These studies demonstrated that BP has a highly reproducible circadian profile, with higher values when the patient is awake and mentally and physically active, much lower values during rest and sleep, and an early morning surge lasting 3–5 h during the transition from sleep to wakefulness. In a patient with hypertension, 24-h BP monitoring has substantial appeal. It yields multiple BP readings during all of the patient's activities, including sleep, and gives a far better representation of the "BP burden" than what might be obtained in a few minutes in the doctor's office. Several prospective clinical studies, as well as population-based studies, have indicated that the incidence of CV events is predicted by BP as measured conventionally or with ambulatory methods, even after adjustment for a number of established risk factors [63, 64].

In clinical practice, measurements are usually made at 20–30-min intervals in order not to interfere with activity during the day and with sleep at night. Measurements can be made more frequently when indicated. Whatever definition of daytime and nighttime is used, at least two-thirds of SBPs and DBPs during the daytime and nighttime periods should be acceptable. If this minimum requirement is not met, the ABPM should be repeated. A diary card may be used to record symptoms and events that may influence ABPM measurements, in addition to the time of drug ingestion, meals, and going to and arising from bed. If there are sufficient measurements, editing is not necessary for calculating average 24-h, daytime, and nighttime values, and only grossly incorrect readings should be deleted from the recording. Table 2.4 summarizes the corresponding values of SBP/DBP for clinic, home BP measurement, and daytime, nighttime, and 24-hr ABPM.

ABPM has a number of advantages: it provides a profile of BP away from the medical environment, thereby allowing identification of individuals with a white-coat response; it shows BP behavior over a 24-h period during usual daily activities, rather than when the individual is sitting in the artificial circumstances of a clinic or office. It can indicate the duration of decreased BP over a 24-h period. ABPM can identify patients with blunted or absent BP reduction at night—the nondippers—who are at greater risk for organ damage and CV morbidity. It can demonstrate a number of patterns of BP behavior that may be relevant to clinical management, such as white-coat hypertension and masked hypertension.

Table 2.4 Corresponding values of SBP/DBP for clinic, HBPM, daytime, nighttime, and 24-h ABPM measurements

Clinic	HBPM	Daytime ABPM	Nighttime ABPM	24-Hour ABPM
120/80	120/80	120/80	100/65	115/75
130/80	130/80	130/80	110/65	125/75
140/90	135/85	135/85	120/70	130/80
160/100	145/90	145/90	140/85	145/90

Adapted Table 11 from Whelton et al. [3]
ABPM indicates ambulatory blood pressure monitoring, *BP* blood pressure, *DBP* diastolic blood pressure, *HBPM* home blood pressure monitoring, and *SBP* systolic blood pressure

The recent 2017 ACC/AHA guidelines for hypertension recommend the following measurements for masked or white hypertension [3]:

- In adults with an untreated SBP greater than 130 mm Hg but less than 160 mm Hg or DBP greater than 80 mm Hg but less than 100 mm Hg, it is reasonable to screen for the presence of white-coat hypertension by using either daytime ABPM or home BP measurement before diagnosis of hypertension.
- In adults with white-coat hypertension, periodic monitoring with either ABPM or home BP measurement is reasonable to detect transition to sustained hypertension.
- In adults being treated for hypertension with office BP readings not at goal and home BP measurement readings suggestive of a significant white-coat effect, confirmation by ABPM can be useful.
- In adults with untreated office BPs that are consistently between 120 mm Hg and 129 mm Hg for SBP or between 75 mm Hg and 79 mm Hg for DBP, screening for masked hypertension with HBPM (or ABPM) is reasonable.
- In adults on multiple-drug therapies for hypertension and office BPs within 10 mm Hg above goal, it may be reasonable to screen for white-coat effect with HBPM or ABPM.
- It may be reasonable to screen for masked uncontrolled hypertension with HBPM in adults being treated for hypertension and office readings at goal, in the presence of target organ damage or increased overall CVD risk.
- In adults being treated for hypertension with elevated HBPM readings suggestive of masked uncontrolled hypertension, confirmation of the diagnosis by ABPM might be reasonable before intensification of antihypertensive drug treatment.

2.8 Evaluation of Hypertension

Following the confirmation of hypertension, a targeted history and physical examination and limited laboratory evaluation should be performed. The standard hypertensive work-up includes an assessment of CV risk and the identification of hypertensive target organ damage and is designed to rule out secondary hypertension. This examination should include information regarding a patient's habits and lifestyle, which could contribute to his or her hypertension.

The identification of other CV risk factors or concomitant disorders may affect prognosis and guide treatment. The major CV risk factors and types of hypertension-associated target organ damage are listed in Table 2.5. The medical history and physical examination are also the most important components of a pretreatment evaluation in the differentiating detailed questioning which focuses on obtaining the following medical information:

Table 2.5 Cardiovascular risk factors

Major risk factors
Hypertension
Cigarette smoking
Obesity (BMI >30 kg/m^2)
Physical inactivity
Dyslipidemia
Diabetes mellitus
Microalbuminuria or estimated GFR (glomerular filtration rate) <60 mL/min
Age (>55 years for men, >65 years for women)
Family history of premature CVD (men <55 years or women 65 years)
Target organ damage
Left ventricular hypertrophy
Angina or prior myocardial infarction
Coronary atherosclerosis
Prior coronary revascularization
Heart failure
Mild cognitive impairment
Stroke or transient ischemic attack
Chronic kidney disease
Peripheral arterial disease
Retinopathy

- Family history of hypertension
- Family history of premature CVD, diabetes, or dyslipidemia
- Estimated duration of hypertension, current and previous hypertension stage, and drug therapy
- Home BP measurements
- Medical history, clinical signs, and symptoms of CV or renal disease
- Medical history, clinical signs, and symptoms of comorbid disease, which may affect selection of drug therapy [asthma, chronic obstructive pulmonary disease (COPD)
- Complete medication history including prescription, over-the-counter (OTC) medications, herbal remedies, and drug allergies
- History of drug and alcohol abuse

The importance of the medication history cannot be overemphasized. A variety of drugs can elevate BP and interfere with the effect of antihypertensive medications.

Corticosteroids, cyclosporine, tacrolimus, and oral contraceptives are well-recognized causes of BP elevation. Ephedrine, sympathomimetics, and amphetamine-like agents, available in OTC cough and sinus preparations, can increase peripheral resistance and interfere with BP control. Commonly used drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) can also cause hypertension or interfere with the effect of a variety of antihypertensive medications.

The initial physical examination should include the following:

- Vital signs, including body mass index (BMI)
- Sitting and standing BP and heart rates
- BP measurement in the contralateral arm
- Examination of the optic fundi, neck, heart, lungs, and abdomen
- Auscultation of the neck and abdomen for bruits
- Palpation of peripheral pulses and extremity check for edema
- Neurological examination

A limited laboratory evaluation is recommended at the time of initial diagnosis. This should include a complete blood count, chemistry (including Na, K, Ca, glucose, and uric acid), a complete lipid profile, and urinalysis. Recent trends have focused on better baseline assessment of renal function in hypertensive patients. Although not mandatory in most hypertensive patients, a measurement of urinary albumin excretion or albumin/creatinine ratio may be useful in diagnosing renal disease or establishing future CV risk. A positive result could affect the intensity and type of antihypertensive therapy. Many reference laboratories now routinely calculate the estimated glomerular filtration rate (eGFR), which can be used to identify or exclude CKD (chronic kidney disease) or to monitor the effect of antihypertensive therapy on renal function.

Additional laboratory and imaging tests may be required to quantify CV risk, to characterize target organ damage, or to screen for secondary hypertension in some complicated patients. Given the high frequency of additional CV risk factors in hypertension, clinicians may want to use a risk assessment tool for determining a patient's 10-year or lifetime risk for developing coronary heart disease (CHD). Such risk assessments may be useful for estimating global CV risk and in modifying patient behavior.

2.9 Treatment

2.9.1 Nonpharmacological Therapy

The stated goal for the treatment of hypertension is to prevent CV morbidity and mortality associated with high BP. Such a goal now requires the treatment of all identified reversible risk factors accompanying hypertension to maximize CV event reduction. The basics of nonpharmacological therapy are a cardiovascular healthy diet and reducing salt intake, regular physical activity, reduction in excessive alcohol consumption, and stop smoking [3]. Nonpharmacological therapy alone is especially useful for prevention of hypertension, including adults with elevated BP, and for management of high BP in adults with milder forms of hypertension. Following recommendations were formulated in the 2017 ACC/AHA guidelines [3]:

1. Weight loss is recommended to reduce BP in adults with elevated BP or hypertension who are overweight or obese [65].
2. A heart-healthy diet, such as the DASH (Dietary Approaches to Stop Hypertension) diet, that facilitates achieving a desirable weight is recommended for adults with elevated BP or hypertension [66].
3. Sodium reduction is recommended for adults with elevated BP or hypertension [67].
4. Potassium supplementation, preferably in dietary modification, is recommended for adults with elevated BP or hypertension, unless contraindicated by the presence of CKD or use of drugs that reduce potassium excretion [68].
5. Increased physical activity with a structured exercise program is recommended for adults with elevated BP or hypertension [69].
6. Adult men and women with elevated BP or hypertension who currently consume alcohol should be advised to drink no more than two and one standard drinks per day, respectively [70].

2.9.2 Pharmacological Therapy

In the 2017 ACC/AHA guidelines for the medical treatment of hypertension, the major focus on lowering BP is not only lowering the number but targeting a BP goal within the global CVD risk of the hypertensive patient in order to obtain a maximal CVD risk reduction in which two different BP thresholds are considered:

1. The use of BP-lowering medications is recommended for secondary prevention of recurrent CVD events in patients with clinical CVD and an average SBP of 130 mm Hg or higher or an average DBP of 80 mm Hg or higher and for primary prevention in adults with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk of 10% or higher and an average SBP of 130 mm Hg or higher or an average DBP of 80 mm Hg or higher [1, 3, 5–8, 71].
2. The use of BP-lowering medication is recommended for primary prevention of CVD in adults with no history of CVD and with an estimated 10-year ASCVD risk <10% and a SBP of 140 mm Hg or higher or a DBP of 90 mm Hg or higher [1].

The 2017 ACC/AHA hypertension guidelines recommend the following for follow-up after initial BP evaluation:

1. Adults with an elevated BP or stage 1 hypertension who have an estimated 10-year ASCVD risk less than 10% should be managed with nonpharmacological therapy

and have a repeat BP evaluation within 3–6 months [3, 72, 73].
2. Adults with stage 1 hypertension who have an estimated 10-year ASCVD risk of 10% or higher should be managed initially with a combination of nonpharmacological and antihypertensive drug therapy and have a repeat BP evaluation in 1 month [3, 72, 73].
3. Adults with stage 2 hypertension should be evaluated by or referred to a primary care provider within 1 month of the initial diagnosis, have a combination of nonpharmacological and antihypertensive drug therapy (with two agents of different classes) initiated, and have a repeat BP evaluation in 1 month [3, 72, 73].
4. For adults with a very high average BP (e.g., SBP ≥180 mm Hg or DBP ≥110 mm Hg), evaluation followed by prompt antihypertensive drug treatment is recommended [3, 72, 73].
5. For adults with a normal BP, repeat evaluation every year is reasonable.

Despite BP-lowering medication, the main goal of antihypertensive medication is to reduce the risk of CVD, cerebrovascular events, and death [4–7]. The primary antihypertensive agents to be used are the primary agents used in the treatment of hypertension which include thiazide diuretics, ACE inhibitors, ARBs, and CCBs [8–11]. There is no evidence to support the initial use of beta-blockers for hypertension in the absence of specific cardiovascular comorbidities (post-myocardial infarction, angina, presence of coronary artery disease). There is also no evidence to combine an angiotensin-converting enzyme inhibitor (ACE-I) and an angiotensin II receptor blocker (ARB) because the risk outweighs the benefit. The longtime dilemma was starting with one single antihypertensive agent or initially already starting with a combination of antihypertensive therapy. Other patient-specific factors, such as age, concurrent medications, drug adherence, drug interactions, the overall treatment regimen, out-of-pocket costs, and comorbidities, should be considered to obtain a maximal patient compliance and BP control. A combination therapy of two antihypertensive drugs will lower BP by acting on two different mechanisms which has a certain advantage instead of going to the maximum dosage on one antihypertensive drug and then adding another one if BP is still not achieved. Moreover the combination therapy can be administered in a lower dose of the two different antihypertensive drugs and consequently will lead to less side effects.

2.10 Classes of Antihypertensive Medication

Table 2.6 summarizes the primary and the secondary classes of antihypertensive drugs. It is a summary of Table 18 from the 2017 ACC/AHA hypertension guidelines in which the different classes of antihypertensive drugs are described in

Table 2.6 Primary and secondary blood pressure-lowering agents

Primary BP-lowering agents		
Diuretics		
Thiazide or thiazide-type diuretics: Chlorthalidone preferred based on prolonged half-life and CVD reduction monitor Na, K, Ca, and uric acid – caution in case of history of gout		
ACE-inhibitors: Not in combination with ARB or DRI Check renal function and K No use in case of history of angioedema Risk for renal insufficiency in case of bilateral renal artery stenosis Avoid in pregnancy		
ARB: Not in combination with ACE-I or DRI Check renal function and K No use in case of history of angioedema Risk for renal insufficiency Avoid in pregnancy		
CCB		
Dihydropyridines	Avoid in HFrEF	
	Peripheral edema more in women than in men	
	Administer preferentially in the evening to avoid peripheral leg edema	
Non-dihydropyridines		
	Avoid combination with BB	
	Do not use it in HFrEF	
	CYP3AR	pharmacological interaction
Secondary BP-lowering agents		
Diuretics		
Loop diuretics:	Preferred diuretics in hypertension in moderate to severe CKD	
Potassium sparing diuretics:	In combination with HCTZ	
Mineralocorticoid receptor antagonist (MRA)	resistant HTN, adrenal hyperplasia	
	Hypertension and HFpEF	
	Potassium-sparing	
Beta-blockers	Avoid abrupt cessation	Avoid in reactive airway disease
	Not recommended as first line except in ischemic heart disease or HF	
Non-selective		
Cardioselective	Preferential if indicated to use as antiHTN drug	
BB with alpha-blocking effects	Carvedilol preferential for HF	
BB with ISA	Avoid in IHD and HF	
BB cardioselective and vasodilatory:	Induces NO-induced vasodilation	
Alpha-1 blocker:	Orthostatic hypotension	
	Second line in case of BPH	
Central alpha-1 agonist and other centrally acting drugs		
	Last line antiHTN drug	
	Risk abrupt clonidine withdrawal and BP rise	
Direct vasodilators: Sodium and water retention and reflex tachycardia		
Direct renin inhibitor: Not in combination with ACE-I and ARB		
	Limited use as antiHTN	

ACE angiotensin-converting enzyme, *ARB* angiotensin II receptor blockers, *DRI* direct renin inhibitors, *CCB* calcium channel blockers, *HFrEF* heart failure with reduced ejection fraction, *BB* beta-blocker, *CKD* chronic kidney disease, *HCTZ* hydrochlorothiazide, *NO* nitric oxide

detail regarding the doses of the individual antihypertensive drug and the preferential indication, the side effects, and the avoidance of combining some of the two classes [3]. The most important point regarding the new guidelines is that the beta-blockers are considered not anymore as first-line antihypertensive drugs but as secondary except if the hypertensive patient has ischemic heart disease or myocardial infarction.

Once antihypertensive therapy has been started, the clinical follow-up evaluation should include assessment of BP control, as well as evaluation for orthostatic hypotension, adverse effects from medication therapy, adherence to medication and lifestyle therapy, need for adjustment of medication dosage, laboratory testing (including electrolyte and renal function status), and other assessments of target organ damage. In order to improve better BP control, home BP is recommended [74].

2.11 Hypertension in Patients with Comorbidities

Arterial hypertension is often diagnosed when patient consults for another problem and is newly diagnosed with diabetes mellitus, chronic kidney disease, ischemic heart disease, heart failure, and peripheral arterial disease. The patient may be admitted for a stroke, acute heart failure, and acute myocardial infarction. These comorbidities will determine and affect the decision-making regarding the treatment of hypertension as well the choice of the antihypertensive drugs.

The 2017 ACC/AHA guidelines have made several recommendations for these hypertensive patients with comorbidities [3]:

2.11.1 Stable Ischemic Heart Disease

1. In adults with stable ischemic heart disease and hypertension, a BP target of less than 130/80 mm Hg is recommended.
2. Adults with stable ischemic heart disease and hypertension (BP ≥130/80 mm Hg) should be treated with medications (e.g., beta-blockers, ACE inhibitors, or ARBs) for compelling indications (e.g., previous MI, stable angina) as first-line therapy, with the addition of other drugs (e.g., dihydropyridine CCBs, thiazide diuretics, and/or mineralocorticoid receptor antagonists) as needed to further control hypertension.
3. In adults with SIHD with angina and persistent uncontrolled hypertension, the addition of dihydropyridine CCBs to beta-blockers is recommended.
4. In adults who have had an MI or acute coronary syndrome, it is reasonable to continue beta-blockers beyond 3 years as long-term therapy for hypertension.
5. Beta-blockers and/or CCBs might be considered to control hypertension in patients with CAD (without HFrEF) who had an MI more than 3 years ago and have angina.

2.11.2 Heart Failure

Treatment of hypertension with heart failure is incorporated in the 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure [75].

2.11.3 Chronic Kidney Disease

The 2017 ACC/AHA recommendations for treatment of hypertension in patients with CKD are [3]:

1. Adults with hypertension and CKD should be treated to a BP goal of less than 130/80 mm Hg.
2. In adults with hypertension and CKD (stage 3 or higher or stage 1 or 2 with albuminuria [≥300 mg/d or ≥ 300 mg/g albumin-to-creatinine ratio or the equivalent in the first morning void]), treatment with an ACE inhibitor is reasonable to slow kidney disease progression.
3. In adults with hypertension and CKD (stage 3 or higher or stage 1 or 2 with albuminuria [≥300 mg/d or ≥ 300 mg/g albumin-to-creatinine ratio in the first morning void]), treatment with an ARB may be reasonable if an ACE inhibitor is not tolerated.

2.11.4 Stroke Prevention

Treatment of hypertension and cerebral hemorrhage and acute stroke and secondary stroke prevention are summarized in the new 2017 ACC/AHA hypertension guidelines based on outcome trials [3].

2.12 Diabetes

Nearly 80% of patients with diabetes have hypertension. The 2017 ACC/AHA guidelines committee made three recommendations [3]:

1. In adults with DM and hypertension, antihypertensive drug treatment should be initiated at a BP of 130/80 mm Hg or higher with a treatment goal of less than 130/80 mm Hg.

2. In adults with DM and hypertension, all first-line classes of antihypertensive agents (i.e., diuretics, ACE inhibitors, ARBs, and CCBs) are useful and effective.
3. In adults with DM and hypertension, ACE inhibitors or ARBs may be considered in the presence of albuminuria.

2.13 Race and Ethnicity

Lifestyle is here priority, but socioeconomic factors play an important role in the success of healthy lifestyle. The 2017 ACC/AHA made the following recommendations:

1. In black adults with hypertension but without HF or CKD, including those with DM, initial antihypertensive treatment should include a thiazide-type diuretic or CCB.
2. Two or more antihypertensive medications are recommended to achieve a BP target of less than 130/80 mm Hg in most adults with hypertension, especially in black adults with hypertension.

2.14 Pregnancy

1. Women with hypertension who become pregnant, or are planning to become pregnant, should be transitioned to methyldopa, nifedipine, and/or labetalol during pregnancy [3].
2. Women with hypertension who become pregnant should not be treated with ACE inhibitors, ARBs, or direct renin inhibitors [3].

2.15 Elderly

1. Treatment of hypertension with a SBP treatment goal of less than 130 mm Hg is recommended for noninstitutionalized ambulatory community-dwelling adults (≥65 years of age) with an average SBP of 130 mm Hg or higher [3].
2. For older adults (≥65 years of age) with hypertension and a high burden of comorbidity and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk/benefit are reasonable for decisions regarding intensity of BP lowering and choice of antihypertensive drugs [3].

2.16 New Developments in BP Monitoring and Antihypertensive Treatment

During the last decade, efforts are made in a better BP monitoring outside the clinic.

The focus in the development of new BP-lowering therapy has mainly focused in resistant hypertension with the emphasis of renal nerve denervation and carotid baroreceptor stimulation [29]. Renal nerve denervation did not fulfill the expectations, but research in newer techniques and more focused hypertensive patients is ongoing. Endothelin antagonists are still studied, and new mineralocorticoid receptor antagonists are studied.

2.17 Conclusions

Arterial hypertension is the most common and modifiable cardiovascular risk factor in the world. The new 2017 ACC/AHA guidelines have altered the standard target BP for decades from 140/90 mmHg to a target goal of 130/90 mmHg and incorporated it in a more CVD risk approach. A healthy lifestyle is still the absolute priority. Antihypertensive drugs have now been considered in a primary class, and HCTZ, ACE-I, ARB, CCBs, and the beta-blockers have been moved to the secondary class. Despite tremendous effort over the years, still more effort needs to be done for early detection and treatment of hypertension. Data obtained from epidemiological studies provided information that based on the current approach, antihypertensive treatment cannot restore cardiovascular disease risk to ideal levels [76]. Moreover, the TROPHY study provided us the evidence that due to pharmacological treatment with an ARB, development of hypertension could be delayed in time [77]. Another fact cannot be ignored; we still treat hypertension based on systolic and diastolic BP, which are the two extreme points of the BP waveform. A more thorough noninvasive blood pressure waveform helps us to provide more precision on how to maintain vascular health [78].

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Management of Dyslipidemia

3

Peter P. Toth

3.1 Introduction

More than 16 million adults in the United States have coronary heart disease (CHD), which accounts for more deaths than any single cause or group of causes of death in the United States [1]. Atherosclerosis is a complex, multifactorial disease. Over the course of the past five decades, numerous prospective observational cohort studies have established beyond any doubt that risk for atherosclerotic disease is driven by a number of risk factors, which include dyslipidemia, hypertension, insulin resistance and diabetes mellitus, heightened systemic inflammatory tone, obesity, sedentary lifestyle and obesity, cigarette smoking, and age. The greater the burden of risk factors, the higher the likelihood for developing such manifestations of atherosclerosis as coronary artery disease (CAD), carotid artery disease, and peripheral arterial disease. Atherosclerotic disease is unequivocally associated with increased risk for myocardial infarction, stroke, renal artery disease and renal insufficiency, claudication and lower extremity amputation, and death. Progressive accumulation of lipid in arterial walls is a cardinal structural manifestation of atherosclerotic disease. Arresting this process of lipid infiltration and retention is an important goal in modern cardiovascular medicine.

Dyslipidemia is characterized by abnormalities in serum levels of a variety of lipoproteins. Dyslipidemia is frequently described as "mixed," in that it simultaneously involves abnormalities in multiple components of the lipid profile. Based on estimates by the World Health Organization, dyslipidemia is highly prevalent in industrialized nations, but its incidence is rising rapidly in all regions of the world [11]. Dyslipidemia is the product of suboptimal diet, obesity, sedentary lifestyle, as well as abnormalities in metabolism and genetic background. Hundreds of polymorphisms in the genes regulating lipid biosynthetic enzymes, serum lipases, and cell surface receptors give rise to many patterns of dyslipidemia, which require highly individualized approaches to therapy. The role of lipid modification therapy in both the primary and secondary prevention settings is one of the most intensively studied issues in modern medicine. Aggressive, sustained lipid management reduces risk for cardiovascular morbidity and mortality. Dyslipidemia is a modifiable risk factor and can be treated with a variety of strategies, including lifestyle modification measures and pharmacologic therapy. This chapter will review principles of lipid metabolism and dyslipidemia management.

3.2 Lipoprotein Metabolism and Atherogenesis

3.2.1 Low-Density Lipoprotein and Very Low-Density Lipoprotein

Cholesterol and lipids such as phospholipids, triglycerides, and cholesterol esters serve diverse purposes in biological systems. Lipids are an important source of energy, are critical structural components of cell membranes, and function in a variety of cellular signaling pathways. Derangements in cholesterol and lipid metabolism induce the development and progression of atherosclerosis. Cholesterol, monoglycerides, free fatty acids, and phospholipids arising from both dietary and biliary sources are absorbed from micelles in the intestinal lumen via a series of translocators located within the brush border of jejunal enterocytes (Fig. 3.1). Absorbed cholesterol and lipid are assimilated with apoprotein B48 (apoB48) to form chylomicrons. Chylomicrons are released into the lymphatic system and ultimately transported to the central circulation via the thoracic duct. The triglycerides in chylomicrons are hydrolyzed by lipoprotein lipase, and this reaction produces chylomicron remnant particles, which are

P. P. Toth
Ciccarone Center for the Prevention of Cardiovascular Disease,
Johns Hopkins University School of Medicine,
Baltimore, Maryland, USA
e-mail: peter.toth@cghmc.com

P. P. Toth, C. P. Cannon (eds.), *Comprehensive Cardiovascular Medicine in the Primary Care Setting*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-319-97622-8_3

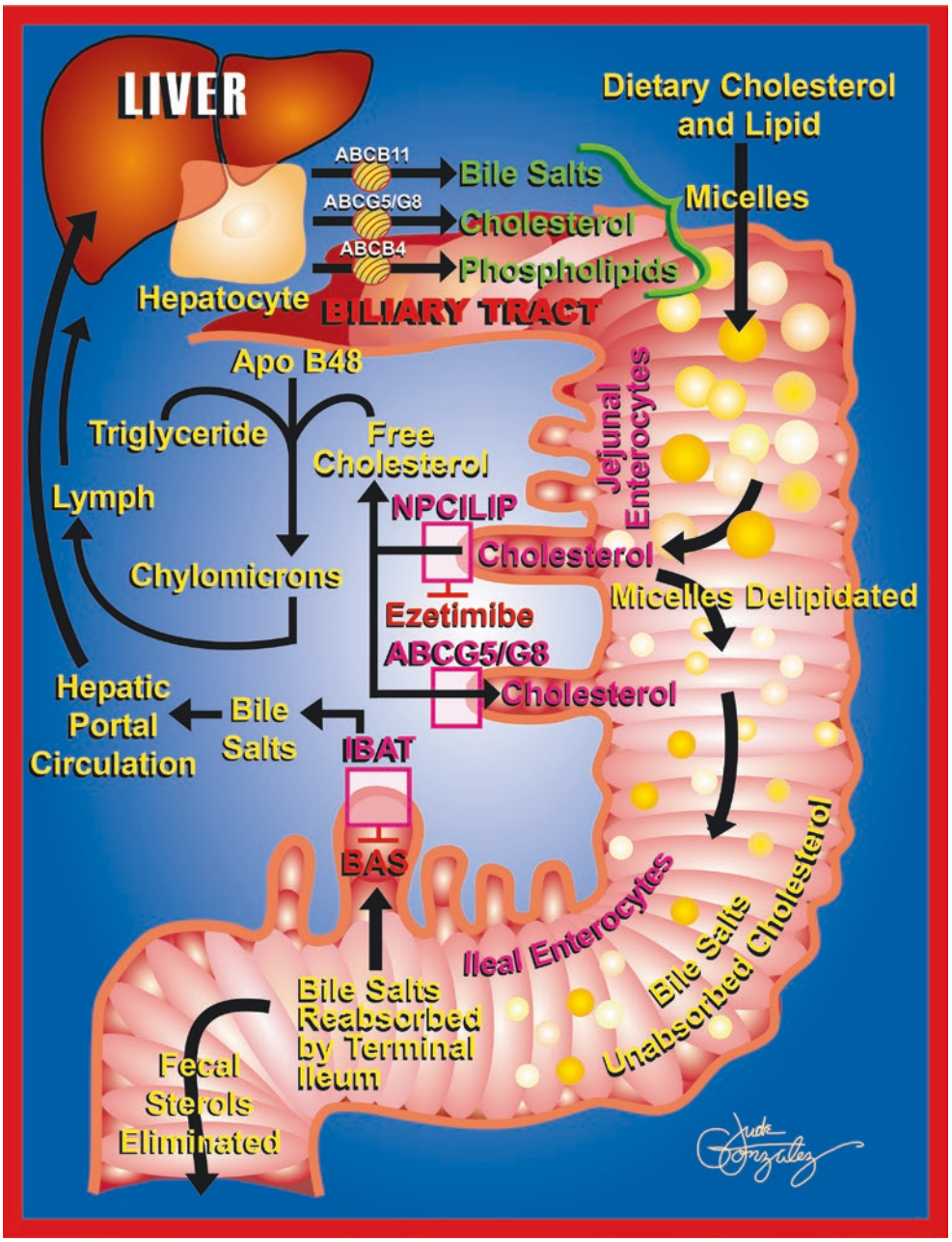


Fig. 3.1 Micelle formation and lipid and bile acid transport in the gastrointestinal tract. Dietary and biliary sources of cholesterol and lipid are solubilized in micelles in the gastrointestinal lumen. Hepatocytes use a variety of adenosine 5′-triphosphate (ATP)-binding membrane cassette (ABC) transport proteins along their canalicular surface to transport cholesterol (ABCG5/G8), bile salts (ABCB11), and phospholipids (ABCB4) from the cytosol into the biliary tract where these species can assimilate through a combination of saponification and thermodynamic driving forces to form micelles. Micelles move down the GI tract and deliver cholesterol and lipid (triglycerides and phospholipids) to specific translocases along the intestinal epithelium for absorption and systemic distribution. Cholesterol and plant sterols (e.g., beta-sitosterol) can be taken up by the Niemann–Pick C1-like 1 protein expressed along the jejunal brush border. This transporter is inhibited by ezetimibe. Once absorbed, the cholesterol can either be packaged into chylomicrons with triglycerides and apoprotein B48 and transported via the lymphatics to the central circulation or transported back into the gut lumen via the activity of ABCG5/G8. Bile salts are reabsorbed in the terminal ileum by the ileal apical sodium bile acid cotransporter. This transporter facilitates the reentry of bile salts into the portal circulation and, ultimately, the hepatic bile salt pool. The bile acid sequestration agents interrupt this uptake process and restrict the enterohepatic recirculation of bile salts and promote their fecal elimination

taken up by receptors along the hepatocyte surface and within the space of Disse. The liver secretes very low-density lipoprotein (VLDL), a lipoprotein enriched with triglycerides, cholesterol, and apoprotein B100 (apoB100). As the triglycerides in VLDL are hydrolyzed by lipoprotein lipase, the size of the lipoprotein particle decreases, yielding intermediate-density lipoprotein and then low-density lipoprotein (LDL) particles. LDL particles are concentrated with cholesterol and cholesterol esters and relatively depleted of triglycerides. LDL is not secreted directly from hepatocytes; rather, it is a by-product of VLDL metabolism. As the VLDL is progressively converted to LDL, it releases constituents from its surface coat (apoproteins A-I, A-II, and phospholipids) that are used to form high-density lipoprotein (HDL) in serum. HDL particles can also be directly secreted from jejunal enterocytes as well as hepatocytes.

Serum VLDL remnant particles and LDL function as delivery vehicles of cholesterol to peripheral tissues, including blood vessel walls. These lipoproteins are atherogenic because they can traverse the endothelial cell barrier. In the setting of an atherogenic milieu, endothelial cells become dysfunctional. The connections (gap junctions) between cells can loosen, thereby weakening the sieving or filtering capacity of the endothelial barrier. Endothelial cells express a variety of adhesion molecules (vascular cell adhesion molecule-1, intercellular adhesion molecule-1, and selectins) that promote the binding, rolling, and transmigration across defective gap junctions along the endothelial layer. This promotes the influx of proinflammatory cells such as T cells, mast cells, and monocytes [12, 13]. Monocytes can transform into macrophages when exposed to monocyte colony-stimulating factor. Macrophages resident within the subendothelial space exposed to LDL oxidized by enzymes such as lipoxygenase or myeloperoxidase upregulate the expression of scavenger receptors (SR-A, CD-36) on their surface and actively take up excessive amounts of cholesterol. The macrophages become progressively more loaded with lipid, culminating in foam cell and fatty streak development, events that contribute to the development of atheromatous plaque formation. The activation of macrophages also promotes an inflammatory response with the elaboration of cytokines, interleukins, C-reactive protein, cell mitogens, matrix metalloproteinases, and reactive oxygen species that facilitate lesion progression and instability [14, 15].

LDL and VLDL remnants not taken up by peripheral tissues can be cleared from the circulation by hepatic LDL receptors, the LDL receptor-related protein, and the VLDL receptor. Therapies targeted at the upregulation of hepatic LDL receptors are antiatherogenic by virtue of their ability to reduce circulating levels of atherogenic lipoproteins.

3.2.2 High-Density Lipoprotein

HDL-C constitutes 20–30% of total serum cholesterol, though it can be substantially less in patients with genetic forms of hypoalphalipoproteinemias. HDL particles may protect the vasculature from progressive injury and atherogenesis in a number of ways, including inhibiting the expression of endothelial cell adhesion molecules and selectins, stimulating endothelial cell nitric oxide and prostacyclin production, inhibiting endothelial cell apoptosis, decreasing platelet aggregability, and reducing LDL oxidation, among other functions [16]. HDL promotes cellular export of cholesterol, or reverse cholesterol transport (RCT), a series of enzymatic reactions in which systemic cholesterol is delivered back to the liver for elimination as bile salts or biliary cholesterol (Fig. 3.2) [17]. Reverse cholesterol transport has been validated in both animal and human studies [18–20]. HDL particles can carry up to 200 different proteins and numerous bioactive lipids, and the specific molecular cargo depends on metabolic conditions and influences its functionality. These proteins include apoproteins, lipid-modifying enzymes (e.g., lecithin cholesterol acyltransferase, cholesteryl ester transfer protein), immunity factors (complement proteins), redox active enzymes (paraoxonase, platelet-activating factor acetyl hydrolase, glutathione peroxidase), and acute phase reactants (serum amyloid A), among many others [21, 22].

A low level of HDL-C (i.e., <40 mg/dL in men and <50 mg/dL in women) constitutes an independent risk factor for the development of CAD and for CV morbidity and mortality and is a component of all major risk scoring algorithms. Because of a lack of any clinical trial evidence, no current guidelines on dyslipidemia management recommend therapeutic effort be made to raise the level of HDL-C [16, 23, 24].

A high baseline HDL-C (e.g., >60 or >90 mg/dL) should not provide a clinician with false reassurance. If a patient is evaluated for risk in a primary prevention setting, appropriate risk scoring should be undertaken irrespective of baseline HDL-C. The risk score will help to determine whether or not a patient requires intervention in order to reduce the burden of atherogenic lipoprotein in serum.

3.2.3 Triglycerides

Recent meta-analyses suggest that hypertriglyceridemia is an independent risk factor for CVD [25–27]. Hypertriglyceridemia is a feature of the metabolic syndrome and occurs in patients with a variety of other clinical

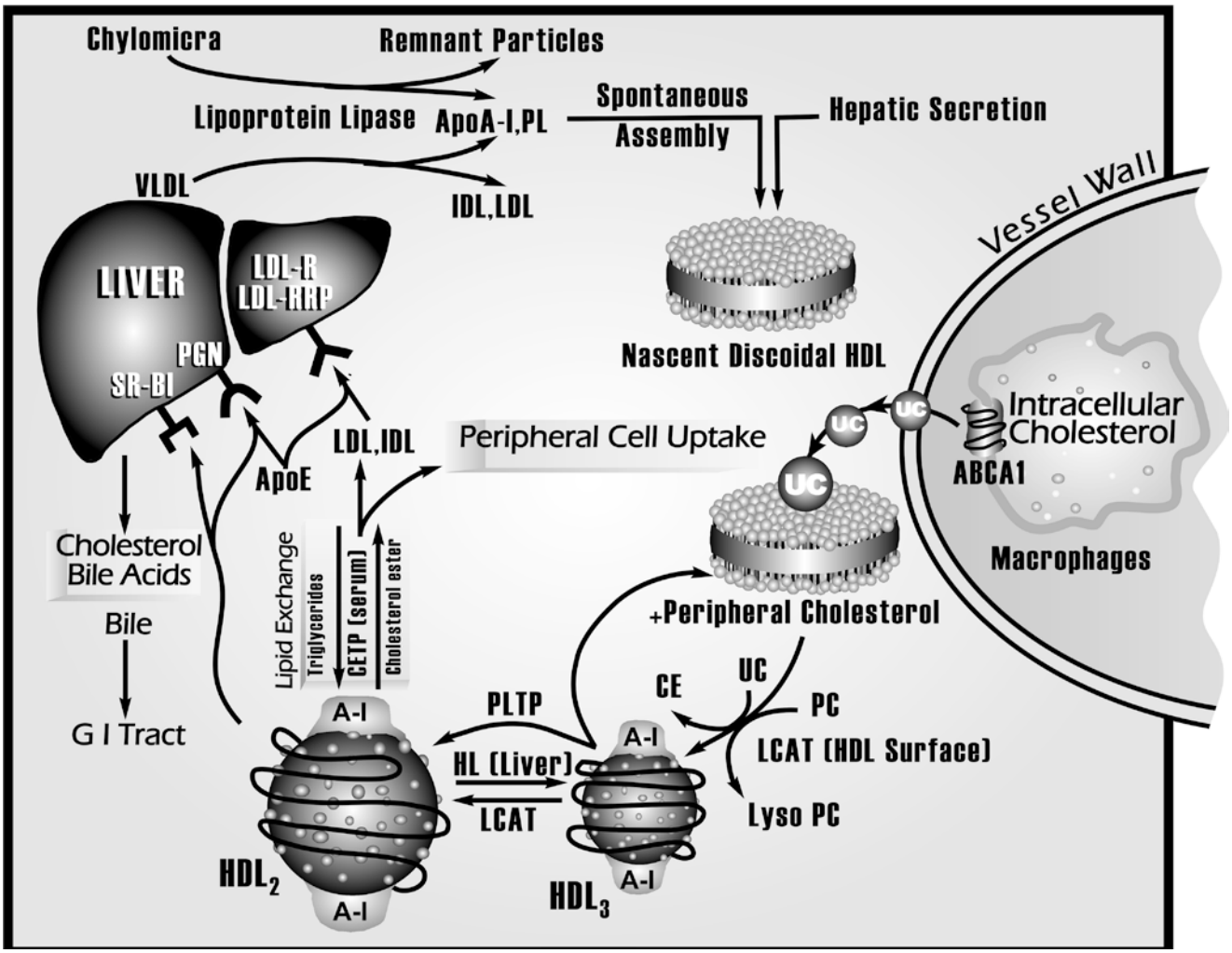


Fig. 3.2 Metabolism of HDL and reverse cholesterol transport. In order to deliver peripheral cholesterol back to the liver or steroidogenic organs (adrenals, placenta, ovaries, testes), apoA-I and nascent discoidal (nd) HDL interact with macrophages within the subendothelial space of the blood vessel walls. ApoA-I and ndHDL are high-affinity cholesterol acceptors that bind to ABCA1 and promote cholesterol mobilization and externalization. HDL undergoes a series of cell receptor- and serum enzyme-dependent maturation reactions (i.e., "HDL speciation"). Externalized cholesterol is esterified by LCAT. The cholesterol esters are compartmentalized within the hydrophobic core of HDL particles. As the particles become more enriched with cholesterol ester, they become larger and rounder, forming in turn, HDL_3 and then the larger HDL_2. These spherical species can also promote cholesterol mobilization from macrophages by interacting with ABCG1. HDL can interact directly with a number of hepatocyte receptors. The cholesterol ester in HDL can be delivered back to the liver via an "indirect pathway" for RCT, which depends upon CETP and the LDL and LDL-RRP receptors. The "direct pathway" for RCT depends upon SR-BI, which binds and selectively delipidates HDL particles and then releases the lipid-poor HDL back into the circulation to begin another cycle of RCT. (Reproduced with permission from [17]). *ABCA1 and G/1G4* ATP-binding membrane cassette transporters A1 and G1/G4, *ApoA-I* apoprotein A-I, *ApoE* apoprotein E, *CE* cholesteryl ester, *CETP* cholesterol ester transfer protein, *HL* hepatic lipase, *IDL* intermediate-density lipoprotein, *LCAT* lecithin: cholesteryl acyltransferase, *LDL* low-density lipoprotein, *LDL-R* low-density lipoprotein receptor, *LDL-RRP* low-density lipoprotein receptor-related protein, *lysoPC* lysophosphatidylcholine, *PC* phosphatidylcholine, *PGN* proteoglycans, *PL* phospholipid, *PLTP* phospholipid transfer protein, *SR-BI* scavenger receptor BI, *Trigly* triglyceride, *UC* unesterified cholesterol, *VLDL* very low-density lipoprotein

conditions, including familial combined hyperlipidemia, chylomicronemia, and dysbetalipoproteinemia, as well as in patients with diabetes mellitus, lipoprotein lipase deficiency, and hepatic lipase deficiency states. Among patients with CAD and a history of an acute syndrome on statin therapy, hypertriglyceridemia is associated with a higher incidence of morbidity and mortality compared to patients who are normotriglyceridemic [28]. Hypertriglyceridemia can arise from excess fat in the diet, impaired capacity to metabolize triglyceride, or increased endogenous biosynthesis of triglyceride. Hypertriglyceridemia is highly correlated with insulin resistance and hepatic steatosis. Steatosis can also occur within skeletal myocytes, pancreatic tissue, and epicardium, among other tissues [29]. In the setting of insulin

resistance, insulin becomes relatively ineffective at inhibiting hormone-sensitive lipase, an enzyme in visceral adipocytes that hydrolyzes triglycerides to free fatty acids. The portal circulation and hepatic parenchyma become flooded with excess fatty acid. In the liver, the fatty acid can be reassimilated into triglyceride and packaged into VLDL (resulting in hypertriglyceridemia), oxidized as fuel by mitochondria (beta-oxidation), or shunted toward gluconeogenesis (potentiating hyperglycemia). If these systems are overwhelmed, then the excess triglyceride is deposited in the hepatic parenchyma leading to steatosis. When triglycerides are severely elevated (>500 mg/dL), patients are vulnerable to the development of pancreatitis. The risk of pancreatitis increases as the level of serum triglycerides increases [30, 31]. Severely elevated triglyceride levels increase intrapancreatic endothelial dysfunction, activate an inflammatory storm, and potentiate parenchymal destruction and loss of islet cell mass, increasing risk for new onset diabetes mellitus.

Triglycerides are not miscible in an aqueous phase; hence, they must be transported in serum by lipoproteins. In the setting of hypertriglyceridemia, VLDL and the level of remnant lipoproteins (small VLDLs and IDLs) are elevated. In general, in Western societies, people are postprandial during most of the day. Remnant lipoproteins are abundant in the postprandial phase. Lipoprotein remnants are atherogenic [32], potentiate inflammation and endothelial dysfunction, and correlate with increased risk for cardiovascular events [33–35]. Some of the toxicity attributable to triglycerides is because they impair the normal flow of lipoprotein metabolism. As triglycerides increase in serum, there is increased transfer of triglyceride mass from VLDL into LDL and HDL particles by the enzyme cholesteryl ester transfer protein. This TG enrichment renders these lipoproteins more vulnerable to lipolysis by hepatic lipase, generating small, dense LDL and increased catabolism of HDL particles, resulting in an atherogenic lipid profile. Consequently, as triglycerides progressively increase, LDL particle number increases, particle size decreases, and serum levels of HDL particles decrease. All of these changes are associated with increased risk for atherosclerotic disease. Small LDL particles may be more atherogenic by virtue of their smaller size and increased permeability into vessel walls, decreased clearance from the circulation because of reduced affinity for the LDL receptor on the surface of hepatocytes, and increased vulnerability to oxidative modification.

3.3 Dyslipidemia

Dyslipidemia is associated with elevations in serum low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDL-C) and low levels of high-density lipoprotein cholesterol (HDL-C). Non-HDL-C is a sensitive measure of the atherogenic lipoprotein burden in serum; includes VLDL, IDL, LDL, and lipoprotein(a); and is calculated by subtracting HDL-C from total cholesterol (non-HDL-C = TC-HDL-C). Some analyses suggest that non-HDL-C is actually a better predictor of risk for CV events than is LDL-C [36]. However, the primary target of dyslipidemia management remains LDL-C. Dyslipidemia is a highly heterogeneous class of metabolic disorders whose etiology can depend upon poor diet and excessive gastrointestinal absorption of cholesterol and lipids, mutations in cell surface receptors, abnormalities in the production or activity of lipolytic enzymes in serum and within cells, and alterations in apoprotein metabolism.

There is evidence that other lipid/lipoprotein markers also have clinical value. These include the size and number of LDL particles [37], serum levels of lipoprotein(a) (Lp(a)) [37], and levels of apoprotein B (apoB) [38], a component of all metabolites resulting from progressive VLDL lipolysis (i.e., VLDL is converted to small VLDL, small VLDL is converted in sequence to IDL and then LDL). Such measures of risk have not yet made it into mainstream guidelines. There is mounting evidence that LDL particle number is an excellent index of CV risk [39, 40], as are serum levels of apoB [41]. With newer drugs in development that substantially reduce Lp(a), this highly atherogenic lipoprotein may in the future be defined as a target of therapy, but prospective randomized trials are needed to better define Lp(a) reduction on CV risk.

Of tantamount importance to this discussion is the fact that dyslipidemia is a ***modifiable risk factor***. The management of dyslipidemia in the context of both primary and secondary prevention must be coupled with the aggressive identification and management of all risk factors, including hypertension, diabetes mellitus, obesity, cigarette smoking, established atherosclerotic disease, as well as nephropathy and chronic kidney disease. Identifying patients at risk for atherosclerotic cardiovascular disease (ASCVD) and intervening at an early stage are crucial if disease is to be prevented or if the clinical event horizon for acute cardiovascular events in patients with established disease is to be forestalled. ASCVD is defined as a history of myocardial infarction (ST-segment elevating or non-ST-segment elevating), transient ischemic attack or ischemic stroke, stable or unstable angina, coronary or other revascularization, and peripheral arterial disease presumed to be of atherosclerotic origin [24]. Since the previous edition of this book, the third Adult Treatment Panel [42] has been replaced by the American College of Cardiology/American Heart Association (ACC/AHA) guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults [24].

3.4 Quantitative Assessment of Cardiovascular Risk

A variety of multivariable risk scoring algorithms for cardiovascular disease (CVD) have been promulgated in recent years. Historically, the most frequently used is that developed from the Framingham Heart Study (FHS) [43]. This algorithm incorporates age, sex, smoking status, total cholesterol, HDL-C, and systolic blood pressure. The FHS risk score provides a quantitative estimate for absolute risk of having a CVD event over the next 10 years. Risk assessment in the primary care setting identifies patients most likely to benefit from lifestyle modification and/or pharmacologic therapy for reducing blood pressure or atherogenic lipoprotein burden in serum. Risk scoring also stratifies patients by how intensively they should be treated. Higher levels of risk demand more intensive therapeutic intervention in order to optimally reduce risk. It is unnecessary to calculate 10-year projected risk in patients with ASCVD because they are already considered to be at high risk for CV events.

Despite the clear benefits that risk estimation provides for the long-term healthfulness of individual patients, the majority of physicians worldwide have not incorporated this important component of care into practice. Reasons for this include:

1. Preference for intuitive assessments of risk, which also tend to be inaccurate.
2. Concern that the risk model does not fully capture risk assessment in specific racial or ethnic groups, a major concern with the FHS algorithm.
3. Risk assessment leads to overtreatment with drugs which may expose patients to unnecessary risk from side effects.
4. It is time-consuming and not practical.
5. Risk algorithms underestimate risk in younger persons and women.
6. Important risk factors such as family history or blood glucose are not included [44].

Despite these concerns, the use of risk algorithms does improve the quality of health care and augments the cost-effectiveness of intervention because the intensity of therapy is matched to the level of risk. Guidelines around the world encourage risk scoring using algorithms based on relevant populations in primary prevention.

In parallel with the development of the ACC/AHA guideline, the National Heart, Lung, and Blood Institute (NHLBI) convened a risk assessment working group (RAWG) to refine CV risk assessment [45].The RAWG expressed concern that available risk-scoring algorithms such as that of the FHS or the Reynolds Risk Score were not sensitive enough to quantify risk in the highly heterogeneous US population. It was time to generate algorithms that were more race- and sex-specific using the data from more contemporary cohorts whose event rates reflect current standards of care in different racial and ethnic groups. The pooled cohort risk equation (PCRE) is based on pooled data from a number of NHLBI cohorts, including the Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Coronary Artery Disease Risk in Young Adults study, Framingham Original Cohort, and the Framingham Offspring Study. It is believed the PCRE more accurately represents the current social, environmental, racial, geographic milieu of the United States. While Caucasians and African-Americans are well represented in the derivation of the PCRE, Asians and Hispanics are not, and more research is needed to more fully evaluate absolute risk differences between these two groups and Caucasians. The online risk calculator for PCRE 10-year risk can be found at http://www.cvriskcalculator.com/, while an example of a lifetime CV risk calculator is located at https://qrisk.org/lifetime/. The latter type of assessment can be particularly valuable when assessing risk in younger persons with a longer time horizon but possibly modest short-term risk.

3.5 Recommendations of 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol

The ACC/AHA guideline introduced substantial changes to dyslipidemia management [24]. The new guideline departed from lipoprotein thresholds and goals and shifted emphasis to tailoring the intensity of statin therapy to level of CV risk. The guideline identifies four groups of patients for whom there is substantial evidence that lipid-lowering with statins reduces risk for CV morbidity and mortality (Fig. 3.3). These four groups are:

1. Individuals with clinical ASCVD.
2. Individuals with primary elevations of LDL-C > 190 mg/dL. These persons likely have at least heterozygous familial hypercholesterolemia (FH).
3. Individuals 40–75 years of age with diabetes mellitus (DM) and LDL-C 70–189 mg/dL.
4. Individuals without ASCVD or diabetes, 40–75 years of age, with LDL-C 70–189 mg/dL and an estimated 10-year ASCVD risk of >7.5% by the PCRE.

Among patients with established ASCVD, there is no need to calculate 10-year projected risk for a CV event. They are already at high risk and should be treated with high-dose, high-potency statin therapy in order to achieve LDL-C lowering of >50%. If they are not candidates for high-dose statin therapy, then moderate doses of a high-potency statin should be considered so as to achieve a level of LDL-C lowering of

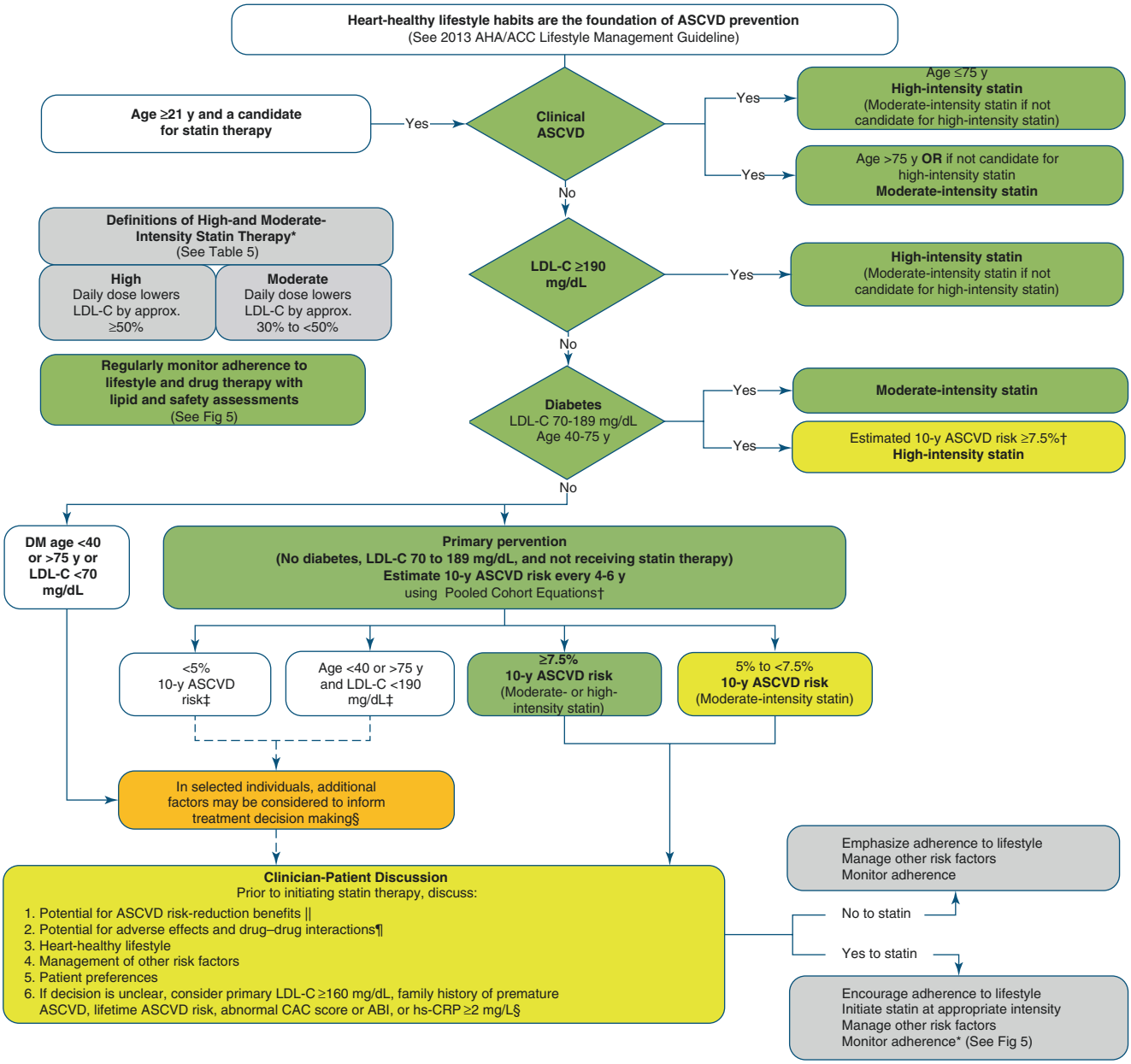


Fig. 3.3 ACC/AHA recommendations for initiating statin therapy to reduce ASCVD risk in adults. (Reproduced with permission from [24])

30–50%. As with patients already diagnosed with ASCVD, those with LDL-C > 190 mg/dL should be treated with high-dose, high-potency statins. There is no need to calculate 10-year projected risk in this group either. Statin intensity is defined in Table 3.1.

For individuals in groups 3 and 4, it is recommended that 10-year projected risk be calculated with the PCRE in order to most appropriately stratify risk and the intensity of statin therapy. Among patients with type 1 or type 2 DM, if 10-year CV risk is ≥7.5% or <7.5%, a statin dosed at high and moderate intensity, respectively, should be given. Diabetes is no longer defined as a CHD risk equivalent. For patients in the primary care setting without DM with LDL-C 70–189 mg/dL, moderate- or high-dose statin therapy should be administered if 10-year risk is ≥7.5%, and moderate-dose statin should be given if 10-year risk is 5 to <7.5%. An approach to monitoring statin response and adherence to therapy is summarized in Fig. 3.4.

In 2016, the ACC released the Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease [46]. Within this document, a

number of new recommendations were made for managing LDL-C in patients at risk for CV events. Notably, LDL-C thresholds were included, and recommendations on the appropriate use of nonstatin therapies were provided. Nonstatin drugs include ezetimibe, bile acid sequestrants (BAS), and the proprotein convertase subtilisin kexin type-9 inhibitor (PCSK9i) monoclonal antibodies. The most important new recommendations included within the Expert Consensus Decision Pathway are the following:

1. In patients with stable ASCVD and no comorbidities: On maximally tolerated statin, if ≤50% LDL-C reduction or LDL-C > 100 mg/dL, then consider the addition of ezetimibe first; if inadequate response, consider PCSK9i; if triglycerides <300 mg/dL, BAS can also be considered.
2. In patients with clinical ASCVD and with comorbidities (DM, recent acute ASCVD event, ASCVD event while on statin, baseline LDL-C ≥ 190 mg/dl, uncontrolled major risk factors, elevated Lp(a), chronic kidney disease [CKD]): On maximally tolerated statin, if <50% LDL-C reduction or if LDL-C > 70 mg/dL or non-HDL-C > 100 in pts. with DM, then consider the addition of ezetimibe first; if inadequate response consider PCSK9; if triglycerides <300 mg/dL, BAS can also be considered.
3. In patients with clinical ASCVD and with baseline LDL-C ≥ 190 mg/dL: On maximally tolerated statin, if <50% LDL-C reduction or if LDL-C > 70 mg/dL, then ezetimibe or PCSK9i may be considered first. In addition, may consider mipomersen, lomitapide, or LDL apheresis for patients with homozygous FH.

Table 3.1 High-, moderate-, and low-intensity statin therapy

High-intensity statin therapy	Moderate-intensity statin therapy	Low-intensity statin therapy
Daily dose lowers LDL-C, on average, by approximately ≥50%	Daily dose lowers LDL-C, on average, by approximately 30% to <50%	Daily dose lowers LDL-C, on average, by <30%
Atorvastatin (40)–80 mg **Rosuvastatin 20 *(40)* mg**	**Atorvastatin 10 *(20)* mg** **Rosuvastatin *(5)* 10 mg** **Simvastatin 20–40 mg** **Pravastatin 40 *(80)* mg** **Lovastatin 40 mg** *Fluvastatin XL 80 mg* **Fluvastatin 40 mg BID** *Pitavastatin 2–4 mg*	*Simvastatin 10 mg* **Pravastatin 10–20 mg** **Lovastatin 20 mg** *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

Boldface type indicates specific statins and doses that were evaluated in RCTs and demonstrated significant reductions in risk for cardiovascular events. Statins and doses approved by the Food and Drug Administration but not evaluated in RCTs are italicized. Reproduced with permission from [24]

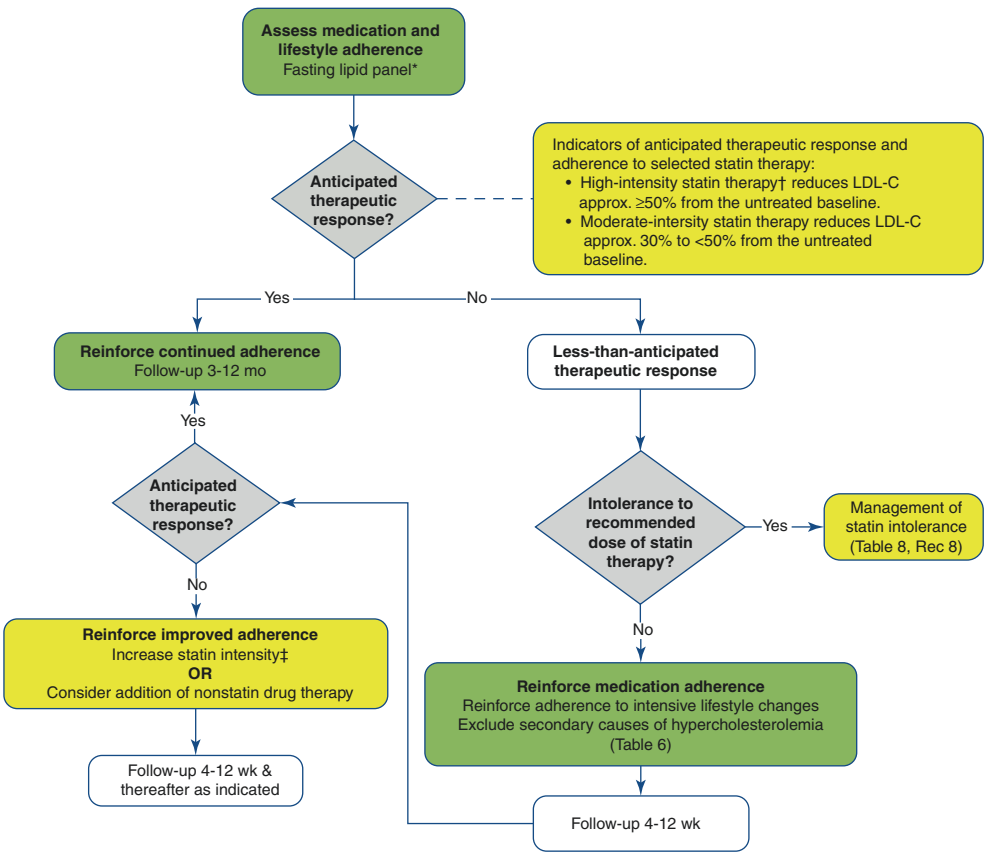


Fig. 3.4 Monitoring therapeutic response and adherence to statin therapy. (Reproduced with permission from [24])

4. In patients without clinical ASCVD and with baseline LDL-C ≥ 190 mg/dL: On maximally tolerated statin, if <50% LDL-C reduction or if LDL-C > 100 mg/dL, then ezetimibe or PCSK9i may be considered first. In addition, may consider mipomersen, lomitapide, or LDL apheresis for patients with homozygous FH.
5. Patients 40–75 years old without clinical ASCVD and with DM, on moderate- or high-intensity statin: increase to high-intensity statin if needed if less than expected percentage LDL-C reduction or if LDL-C > 100 mg/dL or non-HDL-C > 130 mg/dL. Ezetimibe or BAS may be considered in higher-risk patients. PCSK9i not currently indicated in primary prevention for patients with DM.
6. Patients 40–75 years old without clinical ASCVD. Include consideration of high-risk markers (10-year risk ≥20%, LDL-C ≥ 160 mg/dL, uncontrolled risk factors, family history of premature CAD, elevated Lp(a), accelerated subclinical disease, elevated hs-CRP, CKD, HIV infection, or other inflammatory disorders). On moderate- or high-intensity statin, increase to high-intensity statin if needed. If less than expected percent LDL-C reduction of if LDL-C > 100 mg/dL, ezetimibe or BAS (if triglycerides <300 mg/dL) may be considered in higher-risk patients. PCSK9i are not currently indicated in primary prevention patients.

These recommendations greatly clarify the role of non-statin therapies in managing dyslipidemia. It is also helpful that risk-stratified LDL-C thresholds have been reintroduced, which adds clarity to management issues. Specific medications are treated in greater detail below.

3.6 Recommendations of the 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk

Dietary and lifestyle modifications for the reduction of cardiovascular risk were reevaluated by the lifestyle expert working group. Among the most important of these recommendations are the following:

1. The work group assessed the impact of both dietary patterns and macronutrient composition on plasma LDL-C, HDL-C, and triglycerides.
2. The work group focused on evaluating dietary patterns rather than individual components of a diet. A "dietary pattern" is characterized by specific combinations of food intake and lends insight into the composition and quality of eating behaviors in specific population. Eating patterns are comprised of specific macronutrients, vitamins, and minerals. More information on food and dietary patterns may be found at USDA food patterns website. (http://www.cnpp.usda.gov/Publications/USDAFoodPatterns/USDAFoodPatternsSummaryTable.pdf)
3. The saturated, *trans*, monounsaturated, and polyunsaturated fatty acids impact plasma levels of lipids and lipoproteins.
4. "Advise adults who would benefit from LDL-C lowering to: consume a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, non-tropical vegetable oils, and nuts; and limits intake of sweets, sugar-sweetened beverages, and red meats. Adapt this dietary pattern to appropriate calorie requirements, personal and cultural food preferences, and nutrition therapy for other medical conditions (including diabetes). Achieve this pattern by following plans such as the DASH dietary pattern, the US Department of Agriculture (USDA) Food Pattern, or the American Heart Association Diet."
5. "Aim for a dietary pattern that achieves 5% to 6% of calories from saturated fat. Given that reducing saturated fat intake lowers LDL-C regardless of whether the saturated fat is replaced by carbohydrate, monounsaturated fatty acids, or polyunsaturated fatty acids, the Work Group does not specify which of these 3 macronutrients should be substituted in place of saturated fat. However, favorable effects on lipid profiles are greater when saturated fat is replaced by polyunsaturated fatty acids, followed by monounsaturated fatty acids, and then carbohydrates. It is important to note that there are various types and degrees of refinement of carbohydrates. Substitution of saturated fat with whole grains is preferable to refined carbohydrates."
6. "Reduce percentage of calories from *trans* fat. Reducing intake of *trans* fatty acids lowers LDLC, with little or no effect on HDL-C or triglycerides levels. The direction of the relationship between *trans* fatty acids and LDL-C is consistent, regardless of whether the *trans* fatty acids are replaced by carbohydrates, monounsaturated fatty acids, or polyunsaturated fatty acids."
7. There is insufficient evidence to determine whether lowering dietary cholesterol reduces LDL-C.
8. "In adults with average baseline LDL-C level of 130 mg/dL, HDL-C level of 50 mg/dL, and triglyceride level of 100 mg/dL, modifying the DASH dietary pattern by replacing 10% of calories from carbohydrates with 10% of calories from protein lowered LDL-C by 3 mg/dL, HDL-C by 1 mg/dL, and triglycerides by 16 mg/dL compared with the DASH dietary pattern. Replacing 10% of calories from carbohydrates with 10% of calories from unsaturated fat (8% monounsaturated and 2% polyunsaturated) lowered LDL-C similarly, increased HDL-C by 1 mg/dL, and lowered triglycerides by 10 mg/dL as compared with the DASH dietary pattern."

9. "There is insufficient evidence to determine whether low-glycemic diets versus high-glycemic diets affect lipids or BP for adults without diabetes. The evidence for this relationship in adults with diabetes was not reviewed."

3.7 Pharmacologic Management

Several options exist for the pharmacologic management of dyslipidemia (Table 3.2). The intensity of pharmacologic intervention depends upon a given individual's specific type of dyslipidemia and their CV risk.

3.7.1 Statins

The statins are reversible, competitive 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. HMG-CoA reductase is the rate-limiting step of cholesterol biosynthesis. Statins are recognized as first-line therapy for the reduction of serum LDL-C levels. A large number of statin outcome trials have established that lowering LDL-C results in significant reductions in multiple "hard" cardiovascular endpoints, including myocardial infarction, stroke, and death in both primary [47, 48] and secondary prevention [49, 50] studies as well as in patients with hypertension [51], diabetes mellitus [52], or heightened inflammation [53] as measured by serum levels of high-sensitivity C-reactive protein levels (see Table 3.3 for overview). In the recent Heart Outcomes Prevention Evaluation-3 study, men and women at intermediate risk for future cardiovascular events experienced significant CV event rate reduction with fixed-dose statin therapy (rosuvastatin 10 mg daily) irrespective of baseline lipid profile [54].Statins benefit both men and women as well as the elderly [55]. In addition, statin therapy is associated with reduced frequency and severity of angina pectoris as well as claudication [49], need for coronary and peripheral revascularization [53], and slows or even reverses atheromatous plaque progression [56, 57]. As a rule of thumb, when it comes to LDL-C reduction and intensity of statin therapy, lower LDL-C levels are associated with better reductions in cardiovascular endpoints [58–61] (Fig. 3.5) and higher likelihood of coronary plaque regression [62], and patients given more intensive doses of statins generally do better than patients given less intensive doses [59, 63, 64]. In an analysis of 14 prospective randomized statin trials by the Cholesterol Treatment Trialists Collaboration, for every 39 mg/dL (1 mmol/L) reduction in serum LDL-C with statin therapy over a mean 5-year follow-up, there was a 12% reduction in all-cause mortality, a 19% reduction in coronary mortality, a 24% reduction in myocardial infarction or coronary death, a 24% reduction in need for revascularization, and a 17% reduction in fatal/nonfatal stroke [65]. Among diabetic patients in these 14 trials, similar reductions in these endpoints were observed [66]. For patients admitted to hospital with an ACS, it is standard of care worldwide to initiate statin therapy irrespective of baseline lipid profile. Of considerable importance is the observation in both primary and secondary prevention studies that statins are safe and have a very large benefit-to-risk ratio. Despite the safety and therapeutic benefit of statin therapy, approximately 50% of patients discontinue their statin after only 6 months [67–69]. Patients should be carefully counseled on each visit about the importance of remaining adherent with statin therapy.

In addition to reducing cholesterol biosynthesis, the statins augment the clearance of atherogenic apoB100-containing lipoproteins (VLDL, VLDL remnants, and LDL) by upregulating the expression of the LDL receptor on the surface of hepatocytes. By reducing hepatic VLDL secretion, they also decrease serum levels of triglycerides. These drugs stimulate apoA-I expression and hepatic HDL secretion secondary to weak peroxisomal proliferator-activated receptor-α (PPAR-α) agonism [70].

The statins may exert benefit distinct from their ability to alter circulating levels of lipoproteins through their "pleiotropic effects." Statins inhibit the posttranslational modification and activation of small G-proteins (rho and ras) by blocking the production of isoprenoids such as farnesyl-pyrophosphate and geranylgeranyl-pyrophosphate. This is associated with reductions in the production of a large number of atherogenic stimuli (C-reactive protein, reactive oxygen species, tissue factor, interleukins, adhesion molecules, monocyte chemoattract protein-1, angiotensin II receptor, and endothelin-1), decreased platelet reactivity and smooth cell proliferation, and a reversal of endothelial dysfunction, among other effects. Consequently, statins appear to modulate inflammation, oxidative status, vasodilation, thrombotic tendency, and the capacity of a variety of cell types in vessel walls to interact and drive atherogenesis [71].

Statins are used to target the reduction of elevated LDL-C and to improve the lipid profile. Statins have clinically relevant differences in efficacy, pharmacokinetics, and safety profiles. Therefore, the specific choice of a statin should be dictated by the magnitude of LDL-C reduction required. The

Table 3.2 Pharmacologic agents for dyslipidemia management and their effects on lipid fractions

	Lipid fraction		
Agent	LDL-C	HDL-C	TC
Statins	18–5% ↓	5–15% ↑	7–30% ↓
Fibric acids	5–20% ↓	10–20% ↑	20–50% ↓
Nicotinic acid	5–25% ↓	15–35% ↑	20–50% ↓
Bile and sequestrants	15–30% ↓	3–5% ↑	No change
Ezetimibe	18–20% ↓	1–4% ↑	8% ↓

Table 3.3 Prospective randomized statin trials in both primary and secondary prevention

Study	Drug	Design	Outcomes
Primary prevention studies			
AFCAPS/ TexCAPS[a]	Lovastatin, 20–40 mg/ day vs. placebo	6605 men and women	40% reduction in fatal and nonfatal MI; 37% reduction in first ACS; 33% reduction in coronary revascularizations; and unstable angina reduced by 32%
ASCOT[b]	Atorvastatin 10 mg/day vs. placebo	10,305 hypertensive men (n = 8463) and women (n = 1942) with treated high BP and no previous CAD	36% reduction in total CHD/nonfatal MI; 27% reduction in fatal and nonfatal stroke; total coronary event reduced by 29%; fatal and nonfatal stroke reduced by 27%
CARDS[c]	Atorvastatin 10 mg/day vs. placebo	2838 patients with type 2 diabetes mellitus and 1 CHD risk factor(s)	37% reduction of major cardiovascular events; 27% of total mortality; 13.4% reduction of acute CVD events; 36% reduction of acute coronary events; 48% reduction of stroke
Heart protection Study[d]	Simvastatin 40 mg/day vs. placebo	20,536 high-risk (previous CHD, other vascular disease, hypertension among men aged >65 years, or diabetes)	25% reduction in all-cause and coronary death rates and in strokes; need for revascularization reduced by 24%; fatal and nonfatal stroke reduced by 25%; nonfatal MI reduced by 38%; coronary mortality reduced by 18%; all-cause mortality reduced by 13%; cardiovascular event rate reduced by 24%
PROSPER[e]	Pravastatin 40 mg/day vs. placebo	5804 men (n = 2804) and women (n = 3000) aged 70–82 years	15% reduction in combined endpoint (fatal/nonfatal MI or stroke); 19% reduction in total/nonfatal CHD; no effect on stroke (but 25% reduction in TIA)
WOSCOPS[f]	Pravachol therapy 40 mg/day vs. placebo	6595 men	CHD death of nonfatal MI reduced by 31%; CVD death reduced by 32%; total mortality 22% reduction
Secondary prevention studies			
4S[g]	Simvastatin 20 mg/day vs. placebo	4444 patients with angina pectoris or history of MI	Coronary mortality reduced by 42%; myocardial revascularization reduction of 37%; all-cause mortality reduced by 30%; nonfatal major coronary event reduced by 34%; fatal and nonfatal stroke reduced by 30%
AVERT[h]	Atorvastatin 80 mg/day vs. angioplasty + usual care	341 patients with stable CAD	36% reduction in ischemic event; delayed time to first ischemic event reduced by 36%
CARE[i]	Pravastatin 40 mg/day vs. placebo	3583 men and 576 women with history of MI	Death from CHD or nonfatal MI reduced by 24%;death from CHD reduced by 20%; nonfatal MI reduced by23%; fatal MI reduced by 37%; CABG or PTCA reduced by 27%
IDEAL[j]	Atorvastatin 80 mg/day vs. simvastatin 20–40 mg/day	8888 men and women with CHD	Major cardiac events reduced by 13%, nonfatal MI reduced by 17%, revascularization reduced by 23%, peripheral arterial disease reduced by 24%
JUPITER[k]	Rosuvastatin 20 mg/day vs. placebo	17,802 men (>50 years) and women (>60 years) with no history of CAD or DM, entry LDL < 130 mg/dL and CRP > 2.0 mg/L	44% reduction in primary endpoint of major coronary events; 65% reduction in nonfatal MI; 48% reduction in nonfatal stroke; 46% reduction in need for revascularization; 20% reduction in all-cause mortality
LIPID[l]	Pravachol 40 mg/day vs. placebo	9014 patients	Coronary mortality reduced by 24%; stroke reduced by 19%; fatal CHD or nonfatal MI reduced by 24% fatal or nonfatal MI reduced by 29%
LIPS[m]	Fluvastatin 40 mg/day vs. placebo	1667 men and women aged 18–80 years post-angioplasty for CAD	22% lower rate of major coronary events (e.g., cardiac deaths, nonfatal MI, or reintervention procedure)
MIRACL[n]	Atorvastatin 80 mg/day vs. placebo	3086 patients with ACS	Reduction in composite endpoint by 16%; ischemia reduced by 26%; stroke reduced by 50%
PROVE IT[o]	Atorvastatin 80 mg/day vs. pravastatin 40 mg/ day	4162 patient with ACS	16% reduction of composite endpoint; 14% reduction in CHD death, MI, or revascularization; revascularizations reduced by 14%; unstable angina reduced by 29%
REVERSAL[p]	Atorvastatin 80 mg/day vs. pravastatin 40 mg/ day	654 patients with CAD	Atheroma: Atorvastatin −0.4%, pravastatin 2.7%, difference of −3.1%, p = 0.02
TNT[q]	Atorvastatin 10 mg/day vs. 80 mg/day	10,003 patients with CHD and LDL cholesterol 130–250 mg/dL	22% reduction in composite endpoint; MI reduced by 22%; stroke reduced by 25%

(continued)

Table 3.3 (continued)

Abbreviations: *ACS* acute coronary syndrome, *CABG* coronary artery bypass grafting, *CAD* coronary artery disease, *CHD* coronary heart disease, *LDL* low-density lipoprotein, *MI* myocardial infarction, *PTCA* percutaneous transluminal coronary angioplasty. Trial acronyms: *AFCAPS/TexCAPS* The Air Force/Texas Coronary Atherosclerosis Prevention Study: Implications for Preventive Cardiology in the General Adult US Population, *ASCOT* Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm, *CARDS* Collaborative Atorvastatin Diabetes Study, *PROSPER* Pravastatin in elderly individuals at risk of vascular disease, *WOSCOPS* West of Scotland Coronary Prevention Study, *4S* The Scandinavian Simvastatin Survival Study, *AVERT* Atorvastatin versus Revascularization Treatment Investigators, *CARE* Cholesterol and Recurrent Events Trial, *IDEAL* Incremental Decrease in End Points Through Aggressive Lipid Lowering Study, *JUPITER* The Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin, *LIPID* Long-Term Intervention with Pravastatin in Ischemic Disease, *LIPS* Lescol Intervention Prevention Study, *MIRACL*, Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering Study, *PROVE IT* Pravastatin or Atorvastatin Evaluation and Infection Therapy Study; *REVERSAL* The REVERSing Atherosclerosis with Aggressive Lipid Lowering Study, *TNT* Treating to New Targets Trial

[a]Whitney [188]
[b] Sever et al. [51]
[c] Colhoun et al. [52]
[d] Heart Protection Study Collaborative Group [189]
[e] Shepherd et al. [55]
[f] Shepherd et al. [190]
[g] Scandinavian Simvastatin Survival Study Group [49]
[h]Pitt et al. [191]
[i]Sacks et al. [192]
[j]Pedersen et al. [193]
[k]Ridker et al. [53]
[l]The LIPID Study Group [194]
[m]Serruys et al. [195]
[n]Schwartz et al. [196]
[o]Cannon et al. [58]
[p]Nissen [56]
[q]LaRosa et al. [63]

specific statin and dose are chosen based on the patient's level of risk and the percentage of LDL-lowering needed, as specified by the ACC/AHA guideline summarized above.

The LDL-C reducing capacity of the statins is as follows: rosuvastatin (Crestor), 45–63% (5–40 mg daily); atorvastatin (Lipitor), 26–60% (10–80 mg daily); simvastatin (Zocor), 26–47% (10–80 mg daily); lovastatin (Mevacor), 21–42% (10–80 mg daily); fluvastatin (Lescol), 22–36% (10–20 mg daily); pitavastatin (Livalo), 32–43% (1–4 mg daily), and pravastatin (Pravachol), 22–34% (10–80 mg daily). Each doubling of the statin dose yields an additional 6% reduction, on average, in serum LDL-C (the so-called "rule of 6s"). In general, statin therapy provides dose-dependent reductions in serum triglyceride levels (typically 10–25%) and elevations in serum HDL-C (2–14%). Atorvastatin has a tendency to be less effective at raising HDL-C as the dose is titrated to higher levels. In patients with high baseline triglycerides (>300 mg/dL), the statins increase HDL-C significantly more than in patients who are normotriglyceridemic. For instance, simvastatin and rosuvastatin can raise HDL-C up to 18 and 22%, respectively, in these patients. One of the reasons for this has to do with the fact that as triglycerides increase in serum, HDL particles become progressively more loaded with triglyceride via the action of cholesterol ester transfer protein. This renders the HDL particle more vulnerable to lipolysis and eventual catabolism by the enzyme hepatic lipase. As triglycerides rise, HDL thus has a tendency to decrease. Statins help to prevent this by reducing serum concentrations of triglyceride.

The statins also differ in their pharmacokinetic profiles [72]. Due to their relatively short half-lives (1–4 h), lovastatin, pravastatin, fluvastatin, and simvastatin should be taken in the evening so as to intercept the peak activity of HMG-CoA-reductase, which occurs around midnight. Atorvastatin and rosuvastatin can be taken at any time during the day because of their long half-lives (approximately 19 h). The coadministration of cytochrome P450 3A4 inhibitors (azole-type antifungals [ketoconazole, itraconazole], HIV protease inhibitors, macrolide antibiotics [erythromycin, clarithromycin], nefazodone, greater than 1 quart of grapefruit juice daily, and cyclosporine) with simvastatin, lovastatin, and atorvastatin should be avoided as these statins are dependent on this P450 isozyme for metabolism. Concomitant administration can lead to increased risk for toxicity. The dose of Zocor should not exceed 20 mg daily in patients receiving verapamil or amiodarone.

Statin therapy is often insufficient in achieving adequate risk reduction for many patients with CHD, who require the use of combination therapy to achieve their risk-stratified LDL-C reduction goals. As the initial priority of pharmacologic therapy in the management of CVD is to achieve the goal for LDL-C, an LDL-lowering drug such as a statin, but adjuvant therapies with other drugs can and should be provided as indicated, especially in high-risk and very high-risk

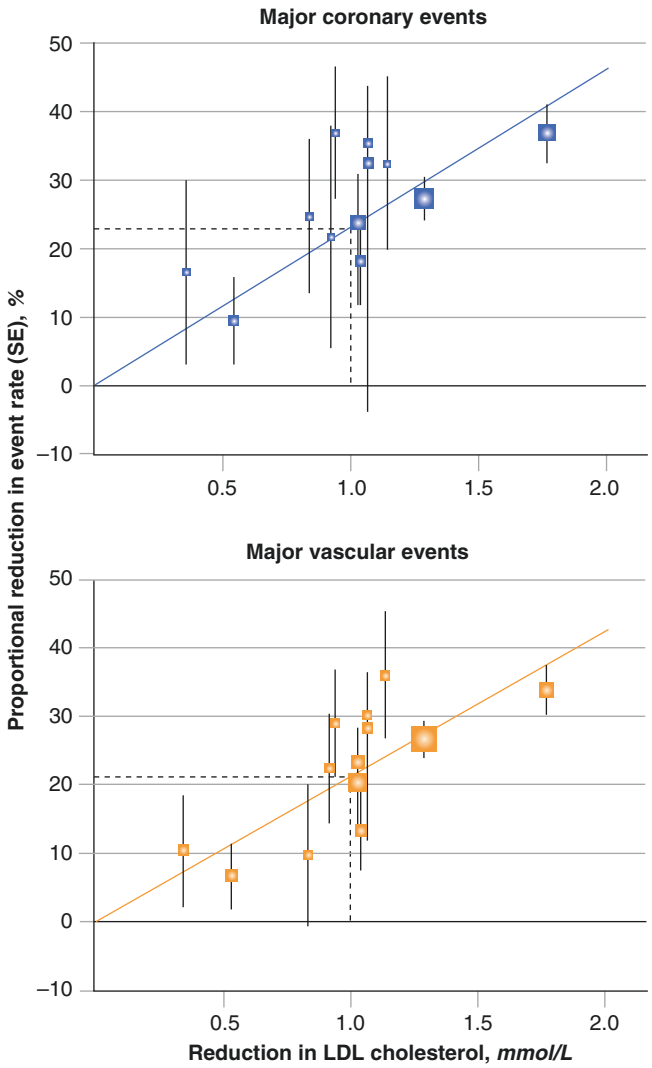


Fig. 3.5 Relation between proportional reduction in the incidence of major coronary events and major vascular events and mean absolute LDL cholesterol reduction at 1 year. Each square represents a single trial plotted against mean absolute LDL cholesterol reduction at 1 year, with vertical lines above and below corresponding to one standard error of unweighted event rate reduction. For each outcome, the regression line represents the weighted event rate reduction per mmol/L (39 mg/dL) of LDL-C reduction. (Reproduced with permission from [65])

patients. In patients unable to achieve their LDL-C reduction goals with TLC and statin therapy, consideration should be given to combination therapy such as the addition of ezetimibe, a PCSK9i, or bile acid-binding resin.

3.7.1.1 Statin Myopathy

The statins have a very favorable benefit-to-risk ratio with respect to liver, muscle, and renal safety concerns. Statin-associated myotoxicity, including skeletal muscle necrosis that may result in life-threatening rhabdomyolysis, is a concern with statin therapy. However, statin-induced myopathy and rhabdomyolysis are relatively rare events (1 in 1000 and 1 in 10,000–100,000, respectively) [73, 74]. A large number of mechanisms have been proposed as causal for statin related myopathy, and hence it is a highly heterogeneous adverse event [75, 76]. Myopathy is a general term for any muscle symptom or pathology, whereas myalgia is defined as muscle symptoms without creatine kinase (CK) elevation. Myositis is defined as muscle symptoms with an elevation in CK, and rhabdomyolysis is defined as muscle symptoms associated with marked CK elevations, typically >10 times the upper limit of normal (ULN) with an elevation in serum creatinine requiring intravenous hydration therapy [77–79]. Drug interactions, muscle injury, thyroid dysfunction, age, renal and hepatic function, abuse of illegal drugs (e.g., heroin), and possibly serum electrolyte disturbances can increase the risk for statin myalgia and myopathy [76]. An algorithm for assessing whether or not muscle-related complaints are associated with statin therapy is presented in Fig. 3.6 [79].

In the Heart Protection Study [80], the largest clinical trial of statin therapy to date, there were five cases (0.05%) of nonfatal rhabdomyolysis (muscle symptoms plus creatine kinase >40 times ULN) reported in patients receiving simvastatin 40 mg compared with three cases (0.03%) in patients receiving placebo. While the risk of rhabdomyolysis is <0.1% (approximately two cases/100,000 patients receiving therapy/year), patients must be counseled about the possibility as well as warning signs for rhabdomyolysis (escalating muscle pain, proximal weakness, brownish-red discoloration of urine suggesting the presence of myoglobin). Muscle metabolism can be adversely impacted by statin therapy in several ways, including changes in fatty acid oxidation, autoimmune phenomena, reduced coenzyme Q_{10} biosynthesis, and increased myocyte protein (actin, myosin) degradation via the activity of atrogin-1 and the ubiquitin-proteasome pathway, among other pathways [50].

Statins can induce myalgia. However, myalgias in general are common throughout the population. Among the 20,536 patients in the Heart Protection Study [80] randomized to either placebo or simvastatin 40 mg daily, the incidence of myalgia was identical in the two groups of patients. It is widely acknowledged that because baseline myalgia was an exclusionary factor in virtually all statin trials, the true incidence of statin-related myalgia is not accurately reflected in the trials. An important evaluation of this issue revealed that 4–17% of patients taking statins in real-world settings develop myalgias and the incidence of myalgia varies with the identity and dose of the various statins, with fluvastatin and simvastatin having the lowest and highest rates, respectively [81]. If a patient is experiencing significant myalgia or muscle weakness, a serum creatine kinase (CK) level can be obtained. Statins should be discontinued in patients who develop intolerable muscle complaints in the absence of

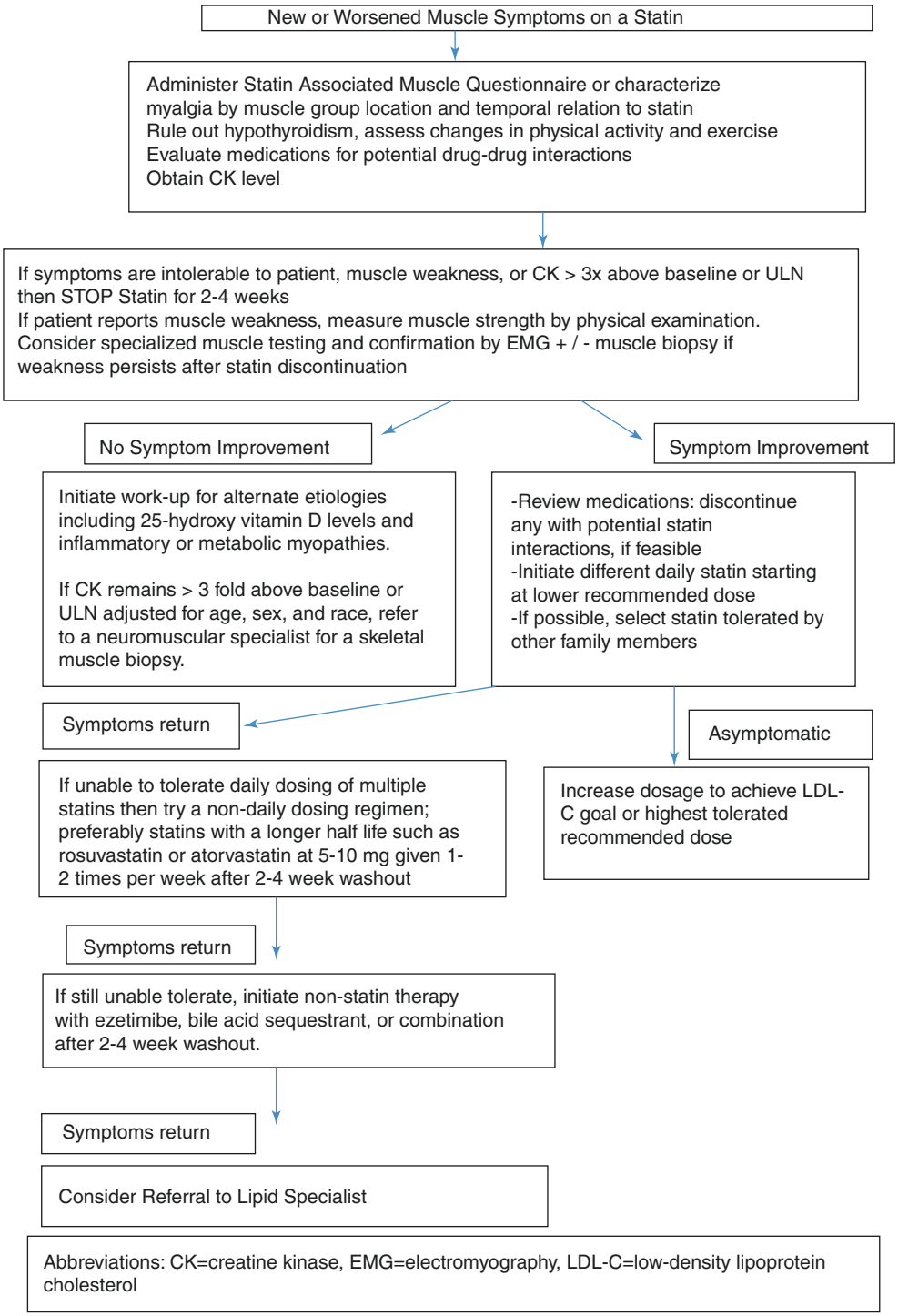


Fig. 3.6 Algorithm for evaluating possible statin-related skeletal muscle adverse events. (Reproduced with permission from [79])

exacerbating factors or other etiologies. However, prior to statin discontinuation, especially in high-risk patients, patients should be thoroughly examined and evaluated. Patients frequently complain of statin-induced myalgia when in fact they are experiencing arthralgia from osteoarthritis, may have sustained muscle or tendon injury unrelated to statin therapy, or have injured muscle from exertion or direct impact. Great care must be exercised in this process. It has been clearly demonstrated that the intensity of negative press is highly correlated with premature statin discontinuation [82]. Of great clinical importance is the observation that premature statin discontinuation in patients with established ASCVD correlates with significantly increased risk for acute CV events compared to patients who remain adherent [82–84] (Fig. 3.7). Statins are contraindicated in pregnant and nursing women.

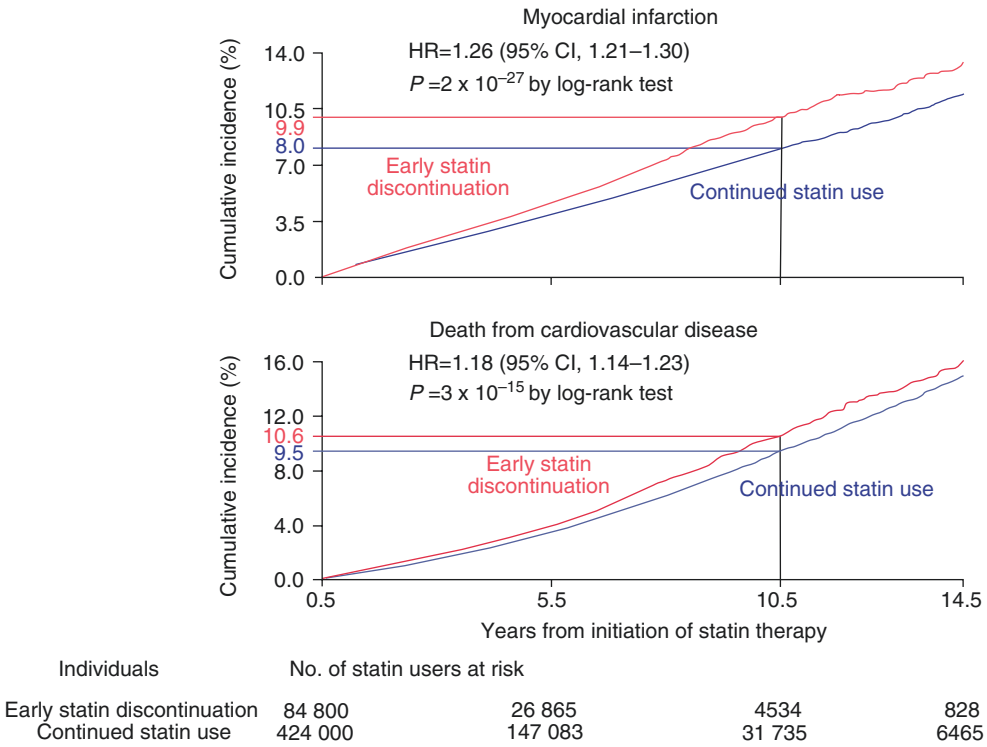


Fig. 3.7 Statin discontinuation in the Copenhagen Heart Study correlates with increased risk for both myocardial infarction and death. (Reproduced with permission from [82])

Analyses from the TNT and PROVE-IT-TIMI trials demonstrated that adverse events were unrelated to statin dose or to the degree of LDL lowering [63–65]. One exception to this is simvastatin, which at a dose of 80 mg daily is associated with a higher risk for myopathy compared to other statins [85, 86]. Simvastatin 80 mg daily is no longer an FDA-approved dose. As myalgia and myopathy are leading reasons cited by patients for statin discontinuation, managing dyslipidemia with optimal statin therapy without adversely affecting patient safety remains an important clinical challenge and goal.

3.7.1.2 Statin Hepatotoxicity

Statins are associated with asymptomatic elevations in serum transaminase levels. The elevation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) >3 times ULN can be seen with all statins and is dose related [87]. It is postulated that ALT and AST are released in response to statin therapy as a result of hepatocyte injury, altered cell membrane integrity, or as an adaptive response to enzyme induction. Other possible mechanisms include disruption of surface transport proteins, cytolytic T-cell activation, apoptosis (programmed cell death) of hepatocytes, mitochondrial dysfunction, or impaired prenylation of proteins.

There is no evidence that minor asymptomatic elevations of ALT and AST precede acute liver failure, nor is there support for routine monitoring for acute liver failure [88]. The majority of patients have baseline elevations in transaminases secondary to established hepatic steatosis. The levels of their serum transaminases can vary from visit to visit because of variation in the intensity of intrahepatic inflammatory tone. Although rare, liver injury can occur with the use of statin therapy. Hepatotoxicity is defined as an ALT elevation ≥3 times the upper limit of normal (ULN) on two occasions at least 1 month apart. The average risk of this on statin therapy approximates 1%, but risk increases as a function of dose. Mild elevations in serum transaminases are relatively common, and they tend to spontaneously resolve. If transaminitis or hepatotoxicity (jaundice, elevated prothrombin time, increased indirect bilirubin, or hepatomegaly) develops, statin therapy should be discontinued until transaminase levels normalize and a different statin can be started at a lower dose. The incidence of liver failure on statin therapy approximates to the background incidence for the population as a whole (approximately 1 case per 1.3 million people). Because diagnostic yield for statin toxicity is low, the FDA no longer recommends routine follow-up measurements of liver functions tests for patients on statin therapy. The National Lipid Association's recommendations on monitoring for statin-induced hepatotoxicity are summarized in Figs. 3.8 and 3.9.

3.7.1.3 Statins and Risk for Diabetes Mellitus

Statin therapy is associated with a low augmented risk for new onset type 2 diabetes mellitus [53]. It is not established how statins increase risk for DM, though a variety of

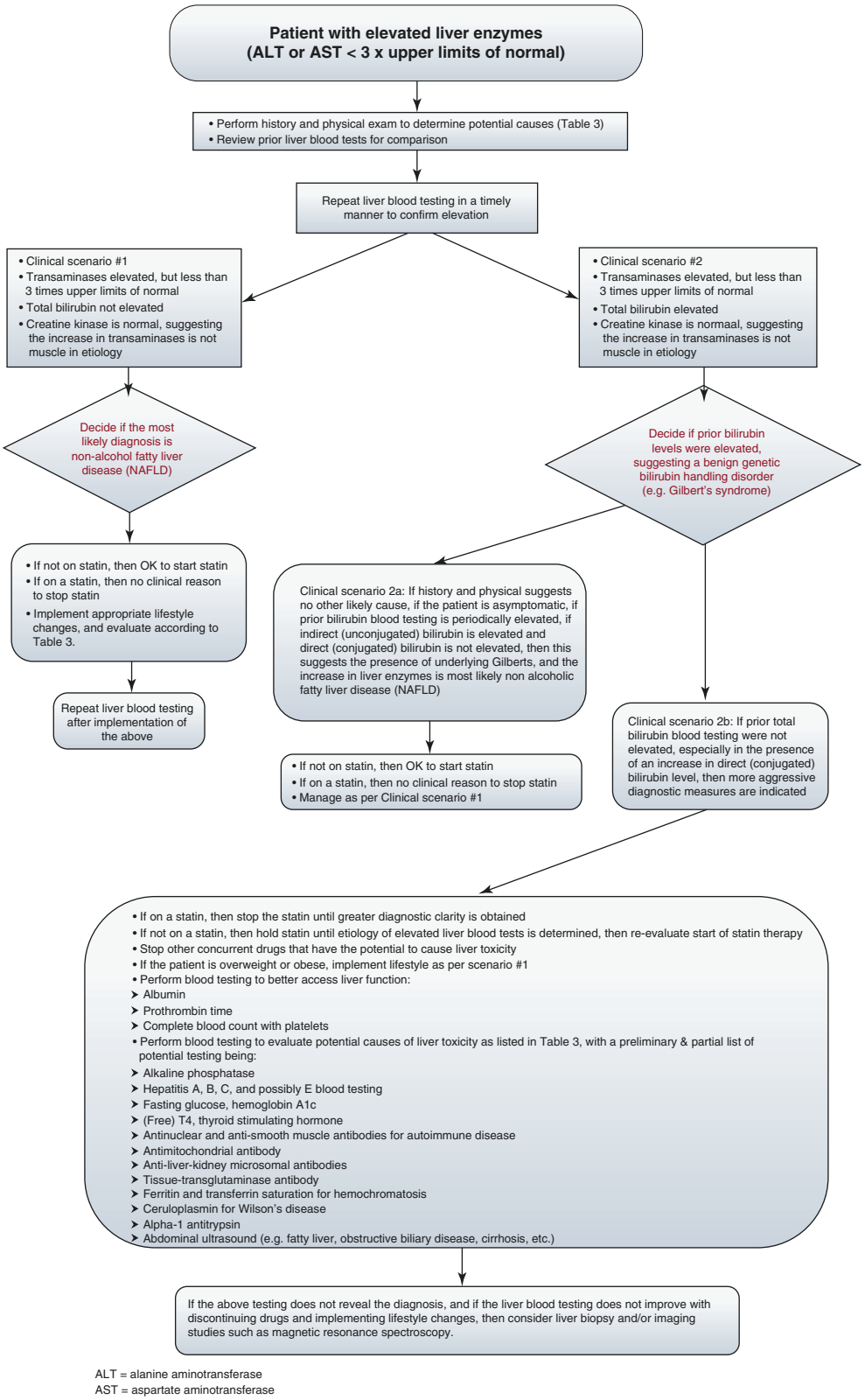
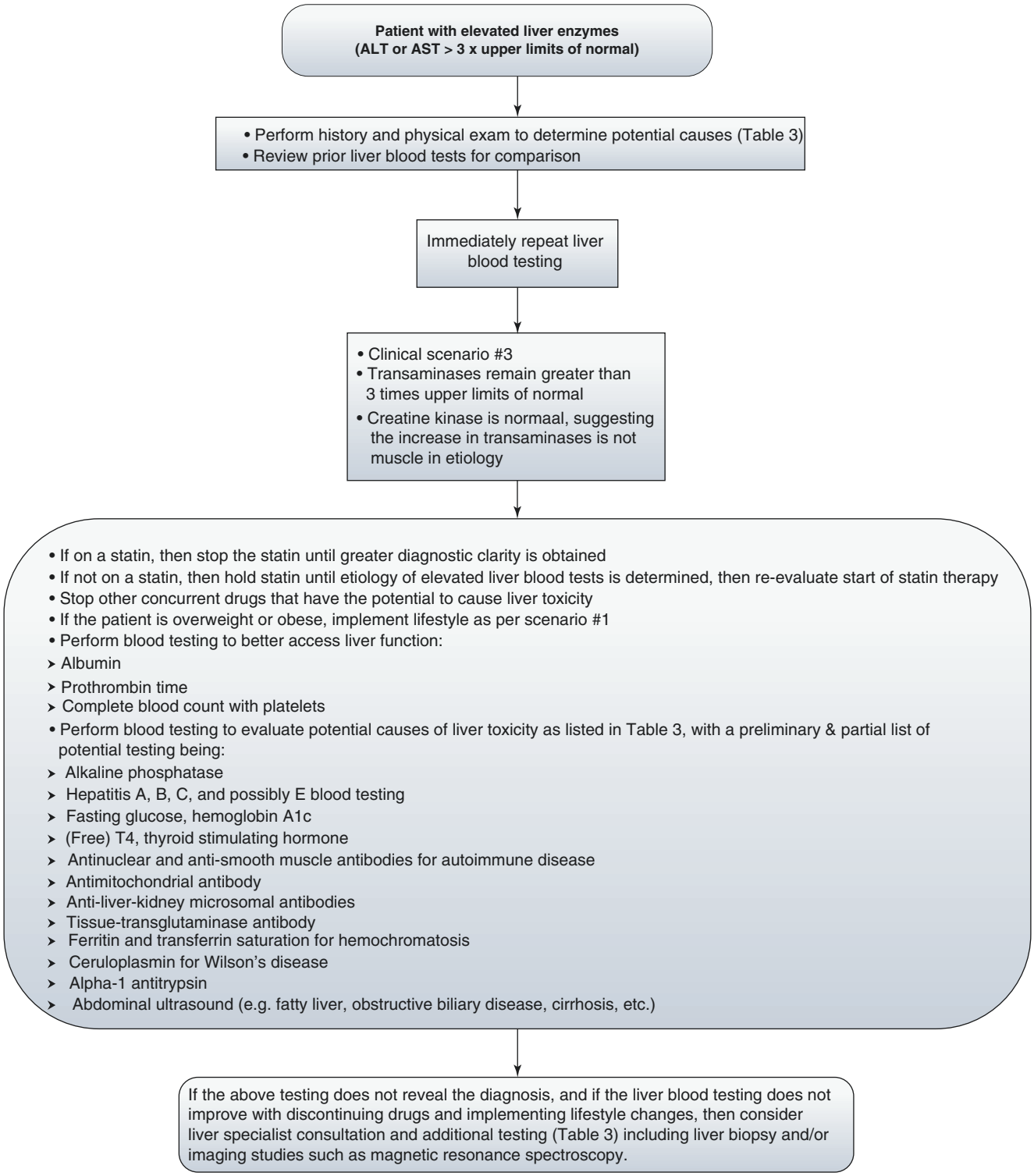


Fig. 3.8 Clinical algorithm for managing patients on statin therapy with serum transaminases less than three times the upper limit of normal. (Reproduced with permission from [89])



ALT = alanine aminotransferase
AST = aspartate aminotransferase

Fig. 3.9 Clinical algorithm for managing patients on statin therapy with serum transaminases greater than or equal to three times the upper limit of normal. (Reproduced with permission from [89])

mechanisms have been proposed [90]. Multiple meta-analyses establish a small but definable risk for DM with no heterogeneity among the statins [91–93]. An analysis from the JUPITER trial suggests that among patients who develop DM on statin therapy, this is accelerated by an average of 5.5 weeks compared to patients on placebo [94]. Two other meta-analyses suggest that the only patients who develop DM on a statin are those with established metabolic syndrome or prediabetes; the more components of the MetS they possess, the higher the risk [95, 96]. Placed in perspective, one has to treat 1000 patients per year to see one new case of DM in patients on low-dose statin therapy, and 500 patients per year to see one new case on moderate to high-dose statin therapy [92]. For this reason, no guideline in the world currently recommends that statin therapy be withheld in patients who warrant statin therapy out of concern that the therapy might be diabetogenic. Moreover, statins benefit patients with or without DM equally.

3.7.2 Ezetimibe

Ezetimibe is a selective cholesterol absorption inhibitor that blocks cholesterol absorption at the jejunal brush border [97, 98]. Ezetimibe blocks cholesterol absorption by binding to the Niemann-Pick C1-like 1 (NPC1L1) protein, a sterol transporter that translocates cholesterol and phytosterols (plant sterols) from the intestinal lumen into the jejunal enterocyte [99]. As monotherapy, ezetimibe reduces levels of LDL-C by approximately 20%, whereas in combination with statins, it has an additive LDL-C-lowering effect [100–104]. Ezetimibe also decreases triglycerides by up to 8% and raises HDL-C by 1–4%. Ezetimibe does not decrease the absorption of bile acids, steroid hormones (ethinylestradiol, progesterone), or fat-soluble vitamins such as vitamin A, D, E, or α- and β-carotenes [105]. Ezetimibe can be used as primary therapy for LDL-C reduction in statin-intolerant patients.

Ezetimibe remains a primary adjunct to statins in reducing elevated LDL-C. Fixed-dose ezetimibe is also available in combination with increasing doses of simvastatin (Vytorin; 10/10; 10/20; 10/40; 10/80 mg daily). Ezetimibe can also be safely used in combination with other statins. Vytorin dosed at 10/20, 10/40, or 10/80 mg, and LDL-C is reduced by 51, 57, and 59% [106]. Ezetimibe therapy equates to approximately three statin titration steps ("rule of 6s"). Vytorin at the 10/20 mg dose helps 82% of high-risk patients reach the LDL-C < 100 mg/dL, and at the 10/40 mg dose, 52% of patients reach the LDL-C goal of <70 mg/dL [106]. The risk of hepatotoxicity with ezetimibe is nearly identical to placebo (0.5% versus 0.3%), and there is no documented evidence of increased risk for myopathy. The addition of ezetimibe to a statin regimen substantially reduces the likelihood of having to titrate the statin. This is a viable alternative for patients who do not tolerate moderate to high doses of statins or who refuse to comply with such doses.

The efficacy of ezetimibe for reducing risk for cardiovascular morbidity and mortality in patients with established CAD was evaluated in the IMProved Reduction of Outcomes: Vytorin Efficacy International (IMPROVE-IT) Trial [107]. Compared to simvastatin monotherapy, the combination of ezetimibe with simvastatin was associated with a significant 6.5% better reduction in the primary composite endpoint over 7 years of follow-up. In addition, nonfatal MI and ischemic stroke were reduced by 13% and 21%, respectively. The secondary composite endpoint comprised of nonfatal MI, stroke, and cardiovascular mortality was reduced by 10% in the combination therapy group compared to patients receiving simvastatin monotherapy.

3.7.3 Bile Acid-Binding Resins

The bile acid sequestration agents (BASA) are orally administered with anion-exchange resins that bind bile acids in the gastrointestinal tract and prevent them from being reabsorbed into the enterohepatic circulation. These drugs reduce serum LDL-C by two mechanisms: (1) increased catabolism of cholesterol secondary to the upregulation of 7-α-hydroxylase, the rate-limiting enzyme for the conversion of cholesterol into bile acids, and (2) increased expression of LDL receptors on the hepatocyte surface, which augments the clearance of apoB100-containing lipoproteins from plasma.

The clinical benefit of bile acid sequestrants has been demonstrated in several clinical trials, including the Lipid Research Clinics Coronary Primary Prevention Trial [108] and the Familial Atherosclerosis Treatment Study [109]. At maximum doses, the BASA can reduce serum LDL-C by 15–30% and increase HDL-C by 3–5%. It is recommended that these drugs be used in conjunction with a statin whenever possible because BASA therapy increases HMG-CoA reductase activity in the liver, which leads to increased hepatic biosynthesis of cholesterol, thereby offsetting the effects of the BASA over time. Combination therapy with statin and colesevelam hydrochloride has been shown to significantly lower LDL-C levels by up to 34% in patients with hypercholesterolemia [110–112]. The BASA are contraindicated in patients with baseline triglycerides >400 mg/dL since they can exacerbate hypertriglyceridemia.

There are currently three different BASA available. These include cholestyramine (Questran; 4–24 g daily in two to three divided doses daily), colestipol (Colestid; 5–30 g in two to three divided doses daily), and colesevelam (Welchol; 1250 mg two to three times daily). The development of constipation, flatulence, and bloating is relatively frequent, though colesevelam has the most favorable side effect profile

of the three available BASA. Increasing water and soluble fiber ingestion ameliorates some of the difficulty with constipation. The BASA bind negatively charged molecules in a nonspecific manner. Consequently, they can decrease the absorption of warfarin, phenobarbital, thiazide diuretics, digitalis, β-blockers, thyroxine, statins, fibrates, and ezetimibe. These medications should be taken 1 h before or 4 h after the ingestion of BASA. The BASA can reduce the absorption of fat-soluble vitamins.

Colesevelam hydrochloride (HCl) has also been demonstrated to reduce hemoglobin A_{1c} (Hgb A_{1c}) in subjects with type 2 diabetes mellitus by approximately 0.4–0.6% [113–115]. The exact mechanism of action by which BASA decrease glucose levels is not yet fully characterized, though it is believed they impact activity of the nuclear transcription factor, farnesoid X receptor-alpha. This leads to alterations in luminal bile acid composition, increases in the incretins cholecystokinin and glucagon-like peptide-1, effects related to hepatocyte nuclear factor 4-alpha, and reduced gluconeogenesis or increased hepatic glycogen synthesis, potentially mediated through enhanced insulin sensitivity [116]. It is not known whether the glucose-lowering effects of colesevelam HCl reduce risk for microvascular disease in patients with diabetes mellitus; however, any manner by which serum glucose can be safely lowered is likely beneficial.

3.7.4 Fibrates

Fibrates are an important class of drugs for the management of combined dyslipidemia as fibrate-statin combination therapy can be used to promote reductions in LDL-C, non-HDL-C, and triglycerides and simultaneous increases in HDL-C. The fibrates are fibric acid derivatives that exert a number of effects on lipoprotein metabolism. These agents reduce serum triglycerides by 25–50% and raise HDL-C by 10–20%. Fibrates activate lipoprotein lipase by reducing levels of apoprotein CIII (an inhibitor of this enzyme) and increasing levels of apoprotein CII (an activator of lipoprotein lipase). This stimulates the hydrolysis of triglycerides in chylomicrons and VLDL. Fibrates increase HDL-C by two mechanisms. First, the fibrates are PPAR-α agonists and stimulate hepatic expression of apoproteins A-I and A-II. Second, by activating lipoprotein lipase, surface coat mass (phospholipids and apoproteins) derived from VLDL is ultimately used to assimilate HDL in serum. In some patients, fibrate therapy may be associated with an increase in serum LDL-C secondary to increased enzymatic conversion of VLDL to LDL. This effect may diminish over time as the patient increases the expression of hepatic LDL receptors but may also be countered with concomitant LDL-C-lowering therapy with either statins or ezetimibe.

Gemfibrozil (Lopid) therapy is associated with reductions in cardiovascular events. The Helsinki Heart Study was a primary prevention trial in 4081 men 40–55 years of age with a non-HDL cholesterol level > 200 mg/dL and compared gemfibrozil therapy (600 mg po bid) to placebo [117]. The group treated with gemfibrozil experienced an overall 34% reduction in first-time CAD-related events. Among subjects with triglycerides >200 mg/dL and HDL <42 mg/dL, risk decreased nearly 72%, though this was not statistically significant. In the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT), men with CAD and mean LDL-C 111 mg/dL, HDL-C 31 mg/dL, and triglyceride 161 mg/dL were randomized to receive either gemfibrozil (600 mg po bid) or placebo over a 5-year follow-up period. The treatment group experienced a 6% elevation in HDL, no change in LDL, and a 31% decrease in triglycerides [118]. Among patients treated with gemfibrozil, there was a 22% ($p = 0.006$) reduction in the composite endpoint of all-cause mortality and nonfatal myocardial infarction. Treatment with gemfibrozil reduced the risk of stroke and transient ischemic attacks by 31% and 59%, respectively, and decreased the need for carotid endarterectomy by 65%. The diabetic patients in VA-HIT derived the greatest benefit from gemfibrozil therapy, with reductions of 32% in the combined endpoint, 40% in stroke, and 41% in CHD death [119]. The VA-HIT trial was the first to demonstrate a reduction in cardiovascular and cerebrovascular events with an antilipidemic medication independent of changes in serum LDL-C. Most of the benefit of gemfibrozil therapy in this trial was attributed to HDL-C elevation and pleiotropic effects of fibrate therapy.

The Bezafibrate Infarction Prevention (BIP) trial was a secondary prevention trial that compared therapy with bezafibrate (400 mg/day) to placebo in 3122 men and women with a documented history of CHD [120]. Patients were followed for an average of 6.2 years, and the primary endpoints in the BIP trial were fatal or nonfatal myocardial infarction and sudden death. Mean lipid parameters in study subjects included LDL 148 mg/dL, HDL 34.6 mg/dL, and triglycerides 145 mg/dL. The patients given bezafibrate experienced a 5% reduction in LDL-C, a 12% increase in HDL, and a 22% decrease in triglyceride (TG). In the cohort, as a whole, bezafibrate therapy reduced risk for the primary composite endpoint by only 7.3%, which was not significant. However, in a post hoc analysis, among patients with a baseline serum triglyceride >200 mg/dL and HDL <35 mg/dL, bezafibrate therapy reduced the composite endpoint by 41%. If baseline HDL levels were ≥ 35 mg/dL among patients with hypertriglyceridemia, the primary endpoint was reduced 35.9% ($p = 0.33$), which was not statistically significant.

In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial, fenofibrate therapy was shown to decrease the risk of nonfatal MI (24%) and revascularization

(21%), and to reduce the progression of microvascular disease, with a 31% reduction in need for photocoagulation therapy for proliferative retinopathy, a 38% reduction in lower extremity amputation, and a 14% reduction in albuminuria in patients with type 2 diabetes mellitus [121]. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, the addition of fenofibrate to simvastatin therapy in patients with type 2 DM showed no benefit in reduction of acute cardiovascular events [122]. The subgroup of patients with high baseline triglycerides and low HDL-C showed a trend for benefit with a 34% reduction in the primary composite endpoint.

Fibrates have been shown to exert many of the same pleiotropic effects as statins and reduce atheromatous plaque progression in native coronary vessels and in coronary venous bypass grafts [123–126]. Based on the studies discussed above, the optimal clinical scenarios to prescribe fibrates include hypertriglyceridemia and in patients with high triglycerides and low HDL-C. Like the statins, fibrates are associated with a low incidence of myopathy and mild elevations in serum transaminases. Fibrate therapy can increase the risk for cholelithiasis and can raise prothrombin times by displacing warfarin from albumin-binding sites. The periodic monitoring of serum transaminases (6–12 weeks after initiating therapy and twice annually thereafter) is recommended. The three most commonly used fibrates are gemfibrozil (Lopid; 600 mg twice daily), fenofibrate (Tricor; 54 or 160 mg daily), and fenofibric acid (Trilipix; 45 and 135 mg daily). Trilipix is the only fibrate that is approved by the Food and Drug Administration for use in combination with a statin. Bezafibrate is available in Europe and is dosed at 400 mg daily. As gemfibrozil significantly reduces the glucuronidation of statins, which decreases their elimination, there is an increased risk for myopathy/rhabdomyolysis and hepatotoxicity [127, 128]. When used in combination with gemfibrozil, the doses for simvastatin and rosuvastatin should not exceed 10 mg daily. A general consideration for the use of fibrate combination therapy is that fenofibrate and fenofibric acid are safer choices, as neither drug adversely impacts the glucuronidation of statins. The efficacy of a novel fibrate (pemafibrate) used in combination with a statin compared to statin monotherapy is being tested prospectively in patients with diabetes mellitus and high triglycerides/low HDL-C in the Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in patients with diabetes (PROMINENT; clinicaltrials.gov/ct2/show/NCT03071692).

3.7.5 Niacin

Niacin, or nicotinic acid, is a form of vitamin B_3, one of the water-soluble B complex vitamins. Niacin is a potent lipid-modifying agent with broad-spectrum effects, which include reduction of LDL-C, TG, and lipoprotein a (Lp[a]) as well as increasing HDL-C. Evidence of niacin's efficacy in reducing CV events was first demonstrated in the Coronary Drug Project, which showed a 26% reduction in risk of nonfatal myocardial infarction and a 24% reduction in stroke compared to placebo in over 3900 subjects with established CAD [129].

Niacin reduces hepatic VLDL and triglyceride secretion according to two mechanisms: (1) it decreases the flux of fatty acids from adipose tissue to the liver by inhibiting hormone-sensitive lipase activity and (2) it inhibits triglyceride formation within hepatocytes by inhibiting diacylglycerol acyltransferase. Niacin also reduces serum LDL-C concentrations by increasing the catabolism of apoB and increases LDL particle size and decreases LDL particle number.

The use of niacin has decreased quite substantially since the publication of two trials that tested its capacity to provide incremental benefit in endpoint reduction in patients treated with statins. In both the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) [130] and Heart Protection Study-2 THRIVE [131] trials, niacin combined with simvastatin was compared to simvastatin monotherapy. Neither trial demonstrated any discernible benefit of niacin adjuvant therapy compared to statin monotherapy. There is one important caveat for both studies, however. In both of these trials, the lipid profiles of patients were already quite well controlled with LDL-C < 70 mg/dL on statin therapy at baseline. Hence, a trial is still needed that tests the efficacy of niacin adjuvant therapy in patients receiving statin therapy but whose lipids are inadequately controlled [16, 132].

If niacin is used, it should be started at a low dose and gradually titrated upward based on the results of follow-up lipid panels. When evaluated as a function of dose (500–2000 mg daily), extended-release niacin (ER niacin, Niaspan) induces the following changes in serum lipid levels: LDL-C, 3–16% reduction; triglycerides, 5–32% reduction; and HDL-C, 10–24% elevation. It is recommended that Niaspan be the preferred formulation for niacin use as it has the highest available purity, is the best tolerated, and has very low rates of hepatotoxicity [133].

The clinical use of niacin has also been limited by cutaneous flushing, a well-recognized associated adverse effect. Niacin-associated flushing is the major reason for the discontinuation of therapy by patients, estimated at rates as high as 25–40% [134, 135]. The flushing is prostaglandin mediated, and a number of studies have established that moderate doses of prostaglandin inhibitors can reduce the cutaneous flushing response. Extended-release niacin has been demonstrated to result in reduced flushing including decreased

incidence, intensity, and duration as a monotherapy and in statin combination therapy. Measures to reduce flushing include the use of consistent dosing and dosing with meals. Limiting fat intake for 2–3 h before taking niacin also helps as fat is a source of arachidonic acid, the substrate for cyclooxygenase. The use of aspirin has been found to be beneficial in the control of niacin-related flushing, with higher doses of aspirin demonstrating greater efficacy compared to lower-dose aspirin (80 or 160 mg compared to 325 mg) [110]. It can also be advantageous to grind the aspirin and suspend it in clear juice. This provides a much more robust, sudden absorption of aspirin and can provide a more substantial level of inhibition of cyclooxygenase. Taking niacin with applesauce can also reduce flushing, possibly because of the pectin, which further slows rates of niacin absorption.

3.7.6 Fish Oils

The cardiovascular benefits of omega-3 fatty acids contained in fish oils, namely, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been demonstrated as monotherapy as well as in combination with statins [136–138]. The American Heart Association guidelines recommend usage of omega-3 FAs in patients with established CHD (to reduce mortality) and in patients with heart failure and reduced left ventricular ejection fraction [139]. Ingestion of EPA and DHA lowers tissue levels of arachidonic acid by inhibiting its synthesis and by taking its place in membrane phospholipids. In addition, the same enzyme systems that convert arachidonic acid into eicosanoids can utilize EPA to produce eicosanoids that are typically less active than those made from arachidonic acids. As a result, when EPA and DHA are added to the diet, the eicosanoid balance shifts to a less inflammatory, less thrombotic, and less vasoconstrictive state.

A number of clinical trials including the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio (GISSI) Prevenzione trial have established the effect of omega-3 FA on CVD mortality [140]. In the GISSI trial, the use of omega-3 FA (850 mg highly purified EPA + DHA per day) demonstrated a significant reduction in mortality (28%) in 11,323 patients surviving a recent (<3 months) myocardial infarction. An even greater reduction (47%) was noted for risk of sudden death; the difference was seen within 6 months of the start of EPA + DHA [117]. The treatment benefit was sustained throughout the 3.5-year follow-up without serious side effects such as bleeding. Additional evidence of the benefits of omega-3 FA was demonstrated in the Japan EPA Lipid Intervention Study (JELIS) in which nearly 19,000 Japanese men and women, with hypercholesterolemia were prospectively randomized to statin therapy with or without 1800 mg/day of EPA [141]. The combination therapy resulted in an additional 19% reduction in major coronary events at 4.6 years of follow-up compared to statin monotherapy. There were no differences between the statin-only- and statin+EPA-treated patients for LDL-C (26% reduction at 5 years for both groups); however, HDL-C was increased by 3% with statin only and by 5% with statin + EPA, leading the investigators to conclude that the EPA helped prevent CHD events through a cholesterol-independent mechanism.

In the United States, two prescription formulations of omega-3 FAs are FDA approved for the management of severe hypertriglyceridemia. These include (1) omega-3 FA ethyl esters containing both EPE and DHA (Lovaza) and (2) EPA ethyl ester monotherapy (Vascepa). Both are dosed at 4.0 g daily and available in 1.0 g capsules. The availability of these products eliminates concerns about purity (heavy metal contaminants such as mercury, oxidized fatty acid, contaminating cholesterol) and standardization of dosage that are raised with nonprescription omega-3 supplements. One potential advantage of EPA monotherapy is that unlike formulations that combine EPA and DHA, it is not associated with increases in LDL-C in patients with hypertriglyceridemia. Two major clinical trials are underway which are testing the impact of prescription grade omega-3 FA on risk for acute cardiovascular events. These include (1) REDUCE-IT (Reduction of Cardiovascular Events, with EPA - Intervention Trial; clinicaltrials.gov/ct2/show/NCT01492361) and (2) Statin Residual Risk Reduction with EpaNova in High CV Risk Patients with Hypertriglyceridemia (STRENGTH; clinicaltrials.gov/ct2/show/NCT02104817).

3.7.7 Familial Hypercholesterolemia

ApoB is a basic building block of all atherogenic lipoproteins and also serves as a ligand that binds circulating LDL particles (LDL-P) with high affinity to LDLRs on the hepatocyte surface. The LDL-P/LDLR complex is internalized into the hepatocyte and removed from plasma [142–144]. In order for LDL-P/LDLR complex uptake to occur, the complexes must concentrate in clathrin-coated pits within the hepatocyte membrane, a process facilitated by LDLR adaptor protein-1 (LDLRAP1; clathrin-associated sorting protein) [145]. The clathrin is used to form a clathrin-enveloped endosome [146, 147]. Loss-of-function polymorphisms in LDLRAP1 are associated with hypercholesterolemia secondary to reduced LDL-P uptake (autosomal recessive hypercholesterolemia) [148]. PCSK9 regulates expression of LDL-R [149]. The LDL-P/LDLR complex binds PCSK9 at the epidermal growth factor-like repeat A (EGF-A) domain of the LDLR, which labels the complex for proteolytic destruction in the lysosome [150]. If the LDL-P/LDLR complex is not bound to PCSK9, once the LDL-P dissociates from LDLR, it is recycled to the cell membrane for another

round of LDL-P uptake. Genetic polymorphisms that increase expression of PCSK9 are associated with reduced surface expression of LDLR and substantial elevations in LDL-C and LDL-P [151, 152].

Familial hypercholesterolemia (FH) is a heterogeneous genetic disorder characterized by abnormal cholesterol metabolism, elevated serum LDL-C, and substantially heightened risk of premature atherosclerotic disease that is proportional to the magnitude of LDL-C elevation [153]. FH is caused by loss-of-function mutations in the genes that encode LDLR, ApoB, and LDLRAP1 and gain-of-function mutations in PCSK9 [154]. These mutations cause (1) defective LDL receptor function or reduced expression density of LDLR on the cell membrane (2); reduced affinity between ApoB and LDLR, resulting in reduced complex formation (3); deficiency in adaptor protein-1, impairing clathrin-coated endosome formation (4); and increased shuttling of LDLR into the lysosome for destruction.

Heterozygous FH (HeFH) is defined by the National Lipid Association as LDL-C ≥ 160 mg/dL for children and ≥ 190 mg/dL for adults and with at least one first-degree relative affected or with premature CAD or by confirmed genetic testing for an LDL-C-raising gene defect which is best performed by whole gene sequencing of LDLR, apoB, PCSK9, and LDLRAP1 [155]. Homozygous FH (HoFH) is usually characterized by no (rare) or very low levels of expression of functional LDLRs on the surface of hepatocytes and is defined clinically by LDL-C ≥ 400 mg/dL and a history of FH in one or both parents [156, 157]. Most healthcare providers will never see a case, as the prevalence of HoFH is between 1/200,000 and 1/million, depending on geographical location. Patients with HoFH experience severe elevations in risk for premature CAD and can become symptomatic by the second or third decade of life, making early screening and identification extremely important. Patients with FH can present with physical stigmata (corneal arcus, xanthomas, xanthelasmas, heart murmurs, aortic outflow obstruction and heart failure, and premature peripheral and carotid arterial disease). Cascade screening targets the relatives of patients with established FH, should be performed in all first-degree relatives, and is cost-effective [158].

3.7.8 PCSK9 Monoclonal Antibodies

Fully human monoclonal antibodies bind to PCSK9 and induce steric hindrance so that PCSK9 cannot bind to the LDL/LDLR complex [159]. This increases expression of LDLR on the hepatocyte surface, promotes increased clearance of LDL-C, and lowers serum LDL-C levels [149–161] (Fig. 3.10.). Alirocumab is indicated, in addition to diet and maximally tolerated statin therapy, for adult patients with

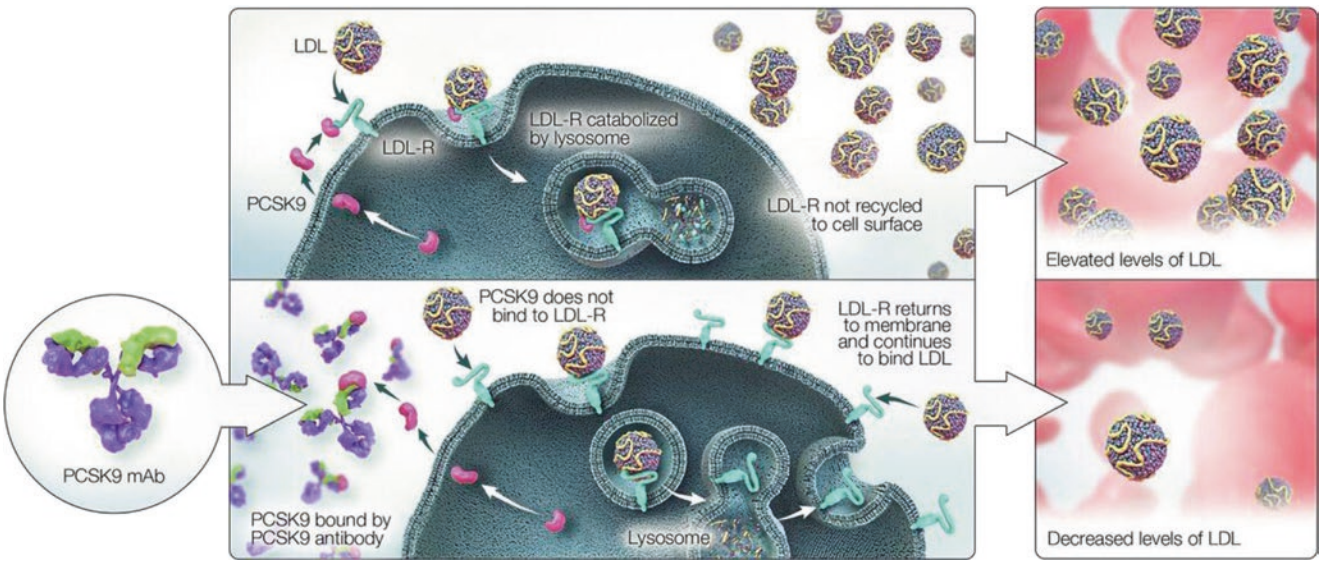


Fig. 3.10 Mechanism of action of PCSK9 inhibition for reducing serum LDL cholesterol. Top panel: PCSK9 secreted by hepatocytes binds to LDLR on the hepatocyte surface. Upon binding of the receptor by an LDL particle, the PCSK9/LDL/LDLR complex is internalized within an endosomal vesicle. Within the cytosol, the endosome fuses with a lysosome, and the PCSK9 chaperones the LDL/LDLR complex into the lysosome for destruction. As a result, the number of LDLRs on the surface of hepatocytes is decreased, resulting in less clearance of LDL from the circulation, and elevated serum LDL concentration. Bottom panel: Monoclonal antibody binds to PCSK9 in the extracellular milieu and prevents it from engaging the LDLR secondary to steric hindrance. In the absence of PCSK9, the LDLR is not routed to the lysosome for degradation and is returned instead to the hepatocyte surface. The recycled LDL-R is available for additional LDL binding and clearance, resulting in decreased levels of LDL. *LDL* low-density lipoprotein, *LDLR* low-density lipoprotein receptor. (Reproduced with permission from [162])

HeFH or clinical ASCVD who require additional lowering of LDL-C. Evolocumab is indicated for use in addition to diet and maximally tolerated statin therapy in adult patients with HeFH, HoFH, or clinical ASCVD who require additional lowering of LDL-C.

Numerous clinical trials have shown that the PCSK9 antibodies significantly reduce LDL-C in patients with primary hyperlipidemia as well as FH [163–172]. Alirocumab can be dosed at 75 mg or 150 mg every 2 weeks or 300 mg every 4 weeks with average reductions (mean reductions minus placebo) in LDL-C of 48%, 58%, and 54%, respectively. When dosed at 75 mg and 150 mg every 2 weeks, alirocumab decreases non-HDL-C by 38% and 50%, apoB by 36% and 51%, and total cholesterol by 31% and 36%, respectively. Evolocumab can be dosed at 140 mg every 2 weeks or 420 mg monthly, with average reductions (mean reductions minus placebo) in LDL-C of 71% and 63%, respectively. When dosed at 140 mg every 2 weeks or 420 mg every 4 weeks, evolocumab decreases non-HDL-C by 58% and 52%, apoB by 55% and 49%, and total cholesterol by 42% and 36%, respectively. Both of these agents have been found to be safe and well tolerated [173, 174]. The most commonly occurring adverse events associated with these drugs are upper respiratory infection, injection site reactions, and flu-like symptoms. Rates of myalgia and transaminase elevations are in the 1% or less range. They do not appear to potentiate new onset diabetes mellitus or neurocognitive deficits. There is no observed tachyphylaxis over time secondary to the generation of autoimmune antibodies observed with either drug.

In the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial, the addition of evolocumab 140 mg every 2 weeks to ongoing statin therapy in 27,564 high-risk patients with established CVD provided a 59% incremental reduction of LDL-C to a median value of 30 mg/dL [175]. The primary (nonfatal MI, stroke, death, need for coronary revascularization, hospitalization for unstable angina) and secondary (nonfatal MI, stroke, and death) endpoints of the study were significantly reduced by 15% and 20%, respectively, with a median 2.4 years of follow-up. Evolocumab therapy was well tolerated. In a substudy of FOURIER, 1974 patients were further evaluated with multiple validated cognitive batteries to ascertain whether or not evolocumab therapy and the attainment of very low levels of LDL-C (<25 mg/dL) were associated with an increased for cognitive abnormalities (EBBINGHAUS study) [176]. No increase in risk for a variety of neurocognitive deficits were discernible over the course of the follow-up period, confirming both the safety of PCSK9 therapy and a lack of harm to patients when their LDL-C is lowered to <25 mg/dL. The efficacy of alirocumab is being evaluated in the ODYSSEY OUTCOMES trial, which includes 18,500 patients with an ACS randomized to alirocumab versus placebo on a statin background. Results are anticipated in 2018 (clinicaltrials.gov/ct2/show/NCT01663402).

3.7.9 Mipomersen

Mipomersen is an antisense oligonucleotide that inhibits the translation of ApoB mRNA to apoB protein. Short, single-stranded synthetic oligonucleotide molecules are used to target specific messenger RNA (mRNA) sequences that code for Apo B-100 (see Fig. 3.11) [177, 178]. The double-stranded polynucleotide formed between ApoB mRNA and mipomersen is hydrolyzed by RNase H within hepatocytes. This substantially reduces the production and secretion of VLDL particles [179, 180]. Mipomersen is only indicated for the treatment of HoFH. It reduces LDL-C approximately 25–37% and is injected subcutaneously on a weekly basis [181, 182]. It is not indicated for the treatment of HeFH or primary hyperlipidemia.

The most common adverse events associated with mipomersen therapy include injection-site reactions (e.g., erythema, pruritus, and pain) and flu-like symptoms (e.g., fatigue, pyrexia, chills, malaise, myalgia, arthralgia) [179]. Mipomersen has been associated with liver toxicity. Elevations in ALT levels are observed, and routine monitoring of liver function studies (including bilirubin, ALT, AST, as well as prothrombin time and partial thromboplastin time) is recommended. Mipomersen therapy is also associated with increased hepatic fat deposition either with or without elevated transaminase levels, which is reversible after cessation of treatment [85, 86]. Hepatic steatosis resulting from mipomersen exposure may heighten risk for steatohepatitis and cirrhosis. Hepatic parenchymal fat content can increase by up to 10%. Mipomersen is available only through a risk education and mitigation strategy (REMS) program due to the risk of hepatotoxicity [86], described in detail at www.kynamrorems.com.

3.7.10 Lomitapide

Microsomal triglyceride transfer protein (MTP) is expressed within the endoplasmic reticulum of hepatocytes. The role of MTP in lipoprotein metabolism is to lipidate ApoB with phospholipid, triglycerides, and cholesteryl esters [183, 184]. Lipid transfer to ApoB results in the production and secretion of VLDL. MTP is thought to promote lipidation of Apo B by at least two mechanisms [184]. The MTP inhibitor lomitapide significantly reduces atherogenic lipoprotein burden in serum [185]. Lomitapide is administered orally and is only approved for the treatment of patients with HoFH as an

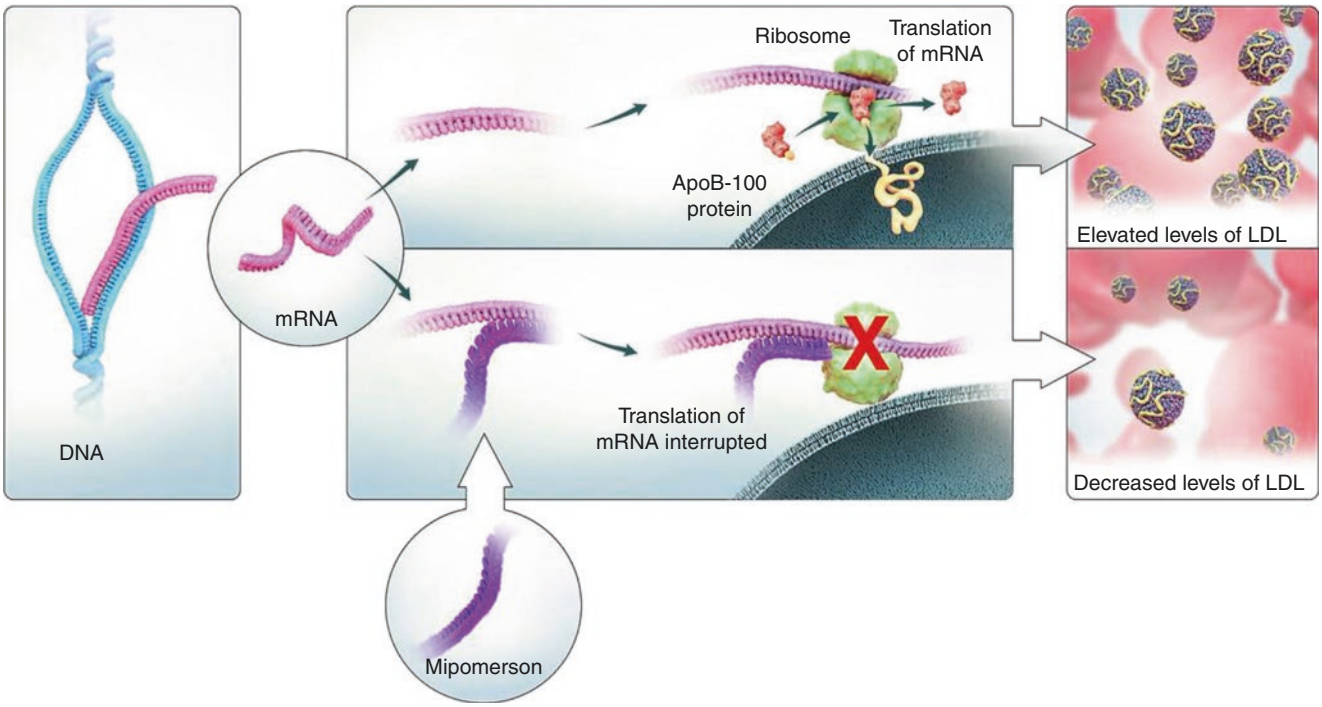


Fig. 3.11 Mechanism of action of mipomersen. Mipomersen is an antisense oligonucleotide that binds to mRNA encoding ApoB-100 protein, an essential scaffold for lipoprotein lipidation and biosynthesis. Interruption of apoB mRNA translation along the endoplasmic reticulum prevents the production of apoB protein, resulting in reduced VLDL production and secretion and decreased LDL formation in serum. LDL, low-density lipoprotein. (Reproduced with permission from [162])

adjunct to diet and other medications [185–187]. The mechanism of action of lomitapide is illustrated in Fig. 3.12.

The efficacy and safety of lomitapide were examined in 29 patients with HoFH [186]. Lomitapide was started at a dose of 5 mg per day, which could be titrated to a maximum of 60 mg day depending on efficacy and safety. Efficacy was evaluated during 26 weeks of follow-up, which was followed by an additional 1-year safety assessment period. Safety assessments included measurement of liver function studies and liver fat evaluation content estimated by magnetic resonance imaging. Mean LDL-C decreased by 50% from baseline at week 26 and remained lower than baseline by 44% at week 56 and 38% at week 78. Mean hepatic fat content increased from 0.9% at baseline to 9.0% at week 26, 7.3% at week 56, and 8.2% at week 78.

Common adverse events associated with lomitapide therapy include diarrhea, nausea, vomiting, dyspepsia, and abdominal pain [90]. Lomitapide can cause elevations in hepatic transaminase levels, and dose adjustment or discontinuation may be required. Increased hepatic steatosis may occur with or without elevated transaminase levels and may also increase risk steatohepatitis and cirrhosis. Due to the risk of hepatic toxicity, lomitapide is available only through a REMS program described at www.juxtapidremsprogram.com.

3.8 Case Studies

3.8.1 Case 1: Heterozygous Familial Hypercholesterolemia

J.D. is a 26-year-old Caucasian male who presents to clinic concerned about his risk for heart disease. His father and two paternal uncles all sustained myocardial infarctions in their early to mid-40s. His paternal grandfather died suddenly of a "heart attack" at age 47. J.D. does not want to suffer a similar fate as he knows that when it comes to family history, history repeats itself. The patient has no symptoms of myocardial ischemia. He runs 3 miles five times weekly. He is on no medications, and his personal past medical history is completely unremarkable. He does not smoke and occasionally drinks one or two glasses of wine. J.D. has a normal physical examination with no xanthomas or infiltrative lipid dermatitis. His blood pressure is 110/70 mmHg, pulse 56 bpm, and respiratory rate 16 per minute. His fasting lipid profile reveals a total cholesterol of 376 mg/dL, LDL-C 300 mg/dL, triglyceride 70 mg/dL, and HDL-C 62 mg/dL. His Framingham risk score is 1%. The patient by risk scoring is low risk, but based on his family history and the fact that he meets criteria for heterozygous familial hypercholesterolemia, he has substantial risk. The patient is advised that it is

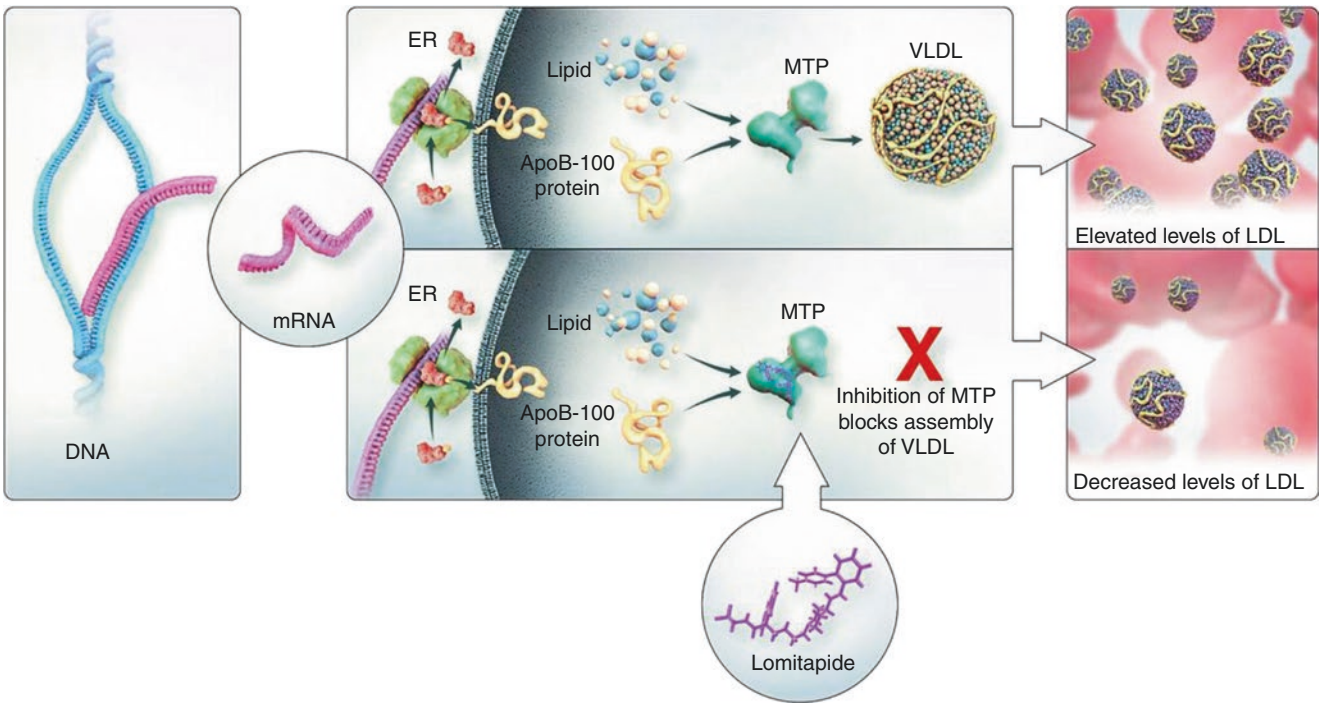


Fig. 3.12 Mechanism of action of lomitapide. MTP lipidates newly translated apoB with phospholipid, triglycerides, and cholesteryl esters, resulting in the formation and secretion of VLDL. Lomitapide, a small-molecule inhibitor of MTP, blocks the formation of VLDL. *LDL* low-density lipoprotein, *MTP* Microsomal triglyceride transfer protein, *VLDL* very low-density lipoprotein. (Reproduced with permission from [162])

extremely important that his LDL-C be lowered aggressively. His markedly elevated LDL-C likely stems from a loss-of-function mutation in the gene for the LDL receptor, resulting in impaired LDL-C clearance from blood. If this is not addressed, he will remain at risk for the development of premature CAD, just like his father and paternal uncles.

The patient is counseled to begin rosuvastatin at 20 mg daily. He understands that statin therapy is associated with risk for skeletal muscle and liver toxicity. After 6 weeks of therapy, his LDL-C decreases to 210 mg/dL. The rosuvastatin is then titrated to 40 mg daily with LDL-C decreasing to 199 mg/dL. The addition of ezetimibe will not help him reach a goal level of <100 mg/dL. He is started on evolocumab at 140 mg every 2 weeks. After 2 months of therapy, his LDL-C decreases to 185 mg/dL. He is tolerating his medications without adverse side effect. J.D. understands that his exercise regimen, attention to diet, and pharmacologic therapy must be lifelong if he is to effectively prevent the development of premature CAD.

3.8.2 Case 2: Severe Hypertriglyceridemia

S.Y. is a 41-year-old African-American female who presents to clinic as a new patient. She just moved to town. She notes that she had an episode of pancreatitis 3 years ago. She was told at the time to take gemfibrozil and to eat a low-fat diet because she had severe hypertriglyceridemia. She was uncomfortable at the time with taking a lipid-lowering medication but did her best to adhere to a low-fat diet as prescribed by a dietitian. She read in a health magazine that pancreatitis causes pancreatic injury and can result in diabetes mellitus, a disease she wishes to avoid at all costs.

Apart from her history of pancreatitis and hypertriglyceridemia, S.Y.'s past medical history is unremarkable. Her father died of an MI at age 47, while her mother is alive and well at age 59. She has no siblings. She does not smoke, and since her episode of pancreatitis strictly avoids alcohol. Blood pressure is 130/78, pulse 80 bpm, and respiratory rate is 14 per minute. Her physical examination is normal with waist circumference of 26 in. A fasting lipid profile shows serum triglyceride to be 4000 mg/dL with HDL-C 32 mg/dL, and LDL-C not calculable because her triglycerides exceed 400 mg/dL. Fasting blood sugar is 89 mg/dL, and her serum electrolytes, renal indices, liver functions, and thyroid profile were all normal.

S.Y. is counseled about the need to normalize her triglycerides as she remains at substantial risk for recurrence of pancreatitis. She understands that she likely has a significant functional lipoprotein lipase deficiency resulting in severely

elevated serum triglyceride levels. She is started on a combination of fenofibric acid 135 mg/dL and Lovaza 4.0 g daily. She is also referred to a dietitian to intensify her dietary restriction of saturated and trans fat. After 8 weeks of this therapy, her triglycerides decrease to 750 mg/dL and HDL-C is 43 mg/dL. She is walking 2.5 miles daily and has severely curtailed her diet. She is willing to take additional medication to lower her triglycerides into a safer range. She is advised to begin the pancreatic lipase inhibitor, orlistat (Xenical), a drug that reduces the absorption of fat within the gastrointestinal tract, with each meal. She understands that this drug can induce the formation of oily, fatty stools with risk for sudden onset diarrhea. After 8 additional weeks, her triglycerides decrease to 210 mg/dL, her HDL-C is 58 mg/dL, and her LDL-C is 120 mg/dL. She is tolerating her pharmacologic regimen. She understands that she must continue her pharmacologic regimen and lifestyle modification lifelong in order to prevent recurrent pancreatitis as well as atherosclerotic disease from her severe baseline dyslipidemia.

3.9 Conclusion

Dyslipidemia remains a major risk factor for CVD and is a leading cause of morbidity and mortality. The treatment of dyslipidemia with lifestyle modification and pharmacologic intervention is associated with significant CVD risk reduction. Statins constitute first-line therapy for the management of both CV risk and dyslipidemia. A variety of adjuvant therapies are also available which can address needs for incremental LDL-C lowering and triglyceride and non-HDL-C reduction. There is no indication for therapeutic effort to raise HDL-C at the present time. Dyslipidemia is a highly modifiable risk factor. Aggressive lipid management for cardiovascular protection is, therefore, crucial to any clinical effort directed at reducing risk for cardiovascular events in both the primary and secondary prevention settings.

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Obesity and Therapeutic Approaches to Weight Loss

4

Robert F. Kushner

4.1 The Burden of Obesity

Weight gain and obesity are becoming the most significant chronic public health conditions of our generation, impacting the well-being, productivity, longevity, and economics of our society. Obesity, along with diet and physical inactivity, is estimated to cause 3.4 million deaths worldwide [1] and lead to future reduction in life expectancy [2]. In 2011–2012, more than two-thirds of US adults were overweight or obese (body mass index [BMI] ≥25 kg/m^2), and 6.4% were severely obese (BMI ≥40 mg/m^2) [3]. The burden of severe obesity is particularly striking among non-Hispanic black women in whom 1 of every 6 have a BMI ≥40 mg/m^2. The etiology of obesity is multifactorial, brought about by an interaction between predisposing genetic and metabolic factors and a rapidly changing environment, one that favors excessive caloric intake while at the same time reducing opportunities to engage in a physically active lifestyle. The net result of the obesity epidemic is a significantly increased total mortality and disease-specific mortality from cardiovascular disease (CVD), some forms of cancers, diabetes, and obstructive sleep apnea among others [4]. Furthermore, the younger the age at onset of obesity along with occurrence of obesity-related morbidity is likely to lead to an increased burden of disability within the obese older population [5–8]. For all of these reasons, it is imperative that clinicians actively evaluate and manage patients with obesity. This chapter reviews the identification, evaluation, and medical management of the adult patient with obesity.

4.2 Assessment of the Patient Who Is Overweight or Obese and Identification of Risk

In recent years, several guidelines and recommendations have been published by professional organizations to assist primary care providers in the assessment and management of their adult patients with obesity [9–12]. Although the documents differ in process, presentation, and scientific rigor, there are common findings and recommendations that bridge the guidelines. These include:

- Obesity is a chronic disease requiring long-term management.
- Patients should be appropriately screened for obesity.
- Practitioners should understand and be prepared to address obesity using a collaborative, shared decision-making approach.
- The use of appropriate treatment modalities should be considered, as indicated.
- Multicomponent interventions are preferred over individual treatments.

The US Preventive Services Task Force (USPSTF) recommends screening all adults for obesity and that patients with a BMI of ≥30 kg/m^2 receive intensive, multicomponent behavioral intervention, either in office or by referral to another practitioner, registered dietitian, or commercial program [13]. The USPSTF also recommends offering or referring overweight and obese adults who have additional CVD risk factors to intensive behavioral counseling interventions to promote a healthy diet and physical activity for CVD prevention [14].

Measuring BMI and waist circumference (for BMI <35 kg/m^2) is a useful strategy to help clinicians identify adult patients at risk for obesity complications. BMI is calculated as weight (kg)/height (m^2) or more conveniently as weight (pounds)/height (inches)^2 × 703. For easy reference,

R. F. Kushner
Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
e-mail: rkushner@northwestern.edu

P. P. Toth, C. P. Cannon (eds.), *Comprehensive Cardiovascular Medicine in the Primary Care Setting*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-319-97622-8_4

Table 4.1 Classification of weight status and disease risk

Classification	Body mass index (kg/m^2)	Obesity class	Disease risk
Underweight	<18.5	–	–
Healthy weight	18.5–24.9	–	–
Overweight	25.0–29.9	–	Increased
Obesity	30.0–34.9	I	High
Obesity	35.0–39.9	II	Very high
Extreme obesity	≥40	III	Extremely high

Source: Adapted from the National Institutes of Health, National Heart, Lung, and Blood Institute: *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults.* U.S. Department of Health and Human Services, US Public Health Service, 1998 [15]

Table 4.2 Obesity-related organ systems review

Cardiovascular	*Respiratory*
Hypertension Congestive heart failure Atrial fibrillation Cor pulmonale Varicose veins Pulmonary embolism Coronary artery disease	Dyspnea Obstructive sleep apnea Hypoventilation syndrome Pickwickian syndrome Asthma
Endocrine	*Gastrointestinal*
Metabolic syndrome Type 2 diabetes Dyslipidemia Polycystic ovarian syndrome (PCOS)/androgenicity Amenorrhea/infertility/menstrual disorders	Gastroesophageal reflux disease (GERD) Nonalcoholic fatty liver disease (NAFLD) Cholelithiasis Hernias Colon cancer
Musculoskeletal	*Genitourinary*
Hyperuricemia and gout Immobility Osteoarthritis (knees and hips) Low back pain	Urinary stress incontinence Obesity-related glomerulopathy End stage renal failure Hypogonadism (male) Breast and uterine cancer Pregnancy complications
Psychological	*Neurologic*
Depression/low self-esteem Body image disturbance Social stigmatization	Stroke Idiopathic intracranial hypertension Meralgia paresthetica
Integument	
Striae distensae (stretch marks) Stasis pigmentation of legs Lymphedema Cellulitis Intertrigo, carbuncles Acanthosis nigricans/skin tags Hidradenitis suppurativa	

most electronic health records (EHR) automatically calculate BMI within the medical record. Table 4.1 is used to define classification of weight status and risk of disease. A desirable or healthy BMI is 18.5–24.9 kg/m^2, overweight is 25–29.9 kg/m^2, and obesity is ≥30 kg/m^2. Obesity is further sub-defined into class I (30.0–34.9 kg/m^2), class II (35.0–39.9 kg/m^2), and class III (≥40 kg/m^2). Corresponding designations are used by ICD-10 for coding and billing purposes. The American Association of Clinical Endocrinologists (AACE) guidelines explicitly recommend using a complication-centric assessment, whereby the presence of obesity comorbidities (such as cardiovascular disease), in addition to anthropometric measures (such as BMI), guides treatment indication, intensification, and goals, with the intent of targeting the most aggressive treatments to those who might derive highest benefit. Symptoms and diseases listed by organ system that are directly or indirectly related to obesity and are used to guide treatment decisions are displayed in Table 4.2.

A waist circumference measurement is recommended for individuals with BMI 25–34.9 kg/m^2 to provide additional information on risk. It is unnecessary to measure waist circumference in patients with BMI ≥35 kg/m^2 because the waist circumference will likely be elevated and will add no additional risk information. The American Heart Association/American College of Cardiology/The Obesity Society (AHA/ACC/TOS) Expert Panel recommends using the cut points (>88 cm [>35 in] for women and > 102 cm [>40 in] for men) as indicative of increased cardiometabolic risk [11]. According to the National Heart, Lung, and Blood Institute (NHLBI) Guide [15, 16], "To measure waist circumference, locate the upper hip bone and the top of the right iliac crest. Place a measuring tape in a horizontal plane around the abdomen at the level of the iliac crest. Before reading the tape measure, ensure that the tape is snug, but does not compress the skin, and is parallel to the floor. The measurement is made at the end of a normal expiration." Overweight persons with waist circumferences exceeding these limits should be urged more strongly to pursue weight reduction. The importance of measuring and documenting waist circumference in patients with a BMI <35 kg/m^2 is due to the independent contribution of abdominal fat to the development of comorbid diseases, particularly the metabolic syndrome [11]. The clinical evaluation of adults with obesity is depicted in Fig. 4.1.

4.2.1 Metabolically Healthy Obesity Phenotype

One of the most intriguing and controversial areas in risk assessment for obesity is the individual who presents as metabolically healthy but obese by BMI standards. It has been recognized for many years that some individuals with obesity did not manifest higher rates of CVD and mortality. This phenotype, called "metabolically healthy obesity (MHO)," is characterized by meeting the standard BMI cut-off point for obesity (≥30 kg/m^2) but regarded as metabolically healthy [17]. Although there is no uniformly agreed

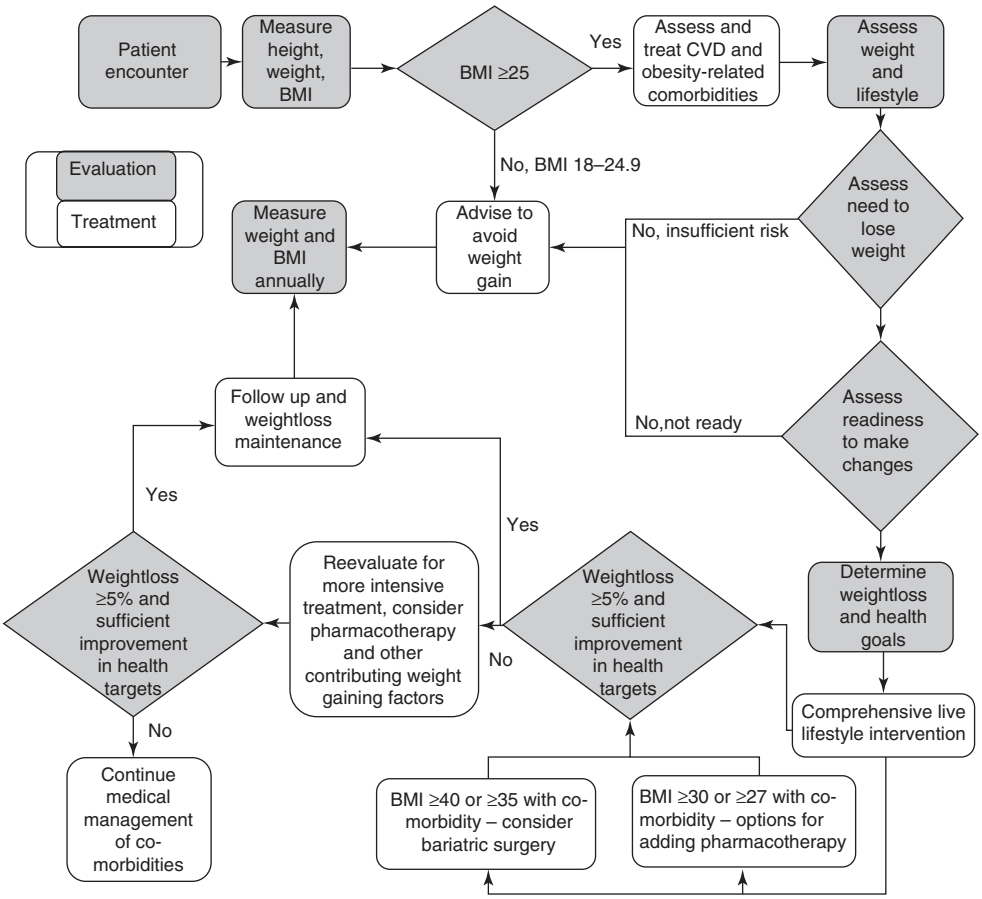

Fig. 4.1 Treatment algorithm – chronic disease management model for primary care of patients with overweight and obesity. (Adapted from AHA/ACC/TOS Obesity guidelines [11])

upon criteria to identify this phenotype, definitions that are commonly used are a measurement of insulin resistance (such as the homeostasis model assessment of insulin resistance, HOMA-IR), various components of the metabolic syndrome according to the ATP III definition, and a marker of inflammation, such as C-reactive protein (CRP) [18]. Additional characteristics of MHO compared to metabolically unhealthy obese are lower levels of visceral and ectopic fat, in particular liver steatosis [19], and a lower degree of systemic inflammation. Due to the diverse definitions of the MHO phenotype, prevalence rates are estimated to vary widely, ranging between 6% and 75% of the population [20, 21].

As an example, cross-sectional data from a sample of 5440 individuals who participated in NHANES 1999–2004 showed that among US adults, 51.3% of overweight adults and 31.7% of adults with obesity were metabolically healthy, defined having 0 or 1 cardiometabolic abnormalities (elevated blood pressure, triglycerides, fasting blood glucose, C-reactive protein, homeostasis model of insulin resistance value, and low HDL cholesterol) [22]. In another study conducted by Stefan et al. [23], 31 of 127 (24%) subjects with obesity were identified as having "metabolically benign obesity," defined by high insulin sensitivity estimated from the OGTT. This insulin-sensitive phenotype was primarily characterized by having less ectopic fat in skeletal muscle and liver and low intima-media thickness (IMT), an early marker of atherosclerosis. Fasting insulin level turned out to be the strongest predictor for identifying the benign phenotype.

Although multiple short-term observational studies suggested that MHO men and women were not at increased risk of CVD and all-cause mortality, longer-term studies suggest that this phenotype may not be a benign condition after all [24, 25]. In a systematic review of eight studies for all-cause mortality and/or cardiovascular events, MHO individuals had an increased risk for events (relative risk 1.24, 95% CI, 1.02–1.55) compared with metabolically healthy normal-weight individuals when only studies with 10 or more years of follow-up were considered [24]. In another meta-analysis of 22 prospective studies, participants with MHO compared with healthy normal-weight participants had a 45% increased risk of cardiovascular events (relative risk of 1.45, 95% CI 1.20–1.70) when analyzed over time [26]. Additionally, in a prospective study of 85 Japanese Americans with MHO followed for over 10 years, nearly 65% converted to a

metabolically unhealthy phenotype [27]. Significant predictors of conversion included dyslipidemia, greater insulin resistance and greater visceral abdominal fat area. Although deemed "healthy" by the metabolic parameters measured, excess weight is often associated with intermediate markers of CVD such as increased carotid artery intima-media thickness, coronary calcification, and impaired vasoreactivity [28, 29]. Thus, for many individuals, MHO should be considered a transient or intermediary state that may progress over time to an unhealthy phenotype.

4.2.2 Staging of Obesity

Efforts are underway to develop more practical and useful assessments to identify patients who require more intense intervention. Analogous to other staging systems commonly used for congestive heart failure or chronic kidney disease, a cardiometabolic disease staging system (CMDS) was developed by Daniel et al. that assign patients to one of five risk categories using quantitative parameters readily available to the clinician [30] without regard to BMI. With advancement from stage 0 to stage 4, there are significant increments in risk and adjusted HR for diabetes, all-cause and CVD-related mortality. Stage 0 would be equivalent to MHO. A refinement of the staging system was incorporated in the recently released Clinical Practice Guidelines for Comprehensive Care of Patients with Obesity issued by the American Society of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) [31]. Using this guideline, obesity disease stage is based on ethnic-specific BMI cutoffs along with assessment for adiposity-related complications. Stage 0 is assigned to individuals who are overweight or obese by BMI classification but have no complications, whereas stages 1 and 2 are defined as individuals who are overweight or obese by BMI classification and having 1 or more mild-moderate complications (stage 1) or at least 1 severe complication (stage 2).

A different functional staging system for obesity was proposed by Sharma and Kushner [32]. Using a risk-stratification construct, called the Edmonton Obesity Staging System (EOSS), individuals with obesity are classified into five-graded categories, based on their morbidity and health-risk profile along three domains – medical, functional, and mental. The staging system was recently shown to predict increased mortality among two large population cohorts [33, 34]. In the first study, mortality data from NHANES III (1988–1994) and NHANES 1999–2004 were analyzed according to the EOSS. Higher scores were a strong predictor of increasing mortality independent of BMI and the presence of metabolic syndrome or hypertriglyceridemic waist. In the second study, mortality data from 5453 men and 771 women who participated in the Aerobics Center Longitudinal Study from the Cooper Clinic were analyzed by EOSS stage. Compared with normal-weight individuals, individuals with obesity in stage 2 or 3 (moderate or severe conditions) had a greater risk of all-cause mortality and cardiovascular-related mortality. After additional adjustment for fitness and dietary factors, only EOSS stage 3 remained significantly associated with elevated all-cause and CVD mortality risk. Future studies will need to determine if the EOSS improves risk stratification over other tools such as the Framingham Risk Score.

4.2.3 Cardiovascular Disease

As seen in Table 4.2, obesity is a risk factor for multiple cardiovascular diseases. In an analysis of cause-specific excess deaths associated with BMI, 13% of total CVD mortality was associated with obesity [4]. Obesity affects the cardiovascular system through multiple known and yet unrecognized mechanisms [35, 36]. The positive association between body weight and blood pressure is well established from multiple epidemiology studies, and weight loss is the cornerstone for non-pharmacological management [37]. The Multi-Ethnic Study of Atherosclerosis (MESA) study showed that the strong relationship between obesity and an increased burden of CVD risk factors is similar in all racial/ethnic and sex groups [38]. As a result of these accumulating risk factors, an increased incidence of atrial fibrillation [39], congestive heart failure [40], and coronary artery disease [41] has been seen among the obese with higher BMI associated with a younger age of first non-ST segment elevation myocardial infarction (NSTEMI) [42]. In addition to traditional risk factors, perhaps the strongest association of obesity with an increased risk of CVD is the occurrence of the metabolic syndrome. The constellation of nontraditional metabolic abnormalities associated with insulin resistance includes increased atherogenic lipoproteins (small dense LDL particles, apolipoprotein B), biomarkers of chronic inflammation (C-reactive protein, tumor necrosis factor-α, interleukin-6), a prothrombotic state (increased plasma plasminogen activator inhibitor (PAI)-1 and fibrinogen), endothelial dysfunction (decreased endothelium-dependent vasodilatation), hemodynamic changes (increased sympathetic nervous activity and renal sodium retention), hyperuricemia, and nonalcoholic fatty liver disease (NAFLD) [43]. Abdominal obesity in particular is more strongly correlated with this cluster of abnormalities [44, 45]. A harmonized definition of the metabolic syndrome utilizing a single set of cut points was previously proposed by a joint statement from multiple organizations [46].

4.3 Medical Management of the Patient Who Is Overweight or Obese

4.3.1 The Goal of Therapy

Information obtained from the history, physical examination, and diagnostic tests is used to determine risk and to develop a treatment plan [47]. The primary goal of treatment is to improve obesity-related comorbid conditions and reduce the risk of developing future comorbidities through lifestyle, pharmacologic, and surgical interventions when indicated. The decision of how aggressively to treat patients and which modalities to use is determined by the patients' risk status, their expectations, and what resources are available. Table 4.3 provides a guide to selecting adjunctive treatments based on BMI category. Therapy for obesity always begins with lifestyle management and may include pharmacotherapy or surgery. Sustained weight loss of as little as 3–5% is likely to result in clinically meaningful reductions in levels of triglycerides, blood glucose, and glycated hemoglobin and in risk of developing type 2 diabetes [11]. Greater amounts of weight loss will reduce blood pressure, improve levels of low-density and high-density lipoprotein cholesterol, and reduce the need for medications to control blood pressure, blood glucose levels, and lipid levels.

The guidelines recommend setting an initial weight loss goal of 10% over 6 months [11]. A meta-analysis of 80 weight loss clinical trials demonstrated that a mean weight loss of 5–8.5 kg (5–9%) was actually observed in clinical practice [48].

4.4 Lifestyle Management

Lifestyle management incorporates the three essential components of obesity care: dietary therapy, physical activity, and behavior therapy.

Since obesity is fundamentally a disease of energy imbalance, all patients must understand how and when energy is consumed (diet), how and when energy is expended (physical activity), and how to incorporate this information into their daily life (behavior therapy).Although intensive behavioral and lifestyle counseling can be effective, it is difficult to implement in the primary care setting [49, 50]. Accordingly, a team approach to obesity care utilizing community and other office-based resources is preferred for effective management. It is recommended that the 5 As framework be used to structure the obesity care encounter: assess, advise, agree, assist, and arrange [51].

4.4.1 Diet Therapy

The primary focus of diet therapy is to reduce overall calorie consumption. The AHA/ACC/ TOS Guidelines [11] recommend initiating treatment with a calorie deficit of 500–750 kcal/d compared with the patient's habitual diet. Alternatively, a diet of 1200–1500 kcal/day for women and 1500–1800 kcal/day for men (adjusted for the individual's body weight) can be prescribed. This reduction is consistent with a goal of losing ~1–2 lbs. per week. The calorie deficit can be instituted through dietary substitutions or alternatives. Examples include choosing smaller portion sizes, eating more fruits and vegetables, consuming more whole-grain cereals, selecting leaner cuts of meat and skimmed dairy products, reducing consumption of fried foods and other foods with added fats and oils, and drinking water instead of sugar-sweetened beverages. It is important that dietary counseling remains patient centered and that the selected goals are SMART (specific, measurable, agreed upon, realistic, and timely).

Since portion control is one of the most difficult strategies for patients to manage, use of pre-prepared products, called meal replacements, is a simple and convenient suggestion. Meal replacements are foods that are designed to take the place of a meal while at the same time providing nutrients and good taste within a known caloric limit [52]. Examples include frozen entrees, canned beverages, and bars. In a meta-analysis of six studies with a study duration ranging from 3 to 5 months, use of partial meal replacements resulted in a 7–8% weight loss [53]. Incorporation of meal replacements as a portion control strategy has also

Table 4.3 A guide to selecting treatment

BMI category	25–26.9	27–29.9	30–35	35–39.9	≥40
Treatment					
Diet, exercise, behavior therapy	With comorbidities	With comorbidities	+	+	+
Pharmacotherapy		With comorbidities	+	+	+
Surgery				With comorbidities	+

Source: NHLBI and NAASO *The Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*. US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung, and Blood Institute. NIH Publication No. 00–4084, October, 2000 [16]

been successfully used in the Look AHEAD study, where average weight loss among patients with type 2 diabetes was 8.6% of initial weight after 1 year of treatment [54]. If meal replacements are used, the patient will need to consider the sodium and sugar content of the products selected since they can vary widely. Beyond prescribing a calorie-controlled diet, an ongoing clinical and research question is the importance of the macronutrient diet content, such as low-carbohydrate, high-protein, or a Mediterranean dietary pattern. However, a systematic literature review performed by the AHA/ACC/TOS Guideline found no superiority for any of the 17 diets reviewed. Similarly, a network meta-analysis of popular, named diets found little difference between individual diets in a much as any diet resulted in weight loss as long as the patient maintained adherence [55]. Clinicians in primary care should prescribe a diet to achieve reduced caloric intake, as part of a comprehensive lifestyle intervention. This does not mean that diet composition is not important. However, without negative energy balance, weight loss will not occur. The clinician should consider the patient's health status in recommending diet composition, as well as the patient's personal preferences about food choices.

4.4.2 Physical Activity Therapy

Although exercise alone is only moderately effective for weight loss, the combination of dietary modification and exercise is the most effective behavioral approach for treatment of obesity. In contrast, the most important role of exercise appears to be in the maintenance of the weight loss [56]. Physical activity is beneficial for improved cardiorespiratory fitness, cardiovascular disease, and cancer risk reduction and improved mood and self-esteem. The 2008 Physical Activity Guidelines for Americans recommends engaging in 2 h and 30 min/week of moderate intensity physical activity [57]. Focusing on simple ways to add physical activity into the normal daily routine, such as walking, using the stairs, doing home and yard work, and increasing recreational activity, is a useful first step in counseling. Studies have demonstrated that lifestyle activities are as effective as structured exercise programs in improving cardiorespiratory fitness [58] and weight loss [59]. The American College of Sports Medicine (ACSM) recommends that individuals who are overweight or obese progressively increase to a minimum of 150 min of moderate intensity physical activity per week as a first goal [60]. However, for long-term weight loss, higher amounts of exercise (e.g., 200–300 min/week or ≥2000 kcal/week) are needed. The ACSM also recommends that resistance exercise supplements the endurance exercise program. Many patients would benefit from consultation with an exercise physiologist or personal trainer.

4.4.3 Behavioral Therapy

Implementing sustainable changes in the patient's diet and physical activity patterns is the most challenging feature of obesity care. Multiple behavioral modification theories and techniques have been applied to obesity with mostly modest outcomes. The most commonly used approaches include motivational interviewing [61], transtheoretical model and stages of change [62], and cognitive behavioral therapy (CBT) [63]. These techniques can be learned and used by physicians, but they do take time. In the setting of a busy practice, they are probably more reasonably applied by ancillary office staff such as a nurse clinician, midlevel provider, or registered dietitian. Nonetheless, a few key behavioral principles should be utilized when possible. It is important to recognize that increasing knowledge by itself does not seem to be useful in promoting behavioral change.

CBT incorporates various strategies intended to help change and reinforce new dietary and physical activity behaviors [64]. Strategies include self-monitoring techniques (e.g., journaling, weighing and measuring food, and activity), stress management, stimulus control (e.g., using smaller plates, not eating in front of the television or in the car), social support, problem solving, and cognitive restructuring, i.e., helping patients develop more positive and realistic thoughts about themselves. When recommending any behavioral lifestyle change, have the patient identify what, when, where, and how the behavioral change will be performed, and have the patient and yourself keep a record of the anticipated behavioral change and follow-up progress at the next office visit. Among the behavioral strategies, self-monitoring of food records has repeatedly been shown to be a significant predictor of greater weight loss [65, 66].

4.5 Pharmacotherapy

Adjuvant pharmacological treatments should be considered for patients with a BMI ≥30 kg/m^2 or with a BMI ≥27 kg/m^2 who also have concomitant obesity-related risk factors or diseases and for whom dietary and physical activity therapy has not been successful (Table 4.3). Anti-obesity drugs require the implementation of lifestyle modification as a foundation for drug action due to the importance of the drug-behavior interaction. Whether the medication acts centrally to suppress appetite or peripherally to block the absorption of fat, patients must deliberately and consciously alter their behavior for weight loss to occur. In other words, for all anti-obesity drugs, the pharmacological action must be *translated* into behavior change. In a randomized trial by Wadden et al. [67], evaluating the benefits of lifestyle modification in the pharmacologic treatment of obesity, investigators showed that the efficacy of sibutramine-induced mean weight loss at

1 year was significantly enhanced when subjects also attended a lifestyle support group (−10.8%) or lifestyle support group plus portion-controlled diet (−16.5%) versus sibutramine alone (−4.1%). Thus, when prescribing an antiobesity medication, patients must be actively engaged in a lifestyle program that provides the strategies and skills needed to effectively use the drug.

The Endocrine Society recently published guidelines on the *Pharmacological Management of Obesity* [68]. Core recommendations include the following:

- Prescribe pharmacotherapy for obesity as an adjunct to diet, exercise, and behavior modification for individuals with BMI ≥30 kg/m^2 or >27 kg/m^2 with at least one comorbidity, who are unable to lose and successfully maintain weight, and who meet label indications.
- Continue pharmacotherapy if the patient has lost at least 5% of initial body weight within 3 months of use; if not, discontinue and seek alternative approaches.
- In patients with uncontrolled hypertension and/or history of CVD, do not use sympathomimetic agents.
- Use weight-losing and weight-neutral medications as first- and second-line therapy, and discuss potential weight gain effects of medications with patients.
- Use a shared decision-making process in selecting medications, providing patients with estimates of weight effects of medications.

There are several potential targets of pharmacological therapy for obesity, all based on the concept of producing a sustained negative energy (calorie) balance. Four new antiobesity medications have been approved by the US Food and Drug Administration (FDA) for weight loss and maintenance of weight loss since 2012: lorcaserin, phentermine/topiramate (PHEN/TPM) extended release, naltrexone sustained release (SR)/bupropion SR, and liraglutide.

4.5.1 Centrally Acting Anorexiant Medications

Appetite-suppressing drugs, or anorexiants, effect *satiation*, the processes involved in the termination of a meal; *satiety*, the absence of hunger after eating; and *hunger*, a biological sensation that initiates eating. The primary target site for the actions of anorexiants is the ventromedial and lateral hypothalamic regions in the central nervous system. The classical sympathomimetic adrenergic agents (benzphetamine, phendimetrazine, diethylpropion, mazindol, and phentermine) function by either stimulating norepinephrine release or blocking its reuptake. Among the anorexiants, phentermine is the most commonly prescribed; there is limited long-term data on its effectiveness. A 2002 review of six randomized, placebo-controlled trials of phentermine for weight control found that patients lost 0.6–6.0 additional kilograms of weight over 2–24 weeks of treatment. The most common side effects of the amphetamine-derived anorexiants are restlessness, insomnia, dry mouth, constipation, and increased blood pressure and heart rate.

PHEN/TPM is a combination drug that contains a catecholamine releaser (phentermine) and an anticonvulsant (topiramate). Topiramate is approved by the FDA as an anticonvulsant for the treatment of epilepsy and for the prophylaxis of migraine headaches. The weight loss associated with topiramate was identified as an unintended side effect of the drug during clinical trials for epilepsy. The mechanism responsible for weight loss is uncertain but is thought to be mediated through the drug's modulation of γ-aminobutyric acid receptors, inhibition of carbonic anhydrase, and antagonism of glutamate. PHEN/TPM has undergone two 1-year pivotal randomized, placebo-controlled, double-blind trials of efficacy and safety: EQUIP and CONQUER [69, 70]. In a third study, SEQUEL, 78% of CONQUER participants continued to receive their blinded treatment for an additional year [71]. All participants received diet and exercise counseling. Participant numbers, eligibility, characteristics, and weight loss outcomes are displayed in Table 4.4. Intention-to-treat 1-year placebo-subtracted weight loss for PHEN/TPM was 9.3% (15-mg/92-mg dose) and 6.6% (7.5-mg/46-mg dose), respectively, in the EQUIP and CONQUER trials. Clinical and statistical dose-dependent improvements were seen in selected cardiovascular and metabolic outcome measurements that were related to the weight loss. The most common adverse events experienced by the drug-randomized group were paresthesias, dry mouth, constipation, dysgeusia, and insomnia. Because of an increased risk of congenital fetal oral-cleft formation from topiramate, women of childbearing age should have a negative pregnancy test before treatment and monthly thereafter and use effective contraception consistently during medication therapy.

Lorcaserin is a selective serotonin (5-hydroxytryptamine, 5-HT)2$_C$ receptor agonist with a functional selectivity ~15 times that of 5-HT2$_A$ receptors and 100 times that of 5-HT2$_B$ receptors. This selectivity is important, since the drug-induced valvulopathy documented with two older serotonergic agents that were removed from the market – fenfluramine and dexfenfluramine – was due to activation of the 5-HT2$_B$ receptors expressed on cardiac valvular interstitial cells. By activating the 5-HT2$_C$ receptor, lorcaserin is thought to decrease food intake through the pro-opiomelanocortin (POMC) system of neurons.

Lorcaserin has undergone two randomized, placebo-controlled, double-blind trials for efficacy and safety [72, 73]. Participants were randomized to receive lorcaserin (10 mg bid) or placebo in the BLOOM study and to receive lorcaserin (10 mg bid or qd) or placebo in the BLOSSOM

Table 4.4 Clinical trials for Anti-obesity medications

		PHEN/ TPM		Lorcaserin		Naltrexone SR/ bupropion SR		Liraglutide	
	EQUIP	CONQUER	BLOOM	BLOSSOM	COR-I	COR-II	COR-BMOD	SCALE	SCALE maintenance
No. of participants (ITT-LOCF)	1230	2487	3182	4008	1742	1496	793	3731	422
BMI (kg/m2)	≥35	27–45	27–45	30–45	30–45	30–45	30–45	≥27	≥27
Age (yrs)	18–70	18–70	18–65	18–65	18–65	18–65	18–65	≥18	≥18
Comorbid conditions (cardiovascular and metabolic)	≥1	≥2	≥1	≥1	≥1	≥1	≥1	≥1	
Mean weight loss (%) with treatment vs placebo	10.9 vs 1.6	7.8 vs 1.2	5.8 vs 2.2	4.8 vs 2.8	6.1 vs 1.3	6.5 vs 1.9	9.3 vs 5.1	8.0 vs 2.6	6.2 vs 0.2
Placebo-subtracted weight loss (%)	9.3	6.6	3.6	3.0	4.8	4.6	4.2	5.4	6.0
Categorical change in 5% weight loss with treatment vs placebo	66.7 vs 17.3	62 vs 21	47.5 vs 20.3	47.2 vs 25	48 vs 16	50.5 vs 17.1	66.4 vs 42.5	63.2 vs 27.1	81.4 vs 48.9
Study completion rate, treatment vs placebo (%)	66.4 vs 52.9	69 vs 57	55.4 vs 45.1	57.2 vs 52	50	54	57.9 vs 58.4	71.9 vs 64.4	75 vs 69.5

study. All participants received diet and exercise counseling. Participant numbers, eligibility, characteristics, and weight loss outcomes are displayed in Table 4.4. Subjects who were overweight or obese had at least one coexisting condition (hypertension, dyslipidemia, cardiovascular disease, impaired glucose tolerance, or sleep apnea) – medical conditions that are commonly seen in the office setting. Intention-to-treat 1-year placebo-subtracted weight loss was 3.6% and 3.0%, respectively, in the BLOOM and BLOSSOM trials. Echocardiography was performed at the screening visit and at scheduled time points over the course of the studies. There was no difference in the development of FDA-defined valvulopathy between drug-treated and placebo-treated participants at 1 year or 2 years. Modest statistical improvements consistent with the weight loss were seen in selected cardiovascular and metabolic outcome measurements. The most common adverse events experienced by the drug group were headache, dizziness, and nausea.

Naltrexone SR/bupropion SR (NB) is a combination of an opioid antagonist and a mild reuptake inhibitor of dopamine and norepinephrine, respectively. Individually, naltrexone is approved by the FDA for the treatment of alcohol dependence and for the blockade of the effects of exogenously administered opioids, whereas bupropion is approved as an antidepressant and smoking cessation aid. As a combination drug, each component works in consort: bupropion stimulates secretion of α-melanocyte-stimulating hormone (MSH) from POMC, whereas naltrexone blocks the feedback inhibitory effects of opioid receptors activated by the β-endorphin released in the hypothalamus, thus allowing the inhibitory effects of MSH to reduce food intake.

The medication has undergone three randomized, placebo-controlled, double-blind trials for efficacy and safety [74–76]. Participants were randomized to receive NB (8-mg/90-mg two tablets bid) or placebo in the three COR studies. Whereas participants received standardized nutritional and exercise counseling in COR-I and COR-II, a more intensive behavior modification program was provided in COR-BMOD. Participant numbers, eligibility, characteristics, and weight loss outcomes are displayed in Table 4.4. Subjects were overweight or obese with concomitant controlled hypertension and/or dyslipidemia. Intention-to-treat 1-year placebo-subtracted weight loss was 4.8%, 5.1%, and 4.2%, respectively, in the COR-I, COR-II, and COR-BMOD trials. Clinical and statistical dose-dependent improvements were seen in selected cardiovascular and metabolic outcome measurements that were related to the weight loss. However, the medication led to slight increased or smaller decreases in blood pressure and pulse than placebo. The most common adverse events experienced by the drug-randomized groups were nausea, constipation, headache, vomiting, dizziness, diarrhea, insomnia, and dry mouth.

Liraglutide, the fourth new medication, is a glucagon-like peptide-1 (GLP-1) analogue with 97% homology to human GLP-1 that was previously approved for the treatment of type 2 diabetes at doses up to 1.8 mg once daily. In addition to its effect as an incretin hormone (glucose-induced insulin secretion), liraglutide inhibits both gastric

emptying and glucagon secretion and stimulates GLP-1 receptors in the arcuate nucleus of the hypothalamus to reduce feeding.

Liraglutide has undergone three randomized, placebo-controlled, double-blind trials for efficacy and safety [77–79]. Participants were randomized to receive liraglutide (3.0 mg subcutaneously daily) or placebo for initial weight loss in the SCALE (patients without diabetes) and SCALE Diabetes (patients with diabetes) studies or for weight maintenance after initial weight loss (SCALE Maintenance). All participants received diet and exercise counseling. Participant numbers, eligibility, characteristics, and weight loss outcomes are displayed in Table 4.4. For SCALE and SCALE Maintenance, subjects were overweight or obese and had treated or untreated hypertension or dyslipidemia. Intention-to-treat 1-year placebo-subtracted weight loss was 5.4% and 6.1%, respectively, in the SCALE and SCALE Maintenance trials. Clinical and statistical dose-dependent improvements were seen in selected cardiovascular and metabolic outcome measurements; however, there is a small increase in heart rate. The most common adverse effects include nausea, diarrhea, constipation, and vomiting. GLP-1 agonists should not be prescribed in patients with a family or personal history of medullary thyroid cancer or multiple endocrine neoplasia.

Although treatment response for these medications was presented as intention-to-treat placebo-subtracted mean percent weight loss at 1 year, differences in outcome between drug and placebo is also commonly expressed as categorical weight loss, i.e., percent of individuals who achieve 5% or 10% weight loss. Results for the four new medications using categorical outcomes are presented in Table 4.4. It is also important to note that there is significant individual variability in weight loss.

In approving the four new anti-obesity medications, the FDA introduced a new provision with important clinical relevance: a prescription trial period to assess effectiveness. Response to these medications should be assessed after 12 weeks of treatment for PHEN/TPM and lorcaserin (or 16 weeks for naltrexone SR/bupropion SR and liraglutide since these medications are up-titrated during the first month). Determining responsiveness at 3 or 4 months is based on the post hoc observed trial data that subjects who did not lose a pre-specified amount of weight early in treatment were less successful at 1 year. For PHEN/TPM, if the patient has not lost at least 3% of body weight at 3 months, the clinician can either escalate the dose and reassess progress at 6 months or discontinue treatment entirely. For lorcaserin and naltrexone SR/bupropion SR, the medication should be discontinued if the patient has not lost at least 5% of body weight. The corresponding responsive target for liraglutide is a 4% weight loss.

4.5.2 Peripherally Acting Medication

Orlistat (Xenical™) is a synthetic hydrogenated derivative of a naturally occurring lipase inhibitor, lipostatin, produced by the mold *Streptomyces toxytricini*. Orlistat is a potent slowly reversible inhibitor of pancreatic, gastric, and carboxyl ester lipases and phospholipase A_2, which are required for the hydrolysis of dietary fat in the gastrointestinal tract into fatty acids and monoacylglycerols. The drug's activity takes place in the lumen of the stomach and small intestine by forming a covalent bond with the active serine residue site of these lipases [80]. Taken at a therapeutic dose of 120 mg tid, orlistat blocks the digestion and absorption of about 30% of dietary fat. The medication was approved by the FDA in 2007 for over-the-counter use at half the prescription dose, trade name Alli™.

A meta-analysis of clinical trials found that orlistat produced a weighted mean weight loss of 5.7 kg (12.6 lb) compared with 2.4 kg (5.3 lb) in the placebo group [81]. Pooled data have also shown that early weight loss (>5% of initial weight after 3 months) predicts weight loss at 18 months. In the longest published follow-up study, mean weight loss after 4 years for the orlistat-treated patients was 5.8 kg (12.8 lb) compared to 3.0 kg (6.6 lb) with placebo [82]. Since orlistat is minimally (<1%) absorbed from the gastrointestinal tract, it has no systemic side effects. Tolerability to the drug is related to the malabsorption of dietary fat and subsequent passage of fat in the feces. Six gastrointestinal tract adverse effects have been reported to occur in at least 10% of orlistat-treated patients: oily spotting, flatus with discharge, fecal urgency, fatty/oily stool, oily evacuation, and increased defecation. The events are generally experienced early, diminish as patients control their dietary fat intake, and infrequently cause patients to withdraw from clinical trials. Psyllium mucilloid is helpful in controlling the orlistat-induced GI side effects when taken concomitantly with the medication [83]. Serum concentrations of the fat-soluble vitamins D and E and β-carotene have been found to be significantly lower in some of the trials, although generally remain within normal ranges. The manufacturer's package insert for orlistat recommends that patients should take a vitamin supplement along with the drug to prevent potential deficiencies.

4.6 Bariatric Surgery

Bariatric surgery should be considered for patients with severe obesity (BMI ≥40 kg/m^2) or those with moderate obesity (BMI ≥35 kg/m^2) associated with a serious medical condition. According to the AHA/ACC/TOS Guideline [11] patients who are motivated to lose weight and who have not responded to behavioral treatment with or without

pharmacotherapy with sufficient weight loss to achieve targeted health outcome goals should be advised that bariatric surgery may be an appropriate option to improve health. Furthermore, they should be offered referral to an experienced bariatric surgeon for consultation and evaluation.

Weight loss surgeries have traditionally been classified into three categories: restrictive, restrictive-malabsorptive, and malabsorptive. However, newer understanding of the physiological and metabolic mechanisms of action has called this classification into question. Nonetheless, in order to appreciate the nutritional implications and consequences of the surgical procedures, using the traditional classification seems reasonable and will be used below.

4.6.1 Restrictive Surgeries

Restrictive procedures limit the amount of food the stomach can hold and slow the rate of gastric emptying. The vertical banded gastroplasty (VBG) is the prototype of this category but is no longer performed due to limited effectiveness in long-term trials. Laparoscopic adjustable gastric banding (LAGB) replaced the VBG and was responsible for a significant increase in the number of procedures performed after 2000. The first banding device, the LAP-BAND, was approved for use in the United States in 2001. A second device, the REALIZE band, was approved in the United States in 2007. In contrast to previous devices, the diameter of these bands is adjustable by way of their connection to a reservoir that is implanted under the skin. Injection or removal of saline into the reservoir tightens or loosens the band's internal diameter, respectively, thus changing the size of the gastric opening. Because there is no rerouting of the intestine with LAGB, the risk for developing nutritional deficiencies is entirely dependent on the patient's diet and eating habits. More recently, the laparoscopic sleeve gastrectomy (LSG) has replaced the LAGB as the most commonly performed operation among academic medical centers, accounting for 61% of all procedures in 2014 [84]. In this procedure, the stomach is restricted by stapling and dividing it vertically and removing approximately 80% of the greater curvature, leaving a slim "banana-shaped" remnant stomach along the lesser curvature. However, unlike the VBG or LAGB, removal of a portion of the stomach results in changes in hormonal metabolism that are similar to the restrictive-malabsorptive procedures described below.

4.6.2 Restrictive-Malabsorptive Surgeries

The restrictive-malabsorptive bypass procedure combines the elements of gastric restriction and selective malabsorption. The Roux-en-Y gastric bypass (RYGB) is the most commonly performed procedure in this class. It involves formation of a 10- to 30-ml proximal gastric pouch by surgically separating the stomach across the fundus. Outflow from the pouch is created by performing a narrow (10 mm) gastrojejunostomy. The distal end of jejunum is then anastomosed 50–150 cm below the gastrojejunostomy. "Roux-en-Y" refers to the Y-shaped section of small intestine created by the surgery; the Y is created at the point where the pancreatobiliary conduit (afferent limb) and the Roux (efferent) limb are connected. "Bypass" refers to the exclusion or bypassing of the distal stomach, duodenum, and proximal jejunum. RYGB is most commonly performed laparoscopically.

4.6.3 Malabsorptive Surgeries

There are two malabsorptive procedures. In the biliopancreatic diversion (BPD), a subtotal gastrectomy is performed, leaving a much larger gastric pouch compared with the RYGB. The small bowel is divided 250 cm proximal to the ileocecal valve and connected directly to the gastric pouch, producing a gastroileostomy. The remaining proximal limb (biliopancreatic conduit) is then anastomosed to the side of the distal ileum 50 cm proximal to the ileocecal valve. In this procedure, the distal stomach, duodenum, and entire jejunum are bypassed, leaving only a 50-cm distal ileum common channel for nutrients to mix with pancreatic and biliary secretions. The biliopancreatic diversion with duodenal switch (BPDDS) is a variation of the BPD that preserves the first portion of the duodenum. In this procedure, a vertical subtotal gastrectomy is performed and the duodenum is divided just beyond the pylorus. The distal small bowel is connected to the short stump of the duodenum, producing a 75- to 100-cm ileal-duodenal "common channel" for the absorption of nutrients. The other end of the duodenum is closed, and the remaining small bowel is connected onto the enteral limb approximately 75–100 cm from the ileocecal valve.

4.6.4 Clinical Aspects

4.6.4.1 Weight Loss

Several meta-analyses and systematic reviews of bariatric surgery outcomes have been conducted [85–88]. In general, weight loss is greatest with the malabsorptive procedures (BPD and BPDDS), followed by the restrictive-malabsorptive procedure (RYGB), the LSG, and least with the restrictive LAGB procedure. As compared to standard care, differences in BMI levels from baseline at year 1 are −11.3 kg/m^2 for BPD, −9.0 kg.m^2 for RYGB, −10.1 kg/m^2 for LGS, and −2.4 kg.m^2 for LAGB [88]. Weight loss at 2–3 years

following a surgical procedure varies from a mean of 20–34% of total weight depending on the procedure. The trajectory of weight loss also differs between procedure types. Whereas the rate of weight loss is slower with LAGB, with maximal weight loss achieved after 2 or 3 years, maximal weight loss with RYGB and LSG is achieved at 12–18 months [89, 90].

4.6.4.2 Effects on Comorbidities

A systematic review and meta-analysis of randomized controlled trials and nonrandomized controlled studies comparing bariatric surgery versus no surgery showed that surgery was associated with a reduced odds ratio (OR) risk of all-cause mortality (OR = 0.55), cancer (OR 0.74), cardiovascular events (OR = 0.71), and stroke (OR 0.66) [91]. Significant improvement in multiple obesity-related comorbid conditions has been reported, including type 2 diabetes, hypertension, dyslipidemia, obstructive sleep apnea, and quality of life [92]. The beneficial effect of weight loss surgery on type 2 diabetes is particularly striking [93–95]. Several randomized controlled studies have demonstrated greater rates of partial or complete disease remission and reduced the use of anti-diabetes medications after 3 years of follow-up [96, 97]. Rates are greater following BPD, RYGB, or LSG than following LAGB, and the extent of remission is influenced by the amount of weight loss, weight regain, duration of diabetes, and the pre-surgery hypoglycemic therapy requirements [98]. The mechanisms of the greater antidiabetic effect following RYGB are primarily thought to involve caloric restriction, enhanced release of the GLP-1, along with alterations of bile acid metabolism and the microbiota [99].

Although the clinical benefits of surgery are well documented, many of the weight loss surgeries, most notably the combined restrictive-malabsorptive surgical procedures, place patients at high risk for development of both macro- and micronutrient deficiencies unless they are properly counseled and supplemented. Because most of the deficiencies can be identified early at a preclinical stage, early treatment will prevent or reduce symptoms and deficiency syndromes [100]. The restrictive-malabsorptive procedures produce a predictable increased risk for micronutrient deficiencies of vitamin B_{12}, iron, folate, calcium, and vitamin D based on surgical anatomical changes. The patients require lifelong supplementation with these micronutrients [101].

4.7 Case Study

SC is a 52-year-old postmenopausal woman with a BMI of 30 kg/m^2 who is frustrated about the 15 lb. weight gain and change in body shape (increased waist circumference) that occurred over the past 5 years. She has developed hypertension, stress urinary incontinence, and GERD. She tries to follow a healthy diet but is unable to control her body weight. She turns to you for help.

The initial goal of treatment is to educate SC about the importance of balancing caloric intake with caloric expenditure. SC should track her dietary intake recording the types, portions, and calories of foods and beverages consumed. She should also set an initial goal of engaging in 150 min/week of moderate intensity physical activity. By helping SC become more calorie conscious, she will feel in control of her body weight and learn to self-regulate her diet and physical activity.

4.8 Case Study

DA is a 38-year-old woman with a BMI of 36 kg/m^2 who presents with a cycling, ratcheting weight gain over the past 15 years. She previously participated in several commercial weight management programs, losing up to 20 lbs., but always followed by weight regain. She also saw a registered dietitian 2 years ago. DA has a history of type 2 diabetes treated with metformin and glipizide. Her most current hemoglobin A1c is 7.8%.

DA is a good candidate for consideration of anti-obesity medication that will target both her obesity and type 2 diabetes. Although any of the FDA-approved medications would be beneficial, liraglutide is particularly attractive based on its independent incretin effects. Treatment would begin with 0.6 mg sc daily along with weekly titration up to either 1.8 mg or 3.0 mg, depending upon treatment goals. Glipizide, a sulfonylurea, should also be discontinued since it is associated with weight gain and increased incidence of hypoglycemia during weight loss. The patient should be counseled on occurrence of the most common side effects of liraglutide that include nausea, diarrhea, constipation, and vomiting.

4.9 Case Study

AK is a 42-year-old man with severe obesity (BMI of 42 kg/m^2). He has a 10 year history of type 2 diabetes treated with insulin, obstructive sleep apnea treated with nightly CPAP, hypertension, and mixed hyperlipidemia. He has experienced a progressive weight gain since childhood and has been unable to control his body weight despite enrollment in several commercial weight loss programs.

AK should consider weight loss surgery as a treatment for his obesity and obesity-related comorbid conditions. He will need to be evaluated by the bariatric surgical team consisting of a registered dietitian, clinical psychologist, and bariatric surgeon. Along with the surgical team, AK will need to have his medical conditions stabilized to reduce perioperative risk and be prepared for the dietary and behavioral changes

necessary for success. AK will require lifelong follow-up after the surgery to monitor for nutritional deficiencies and for relapse of his weight and diabetes.

4.10 Conclusion

Obesity is a serious and highly prevalent disease associated with increased morbidity and mortality. Assessment and evaluation of obesity by BMI and risk classification should be part of the patient encounter. Treatment modalities should include diet, physical activity and behavior therapy for all patients, and use of pharmacotherapy or surgery in those selected as reasonable candidates. Primary treatment should be directed at controlling obesity-related comorbidities and achieving an initial modest 5–10% weight loss for obese patients.

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Inflammatory Markers and Novel Risk Factors

5

Stephen J. Nicholls

5.1 Introduction

Atherosclerotic cardiovascular disease is the leading cause of morbidity and mortality in the Western world. The escalation in global prevalence of abdominal adiposity and its associated metabolic risk factors have fueled speculation that cardiovascular disease will become the leading cause of mortality worldwide by 2020 [1]. Increasing interest has focused on the development of new systemic biomarkers to assist in the prediction of cardiovascular risk. This should facilitate more effective use of therapeutic strategies developed for cardiovascular prevention.

5.2 Traditional Prediction of Cardiovascular Risk

Population studies have identified a number of clinical characteristics associated with an elevated prospective risk of developing coronary heart disease [2]. These factors include age, male gender, family history of premature CVD, hypercholesterolemia, hypertension, diabetes mellitus, smoking, obesity, and low levels of high-density lipoprotein cholesterol (HDL-C). As a result, risk prediction algorithms have been developed that take into account the presence or absence of the totality of these factors in order to estimate the 10-year prospective cardiovascular risk [3]. Using such approaches, it has been possible to stratify patients as low (<10%), intermediate (10–20%) and high (>20%) risk. The use of risk prediction algorithms has been employed by guidelines for use of lipid-modifying therapies [4].

However, it has become apparent that these approaches to risk prediction are limited. Conventional risk prediction algorithms may fail to predict the prospective risk of coronary heart disease in 25–50% of subjects [5]. Furthermore, in a pooled analysis of more than 120,000 subjects enrolled in 14 clinical trials of patients with established CHD, it was reported that up to 20% of subjects did not have a single traditional risk factor [6]. These findings suggest that evaluation of additional clinical factors will be required in order to achieve more effective prediction of cardiovascular risk.

5.3 Disease Pathology and Relevance to Novel Biomarkers

As the factors that promote the pathogenesis of atherosclerotic cardiovascular disease continue to be elucidated, they identify not only targets for the development of new therapies but also potential markers of increased cardiovascular risk. In particular, it has become increasingly apparent that atherosclerosis is a chronic inflammatory process, with evidence of activation of a range of inflammatory cascades observed at all stages of the disease process [7]. In the earliest stages, prior to the development of atherosclerotic plaque, dysfunction of the endothelial layer is accompanied by an increase in expression of proinflammatory adhesion molecules [vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and chemokines (monocyte chemoattractant protein-1 [MCP-1])]. These factors promote adhesion of circulating monocytes to the endothelial layer and their subsequent migration into the artery wall.

Within the vessel wall, monocytes undergo a morphological change to become macrophages. Uptake of oxidized LDL by macrophages forms foam cells, the cellular hallmark of atherosclerotic plaque. The foam cell subsequently plays a pivotal role in the ongoing development of atheroma, via its ability to elaborate a host of proinflammatory and proliferative factors, leading to ongoing accumulation of leukocytes and smooth muscle cells within the artery wall. As a

S. J. Nicholls
Department of Cardiovascular Medicine, Center for Cardiovascular Diagnostics and Prevention, Heart and Vascular Institute, Cleveland Clinic Foundation, Cleveland, OH, USA
e-mail: stephen.nicholls@sahmri.com

P. P. Toth, C. P. Cannon (eds.), *Comprehensive Cardiovascular Medicine in the Primary Care Setting*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-319-97622-8_5

result, a developing lesion that contains foam cells, inflammatory material, and smooth muscle cells under a collagenous fibrous cap represents the mature atherosclerotic plaque.

The translation of atherosclerosis to acute ischemia is typically promoted by rupture of the fibrous cap. Elaboration of matrix metalloproteinases by macrophages within the atherosclerotic plaque results in a breakdown of collagen and elastin within the fibrous cap, creating a milieu that promotes cap rupture. Upon exposure of circulating blood to plaque components including lipid, inflammatory, and necrotic material, activation of a number of thrombotic pathways leads to clot formation, with ensuing luminal compromise and ischemia. As a result, it has become clear that inflammatory, oxidative, and thrombotic events are critical for the development and subsequent progression of atherosclerotic disease. Accordingly, it is possible that these pathways may identify novel markers that can enhance prediction of cardiovascular risk.

5.4 Emerging Inflammatory Markers

5.4.1 C-Reactive Protein

C-reactive protein (CRP) is a circulating pentraxin, largely produced by the liver in response to cytokine stimulation, and is a major component of the acute phase response. While its predominant role appears to be involved in the innate immune response, increasing evidence suggests that CRP may also participate in the promotion of atherosclerosis. CRP is also produced by smooth muscle cells within atherosclerotic plaque, and CRP receptors have been identified on the surface of neutrophils and endothelial cells [8–10]. The ability to localize CRP at the level of the artery wall [8–10] and reports that CRP promotes expression of cellular adhesion molecules and chemokines, activates thrombotic pathways, and inhibits nitric oxide synthesis [10] support a potential role in the pathogenesis of atherosclerosis. This is further supported by reports that CRP transgenic mice demonstrate increased thrombus formation in response to arterial injury [11].

A large number of population cohorts have demonstrated that levels of high-sensitivity CRP independently predict the risk of developing a first vascular event [12–15]. In the Physicians' Health Study of more than 22,000 apparently healthy middle-aged males, those subjects with a CRP in the highest quartile had a threefold greater risk of myocardial infarction and a twofold greater risk of stroke [15]. CRP has also been reported to predict the risk of a first event in women, with both the Women's Health Study and Nurses' Health Study demonstrating that CRP independently predicts cardiovascular risk, after controlling for traditional risk factors [14]. In particular, elevated CRP levels predict risk at all levels of LDL-C and measures of global risk [12–15]. As a result, it was estimated that measurement of CRP would reclassify the 10-year predicted risk in as many as 40% of women [12–15].

The ability of CRP levels to predict prospective cardiovascular risk has also been reported in many studies of subjects with an established diagnosis of coronary heart disease. In cohorts of subjects with stable or unstable coronary disease and in patients undergoing percutaneous coronary intervention or bypass grafting, elevated CRP levels are associated with an elevated risk of future cardiovascular events [16–23].

However, other investigators have suggested that the link between CRP and cardiovascular risk is relatively modest. In fact, some authors have suggested that the presence of an isolated elevation of CRP is uncommon, with some additional risk factor identified in up to 80% of subjects [24]. While associations have been reported, it has yet to be unequivocally demonstrated that CRP plays a direct role in the pathogenesis of plaque formation and progression. This is further complicated by the observation that it is difficult to exclude contaminants such as endotoxin from CRP samples used in laboratory studies [25]. Furthermore, some groups have suggested that the ability of CRP to predict the risk of a first vascular event is not as strong as previously reported. In a case-control analysis of a prospective study from Reykjavik, it was demonstrated that while CRP did predict the risk of an adverse cardiovascular outcome, this was not particularly strong with an odds ratio of 1.45 (95% confidence interval 1.25–1.68) [26].

Nevertheless, on the basis of findings from a large number of cohorts and the use of well-validated and inexpensive assays, the Centers for Disease Control and Prevention and American Heart Association recommended use of CRP in the assessment of subjects which is deemed to be intermediate risk on the basis of conventional algorithms [27]. Using this approach, risk can be classified as low (<1 mg/L), intermediate (1–3 mg/L), and high (>3 mg/L) on the basis of CRP testing [27]. Ongoing exploration has endeavored to evaluate the risk prediction ability of incorporating CRP values in addition to assessment of traditional risk factors. Early studies of the role of the Reynold's risk score demonstrate a superior risk prediction role, resulting in reclassification of 40–50% of intermediate-risk subjects into higher- and lower-risk categories [28].

Additional interest in CRP has come from its ability to identify the likelihood of clinical benefit with therapeutic interventions. Increasing data suggest that statins can lower CRP levels in a manner that is independent of their LDL-C lowering properties [29–31]. Post hoc analyses of placebo-controlled trials demonstrated the ability of CRP levels to identify those subjects likely to benefit from statin therapy.

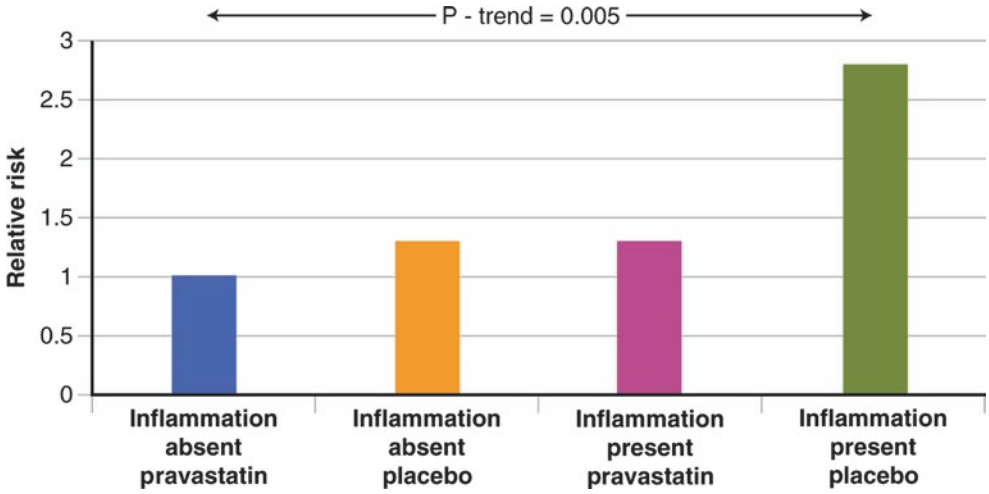

Fig. 5.1 Relative risk of recurrent coronary events among post-myocardial infarction patients according to the presence or absence of evidence of inflammation (both CRP and serum amyloid A levels above the ninetieth percentile) and by randomization to placebo or pravastatin in patients participating in the CARE study. (Copied with permission from [23])

In the secondary prevention setting of the Cholesterol and Recurrent Events (CARE) Study, the presence of an elevated CRP at baseline predicted a greater reduction in clinical events with pravastatin, regardless of the baseline LDL-C [23] (Fig. 5.1). A similar finding was subsequently reported in the primary prevention setting in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) [32]. More recently, lowering CRP levels was reported to independently predict the benefit of high-dose atorvastatin on atheroma progression in the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) Study [33] and clinical events in the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) Study [34].

The benefit of statin therapy in subjects with elevated CRP levels was further demonstrated in the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) Study [35]. Seventeen thousand eight hundred and two individuals with an LDL-C less than 130 mg/dL were identified on the basis of a CRP of 2 mg/L or higher and treated with rosuvastatin 20 mg daily or placebo for a median of 1.9 years. Lowering of LDL-C by 50% and CRP by 37% with rosuvastatin was associated with a 44% reduction in the combination of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, and cardiovascular mortality ($p < 0.00001$) and a 20% reduction in all-cause mortality ($p = 0.02$). These findings provided further support for the importance of inflammation influencing cardiovascular risk. While no subjects with normal CRP levels were enrolled in the study, the findings suggest that evidence of inflammation does identify a patient who is likely to benefit from use of statin therapy, even in the setting of apparently normal LDL-C levels. The relative contribution of LDL-C and CRP lowering to the clinical benefit remains to be determined by ongoing analysis. While no specific CRP lowering therapy has been evaluated in clinical trials of cardiovascular prevention, it appears that the presence of an elevated CRP does identify a subject, with evidence of systemic inflammation and increased cardiovascular risk, who is likely to derive benefit from a more intensive approach to risk reduction strategies.

5.4.2 Myeloperoxidase

Myeloperoxidase (MPO) is leukocyte-derived member of the heme peroxidase superfamily. MPO is stored in azurophilic granules of circulating neutrophils, monocytes, and some macrophages found within tissues such as atherosclerotic plaque. The major oxidant products of MPO-catalyzed pathways have been demonstrated to play an important role in the generation of lipid hydroperoxides, conversion of LDL to a high-uptake form, reduced bioavailability of nitric oxide, endothelial cell apoptosis, and platelet activation. More recently, MPO has been implicated as a pivotal factor involved in the oxidation and inactivation of apoA-I and the generation of dysfunctional HDL particles, possibly leading to reduced capacity for reverse cholesterol transport. As a result of these effects, it is likely that MPO plays a role in promoting each stage of atherosclerosis from endothelial dysfunction to formation and rupture of atherosclerotic plaque [36].

A number of lines of evidence from human studies further implicate the role of MPO in cardiovascular disease. MPO and its oxidant products have been localized within atherosclerotic plaque specimens [37–39]. This is supported by the observation of relative protection from cardiovascular disease in individuals with genetic forms of MPO deficiency [20–42]. More recently, an increasing

number of studies have reported an association between systemic MPO levels and prospective cardiovascular risk. In asymptomatic patients evaluated with serial carotid ultrasound measurements, accelerated progression of lumenal stenoses was observed in association with elevated MPO levels [43]. This relationship between MPO and progression of subclinical disease is supported by nested case-control reports from the European Prospective Investigation into Cancer and Nutrition (EPIC-Norfolk) cohort, which demonstrated a direct relationship between increasing baseline MPO levels and prospective risk of cardiovascular events during 8 years of follow-up, a finding that was independent of the presence of traditional risk factors [44].

In symptomatic patients with stable CAD presenting for diagnostic coronary angiography, the extent of angiographic disease has been reported to be associated with both the systemic MPO levels [45, 46] and the MPO content per leukocyte [47]. A number of reports have demonstrated the ability of MPO levels to predict prospective clinical risk in patients with acute ischemic syndromes. In a study of 604 sequential patients evaluated in the emergency room for acute chest pain of suspected cardiac etiology, MPO levels predicted the diagnosis of myocardial infarction and acute coronary syndromes and independently predicted likelihood of experiencing a major adverse cardiovascular event during the next 6 months. These findings were also found in patients whose troponin levels were persistently within normal limits during their hospitalization, suggesting that MPO levels correlate with outcome even in the absence of evidence of myocardial necrosis [48]. An MPO level less than the upper limit of normal (650 pmol/L) appears to predict a lower incidence of cardiovascular events [48]. MPO levels were also found to be the most accurate predictor of future ischemic events in patients with an acute coronary syndrome who were enrolled in the c7E3 AntiPlatelet Therapy in Unstable Refractory angina (CAPTURE) [49] and Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS-TIMI 18) [50] trials.

Beyond its relationship with outcome in patients with clinical ischemia, MPO also plays a prognostic role in the setting of myocardial infarction and heart failure. MPO levels predict outcome in patients with evidence of myocardial infarction, regardless of the presence of ventricular dysfunction or cardiogenic shock [51, 52], and predict the presence of occult left ventricular systolic dysfunction, augmenting the role of BNP levels [53], and also are elevated in patients with overt clinical heart failure [54]. These findings are consistent with reports that MPO plays an important role in the promotion of ventricular remodeling in murine models of chronic coronary artery ligation and ischemia-reperfusion [55, 56].

5.4.3 Lipoprotein-Associated Phospholipase A_2

Lipoprotein-associated phospholipase A_2 (Lp-PLA_2), also known as platelet-activating factor acetylhydrolase (PAF-AH), is a member of a family of intracellular and systemic enzymes that hydrolyze the sn-2 fatty acid bond of phospholipids, resulting in the generation of oxidized fatty acids and lysophospholipids. Produced by leukocytes, Lp-PLA_2 circulates in association with lipoproteins, predominantly on LDL particles. Considerable controversy has focused on the relative role of Lp-PLA_2 in atherosclerosis. The products of Lp-PLA_2 activity upregulate activation of inflammatory pathways involved in formation and propagation of atherosclerotic plaque. Lp-PLA_2 is found within matured and ruptured, but not early, plaques and colocalizes with foam cells and macrophages, which permit ongoing generation within the atherosclerotic plaque. In contrast, its activity has been proposed to promote the antioxidant and anti-inflammatory properties of HDL, and in a Japanese cohort, heterozygous deficiency of Lp-PLA_2 is associated with an increased rate of myocardial infarction, stroke, and peripheral arterial disease. Regardless, it appears that Lp-PLA_2 plays an important role in orchestrating localized inflammatory events within the vessel wall [57].

The ability of Lp-PLA_2 to reflect localized, rather than systemic, inflammation potentially provides greater specificity with regard to monitoring cardiovascular risk. Meta-analysis of a large number of cohorts has demonstrated that elevated Lp-PLA_2 levels are associated with greater prospective risk of cardiovascular events [58]. This association has been reported in studies that have employed assessment of either Lp-PLA_2 activity or mass. In a nested case-control analysis of the West of Scotland Coronary Prevention Study (WOSCOPS), baseline Lp-PLA_2 independently predicted the risk of a first vascular event, after controlling for traditional risk factors [59]. This finding is supported by the Atherosclerosis Risk in Communities (ARIC) Study, although the ability to predict an adverse outcome was only observed in subjects with an LDL-C less than 130 mg/dL [60]. However, other investigators have reported that the ability of Lp-PLA_2 to predict cardiovascular risk does not persist after controlling for LDL-C levels [61]. The finding that Lp-PLA_2 predicts vascular events in patients presenting for coronary angiography, despite a lack of relationship with disease burden, supports its association with factors within the plaque that promote breakdown of the fibrous cap and progression to acute ischemia [62].

Given the clear association with LDL-C, it is not surprising that Lp-PLA_2 levels decline in response to use of lipid-modifying therapies, and in contrast to CRP, this decline is largely predicted by reductions in LDL-C [63, 64]. The FDA has approved an assay for assessment of subjects deemed to

be intermediate risk by traditional approaches, with recommendations that levels greater than 235 ng/mL identify an increase in prospective cardiovascular risk [65]. The development of new therapeutic agents that directly inhibit Lp-PLA_2 has been demonstrated to have a favorable impact on the size of the necrotic core in human atherosclerosis and is undergoing further evaluation in clinical trials [66].

5.4.4 Additional Markers

Additional inflammatory mediators in atherosclerosis have been proposed as potential markers for use in risk prediction. Some, but not all, cohorts report an association between systemic levels of adhesion molecules [67–69], chemokines [70–72], and cytokines [73] with the prevalence of coronary heart disease and prospective cardiovascular risk; it remains to be determined whether this persists after controlling for traditional risk factors.

5.4.5 Matrix Metalloproteinases

Pathology studies have established that matrix metalloproteinases (MMP) play an important role in vascular and ventricular remodeling and in the progression of atherosclerotic plaque to fibrous cap rupture and acute ischemic events [74]. Elevated systemic MMP levels have been reported in the setting of expansive arterial remodeling, a pattern of change in vascular dimension associated with acute coronary syndromes [75]. Several investigators have reported that MMP levels predict an increased risk of future cardiovascular events [76]. However, it remains to be determined whether the accuracy of risk prediction varies according to the specific form of MMP measured or if determination of activity rather than mass is more accurate. Furthermore, measurement of endogenous tissue inhibitors of metalloproteinases (TIMPs) may also provide important prognostic information [77]. Pregnancy-associated plasma protein A (PAPP-A) is a specific metalloproteinase located within unstable, but not stable, plaques. The finding that circulating PAPP-A levels are elevated in patients with acute ischemic syndromes compared with stable angina or healthy controls suggests a potential role for this specific MMP in risk prediction [78]. Further evaluation is required to determine whether any measure of MMP provides clinical utility above and beyond that observed with assessment of traditional risk factors.

5.4.6 ADMA

Nitric oxide plays a pivotal role in the maintenance of vascular homeostasis. A reduction in nitric oxide bioavailability is the hallmark of changes in endothelial function that precede the formation of macroscopic changes within the artery wall. Given their short circulating half-life, no reliable and high-throughput assay for the detection and quantitation of either nitric oxide or its metabolites has been developed. Increasing interest has focused on the role of methylated species of the nitric oxide precursor, L-arginine, in the pathogenesis of cardiovascular disease. The methylation product asymmetric dimethylarginine (ADMA) has been demonstrated to inhibit the activity of nitric oxide synthase (NOS) [79]. ADMA levels have been reported to be elevated in patients with cardiovascular risk factors and established atherosclerotic disease [79]. More recently elevated ADMA levels have been demonstrated to portend a poor prognosis in patients with acute myocardial infarction complicated by cardiogenic shock [80].

5.5 Emerging Thrombotic Markers

Given that thrombus formation is the major event leading to lumen occlusion and acute ischemia in the setting of plaque rupture, there is considerable interest in evaluating the propensity to thrombosis as a potential risk factor. Fibrinogen is an acute phase reactant that acts an important link between inflammation and thrombosis, via its pivotal role in promoting the coagulation cascade and plasma viscosity. Elevated fibrinogen levels are commonly observed in association with a number of risk factors including smoking, diabetes, obesity, and increasing age [81]. Case-control studies have demonstrated that fibrinogen levels predict cardiovascular risk within all vascular territories persisting following adjustment for conventional risk factors [81]. The lack of standardized assay, uniform cutoffs, and evidence of benefit with a specific fibrinogen-lowering intervention has limited its acceptance.

A number of additional factors involved in the regulation of thrombosis have been investigated with regard to a potential role in risk prediction. A range of platelet activation and aggregation assays has been used to characterize both the association between platelet activity and cardiovascular risk and the potential antiplatelet impact of medical therapies [82]. However, the lack of standardization of these assays has limited their use. The discovery that platelet-derived microparticles and CD40 both play a role in promoting both inflammatory and thrombotic pathways suggests that monitoring their systemic levels may predict cardiovascular risk. In studies of patients with acute coronary syndromes, systemic levels of soluble CD40 ligand predict prospective risk and correlate with the clinical benefit of early statin administration [83]. Monitoring systemic levels of factors involved in the control of thrombus dissolution, such as plasminogen activator inhibitor (PAI-1), has also been demonstrated to predict cardiovascular risk in case-control studies [84].

5.6 Additional Markers

5.6.1 Homocysteine

Homocysteine is a thiol-containing intermediate of methionine metabolism. Evidence supporting a potential role of homocysteine in cardiovascular disease is supported by the finding of atherosclerosis in young subjects with inborn errors of homocysteine metabolism and that laboratory experiments have demonstrated that homocysteine possesses inflammatory, oxidative, thrombotic, and proliferative properties [85]. A meta-analysis of case-control studies revealed that elevated homocysteine levels greater than 15 μmol/L are associated with a greater prevalence of atherosclerotic disease within coronary, cerebral, and peripheral vascular territories [86]. Subsequent meta-analyses also revealed that elevated homocysteine levels predict, albeit to a modest degree, the prospective risk of cardiovascular events [87].

The ability of homocysteine to predict cardiovascular risk appears to be enhanced in the setting of concomitant risk factors, such as diabetes mellitus, smoking, and chronic renal impairment, and in the setting of genetic variation in homocysteine metabolism [88–92]. Meta-analyses have consistently demonstrated an association between a 677C → T polymorphism of methylenetetrahydrofolate reductase and a prospective cardiovascular risk [91, 92]. Highlighting the distinction between the ability of a factor to predict risk and the ability of a factor to serve as a therapeutic target is consistent with the data from large prospective clinical trials that demonstrate that lowering of homocysteine levels with folic acid and vitamins is not associated with cardiovascular benefit [93].

5.6.2 Brain Natriuretic Peptide

A number of members of the natriuretic peptide family play an important role in the regulation of the cardiovascular system. Brain natriuretic peptide (BNP) is released from cardiac myocytes, predominantly in response to stretch. As a result, BNP levels have been consistently demonstrated to be elevated in the setting of heart failure [94]. BNP has been subsequently incorporated into the diagnostic algorithm of patients evaluated for dyspnea and has been proposed to have a role in the titration of heart failure therapies. Similar findings have been demonstrated with the use of the amino terminus proBNP (NT-proBNP) [95]. Increasing evidence suggests that BNP may play a prognostic role as a biomarker in patients with atherosclerotic cardiovascular disease, without heart failure. BNP levels typically rise early in the setting of acute ST-elevation myocardial infarctions, followed by relatively rapid stabilization [96]. Patients who demonstrate a biphasic pattern with an additional rise at day 5 are more likely to have large anterior wall infarcts with evidence of systolic dysfunction and clinical heart failure [96]. Early observation that baseline BNP levels greater than 80 pg/mL at presentation with an acute coronary syndrome predict an elevated risk of cardiovascular events during the next 6 months [97] was confirmed by analysis of patients who participated in the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction (TACTICS-TIMI 18) Study [98] (Fig. 5.2).

The role of serial evaluation of BNP levels in patients presenting with an acute coronary syndrome was investigated in subjects participating in the A–Z trial. The subsequent presence of a BNP level greater than 80 pg/mL within the 12 months following presentation, despite having a lower level at baseline, was associated with an adverse outcome in terms of mortality and heart failure. In contrast, an initially high value, which decreased during follow-up, was accompanied by a relatively favorable prognosis. This highlights the potential importance of long-term serial measurements [99, 100]. Similar findings for risk prediction in patients with acute coronary syndromes were found when levels of NT-proBNP were measured [101–103].

The underlying mechanistic link between BNP and subsequent incidence of ischemic cardiovascular events is supported by observations that BNP levels predict the extent of ischemic perfusion defects on exercise myocardial scintigraphy [104, 105] and measures of atherosclerotic burden including the number of coronary arteries diseased on angiography [106, 107] and the degree of coronary calcification [108]. These observations support more recent findings that BNP levels can predict outcome in more stable patients with CAD at levels far below those used for the diagnostic threshold for heart failure. It remains to be determined whether BNP plays a direct pathologic role in the progression of atherosclerosis or reflects an increase in wall stress within the vascular system or some other aspect of the disease process.

5.6.3 Oxidative Stress

The pivotal role of oxidation in the pathology of atherosclerosis has also prompted the search to develop reliable markers of oxidative stress. The inability to monitor oxidant activity has been proposed as one of the limitations of clinical studies that have consistently demonstrated the lack of clinical efficacy of multivitamins. F_2-isoprostanes are stable peroxidation products of the arachidonic acid pathway, which can be reliably measured in a range of biological specimens. Increasing levels of F_2-isoprostanes have been reported in association with a range of cardiovascular risk factors [109] and within atherosclerotic lesions [110]. While F_2-isoprostane levels have been demonstrated to decrease in

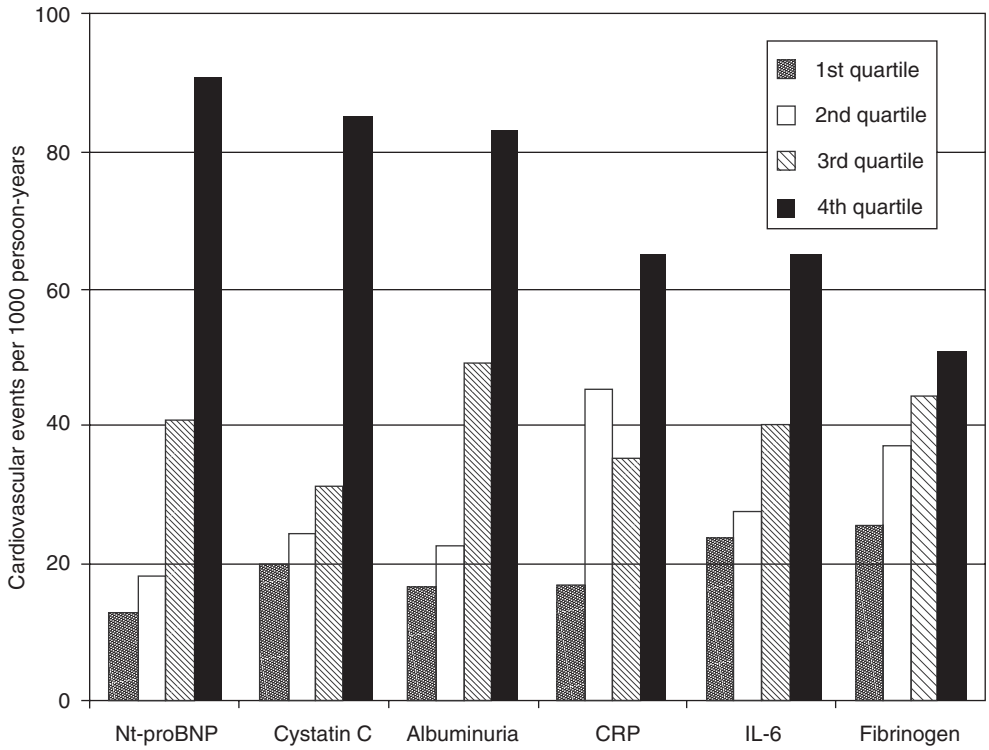

Fig. 5.2 Risk of death or myocardial infarction (MI) at 30 days stratified by B-type natriuretic peptide (BNP) and cardiac troponin I (cTnI) in the TACTICS-TIMI 18 study. (Copied with permission from [98])

response to statin therapy [111, 112], their use to predict prospective cardiovascular risk in case-control studies has not been elucidated.

Oxidative modification is an essential event required to convert LDL into an atherogenic species. Detection of oxidized LDL species reflects a broad spectrum of targets including both lipid and protein components of LDL particles. Support for the development of assays for quantitation of oxidized LDL (oxLDL) comes from findings of their localization within human atherosclerotic plaque [113, 114] and that immunization against a range of oxLDL epitopes is protective in animal models of atherosclerosis [115]. Three specific epitopes underlie the major oxLDL assays currently in use, targeting either phosphatidylcholine (E06 and DLH3) or apoB (4E6) [61]. A number of groups have reported that systemic oxLDL levels are elevated in the setting of the metabolic syndrome and endothelial dysfunction [116, 117]. Furthermore, elevated oxLDL levels predict the prospective risk of cardiovascular risk and progression of carotid intimal-medial thickness [118, 119], but not coronary atherosclerosis [120]. Given the high correlation with LDL cholesterol and reduction in levels in response to statin therapy [121], it remains to be determined what the incremental value of oxLDL measurement is in risk assessment. As a result, ongoing investigation and standardization are required to evaluate its potential clinical utility.

Endogenous antioxidant factors have also received attention with regard to development of therapeutic and diagnostic approaches. Paraoxonase (PON) is a lactase/esterase that is carried in the systemic circulation predominantly on the surface of high-density lipoprotein (HDL) particles. The demonstration that PON possesses antioxidant and anti-inflammatory activities in cellular studies and that genetic deletion of PON is associated with accelerated lesion formation in animal models of atherosclerosis suggests a potential role in vascular protection in humans [122]. However, considerable debate has continued on the role of PON in humans given that levels of PON mass and activity have been reported to be inversely associated with cardiovascular risk in some, but not all, patient cohorts and that it remains to be unequivocally demonstrated that PON actually acts as an antioxidant in humans [123]. A recent report appears to have provided some clarity in which increasing levels of PON activity were associated with low levels of measures of oxidative stress and relative protection from cardiovascular events [123].

5.7 Measures of Renal Impairment

Renal impairment is associated with an increase in cardiovascular disease, largely due to abnormalities of blood pressure and lipids. A number of reports have emerged that suggest an increase in cardiovascular risk in patients with biochemical evidence of impaired renal function that is independent of the presence of traditional risk factors. Cystatin C, calculated glomerular filtration rate (GFR), and

the urinary albumin/creatinine ratio (UACR) are each markers of various degrees of renal impairment [124]. Each of these markers has been reported to predict incident cardiovascular events in cohorts of subjects with and without an established diagnosis of CAD. Neutrophil gelatinase-associated lipocalin (NGAL) is a marker of leukocyte elevation, which has emerged as a marker of early renal injury [125]. Pathology studies that localize NGAL within atherosclerotic plaque and the ventricular wall and its association with activation of matrix metalloproteinases implicate a potential role in the progression of atherosclerosis and remodeling [126]. While a number of reports suggest that an elevated NGAL level is associated with an increased risk of cardiovascular events [127], this remains to be characterized in large cohorts.

5.8 Panels of Multiple Novel Biomarkers

Pathological insights into the pathways that promote formation and subsequent clinical complications of atherosclerosis have stimulated the development of a large number of systemic biomarkers. The complexity of the disease process, involving the interaction of multiple pathological events, would imply that a panel of biomarkers that monitored a combination of these pathways might potentially be of greater clinical utility. In a review of 3209 participants in the Framingham Heart Study, a panel of biomarkers including CRP, BNP, NT-pro-atrial natriuretic peptide, aldosterone, rennin, fibrinogen, D-dimer, PAI-1, homocysteine, and the urinary albumin-to-creatinine ratio was evaluated. Subjects with a calculated multimarker score in the highest quartile were at a higher risk of a future cardiovascular event. However, the incremental increase in risk prediction when the multimarker score was combined with traditional risk factors was minimal [128]. In a cohort of elderly men in the Uppsala Longitudinal Study of Adult Men (ULSAM), the integration of a panel of markers reflecting myocardial necrosis (troponin I), ventricular dysfunction (NT-proBNP), renal impairment (cystatin C), and inflammation (CRP) improved the ability of traditional risk factors to predict the risk of cardiovascular death [129].

The approach of a biomarker panel was recently evaluated in patients with an established diagnosis of coronary heart disease in the Heart and Soul Study. When NT-proBNP, albuminuria, and CRP were added to traditional risk factor assessment, a significant increase in risk discrimination was observed [130] (Fig. 5.3). Accordingly, it would appear that there is a potential for multiple markers to be of clinical utility in both primary and secondary prevention settings. Further study is required to determine what combination of biomarkers improves risk stratification above and beyond that observed with assessment of traditional risk factors.

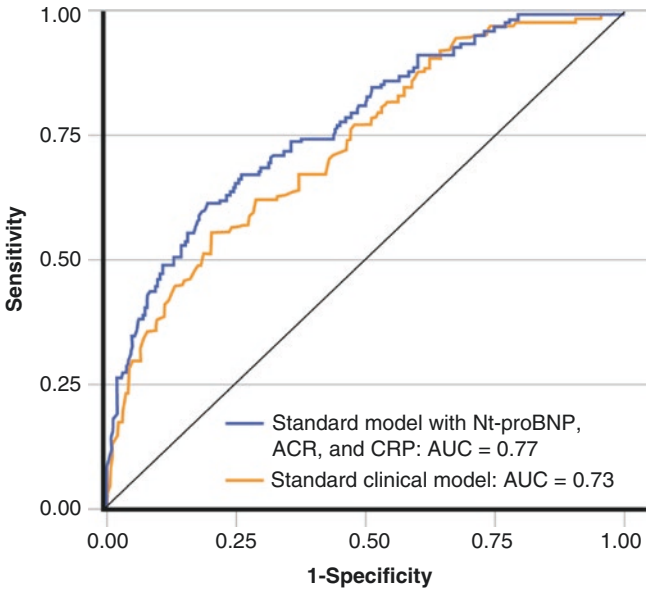

Fig. 5.3 Receiver operator characteristic curves for the standard clinical model and the standard clinical model plus NT-proBNP, albuminuria, and CRP to predict major adverse cardiac events in the Heart and Soul Study. (Copied with permission from [130])

5.9 Plaque Erosion

Emerging insights from pathology studies have revealed that not all plaques underlying acute ischemia demonstrate rupture and the vulnerable histologic phenotype that has promoted the development of many of these circulating cardiovascular risk biomarkers. The observation that up to one third of culprit lesions demonstrate erosion of the endothelial cell layer has been confirmed by intravascular imaging with optical coherence tomography in patients with acute coronary syndromes [131, 132]. Erosion appears to differ from rupture in terms of the presence of less plaque lipid and inflammation and a greater propensity in women, smokers, and patients with hypertriglyceridemia [131]. While experimental studies have implicated the roll of toll-like receptor activation in the genesis of erosion [131], there currently are no circulating markers that predict this phenomenon. Further work is required in the area in order to develop new biomarkers of direct relevance in this setting.

5.10 Summary

The inability of traditional risk factor algorithms to accurately stratify cardiovascular risk in all subjects has stimulated the search to develop additional systemic biomarkers to enhance risk prediction. Systemic biomarkers that reflect the degree of inflammatory, oxidative, and thrombotic activity within the coronary arteries provide an opportunity to iden-

tify patients who are more likely to progress to acute ischemic events. Emerging data suggest that a number of markers, particularly those that reflect systemic inflammatory activity, are independent predictors of clinical events.

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Deciphering Cardiovascular Genomics and How They Apply to Cardiovascular Disease Prevention

6

Sumeet A. Khetarpal and Kiran Musunuru

6.1 Why Is Genomics Important?

Genomics, or the study of genomes, is concerned with understanding how the deoxyribonucleic acid (DNA) of which genomes are constituted contributes to making an organism unique. Accordingly, human genomics focuses on how DNA sequences produce individuals' traits, e.g., skin color and cholesterol levels, and contribute to diseases, e.g., myocardial infarction and diabetes mellitus. The last decade has witnessed a remarkable leap forward in the use of genomics technology to understand human traits and diseases, to the point that new discoveries regarding what makes each person unique are being widely reported in the press and advertised by companies to the lay public. Although *currently practical use of genomics is limited*, there are high expectations that it will be clinically useful in the near future. Discussions with patients of the implications of genomics – whether it is in the form of genetic testing for disease risk, pharmacogenomics, or personalized medicine – will be unavoidable for primary care providers. This chapter seeks to (1) explain the basic biology underlying genomics technology; (2) describe the potential future uses of genomics to improve patient care, particularly in cardiovascular medicine; and (3) set realistic expectations for the utility of genomics and explore the ethical implications of the technology.

6.2 A Brief Introduction to Molecular Biology

Deoxyribonucleic acid (DNA) is a molecule with two strands that are wrapped around each other in a helical formation, hence its description as a "double helix." The outer part of the helix contains the sugar and phosphate "backbone" of the DNA, and the inner part contains the "coding" portion of the molecule with four types of bases – adenine (A), cytosine (C), guanine (G), and thymine (T). An organism's genetic information is determined by the order of the sequence of the bases – with four bases available; the number of potential sequences is almost endless. The versatility of DNA results from the obligatory pairing of bases in the two strands. An adenine in one strand is always matched up with a thymine in the other strand, and cytosine is always paired with guanine. Thus, the two strands contain redundant information, and each can serve as a template on which a new complementary strand can be synthesized. This allows for easy duplication of the DNA so that when a cell divides into two, each descendant cell receives the same genetic information as the original cell.

An organism's DNA is organized into superlong strands that are packaged by a large complex of supporting proteins into chromosomes. Humans have 23 pairs of chromosomes, including the pair that determines gender, which in females comprises two X chromosomes, and in men, one X and one Y chromosome. For each chromosome pair, one was inherited from the mother and one from the father. The full set of chromosomes is collectively called the genome. The human genome is contained within the nucleus of each cell, where it is separated from the rest of the cell's functions.

In general, the genome is characterized by vast stretches of "noncoding" DNA sequence punctuated by small areas of "coding" DNA, also called genes, that represent the instructions needed by cells to perform their functions. Coding DNA is "transcribed" into a single-stranded molecule called ribonucleic acid (RNA) by a transcription enzyme complex. RNA is structurally similar to a DNA strand and also contains four types of bases, including adenine, cytosine, and guanine [in RNA, uracil (U) is substituted for DNA's thymine (T)]. The transcription enzymes have proofreading functions that ensure that the sequence of the RNA molecule perfectly matches the sequence of the DNA template from which it was synthesized. RNA is more flexible and mobile than DNA and is transported out of the nucleus of the cell

S. A. Khetarpal · K. Musunuru (✉)
Departments of Medicine and Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

P. P. Toth, C. P. Cannon (eds.), *Comprehensive Cardiovascular Medicine in the Primary Care Setting*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-319-97622-8_6

into the outer compartment, the cytoplasm. Thus, RNA production is the mechanism by which genetic information is "expressed" and relayed from the central repository (DNA) to the rest of the cell, where it directs cellular functions.

While some RNAs have specialized functions – e.g., serving as structural components of certain parts of the cell – most RNAs take the form of "messenger" RNAs (mRNAs) that are "translated" by ribosomes into proteins. The ribosome reads from the beginning of the mRNA and uses it as a coding template with which to build proteins, with each nonoverlapping set of three consecutive bases ("codons") serving to specify a particular amino acid. With four available types of bases, there are 64 possible codon combinations; with some redundancy, these codons are translated into any of 20 different amino acids or into a "stop" signal. In this way the RNA sequence is converted into an amino acid sequence until a stop signal is reached that prompts the ribosome to finish and release the protein. The protein is then processed by the cell and then deployed to serve its purpose (as an enzyme, as a secreted factor, etc.).

This highly organized progression from DNA, to transcribed RNA, to translated protein is known as the "central dogma" of molecular biology (Fig. 6.1), and while there are exceptions to this sequence of events, the central dogma explains the vast majority of cellular processes. By and large, in humans these processes combine with environmental influences to determine each person's individual characteristics, susceptibility to diseases, and responses to medications. The technology is now available to study the cellular processes at any step of the central dogma. When the investigation occurs at the level of DNA, it is termed "genomics"; when at the level of mRNAs, "transcriptomics"; and when at the level of proteins, "proteomics." Processed proteins or other products of enzymatic reactions are called metabolites, the study of which is termed "metabolomics." The study of structural modifications to the chromosomes, which can have effects on the transcription of DNA, is termed "epigenomics."

6.3 The Principles of Human Genomics

The human genome is roughly 6 billion DNA bases in size, spanning the 23 chromosome pairs, and represents the complete list of coded instructions needed to make a person. There are an estimated 20,000–25,000 genes in the human genome, most of which encode proteins or components of proteins. What makes each person unique is a large number of DNA variations distributed throughout the genome. Some people have particular genetic variations that can predispose to heart disease; some of these variants require the presence of environmental factors (such as smoking and obesity) to trigger heart disease. Less commonly, certain variations have such a strong effect that they can cause heart disease outright. Other variations may determine how well patients respond to particular medications.

One reason some people are more susceptible to getting a disease than other people or respond differently to medications is that their DNA variants affect the function of genes. There are rare variants that have a large effect on a gene's function, either by significantly increasing or decreasing the gene's activity; these are the kind of variants that cause disease in many members of a single family and are also known as "mutations." There are common variants (>1% of the general population) that have a small effect on a gene's function. These variants do not change gene activity enough to cause disease by themselves but, instead, need to be combined with other gene variants or with environmental factors in order for

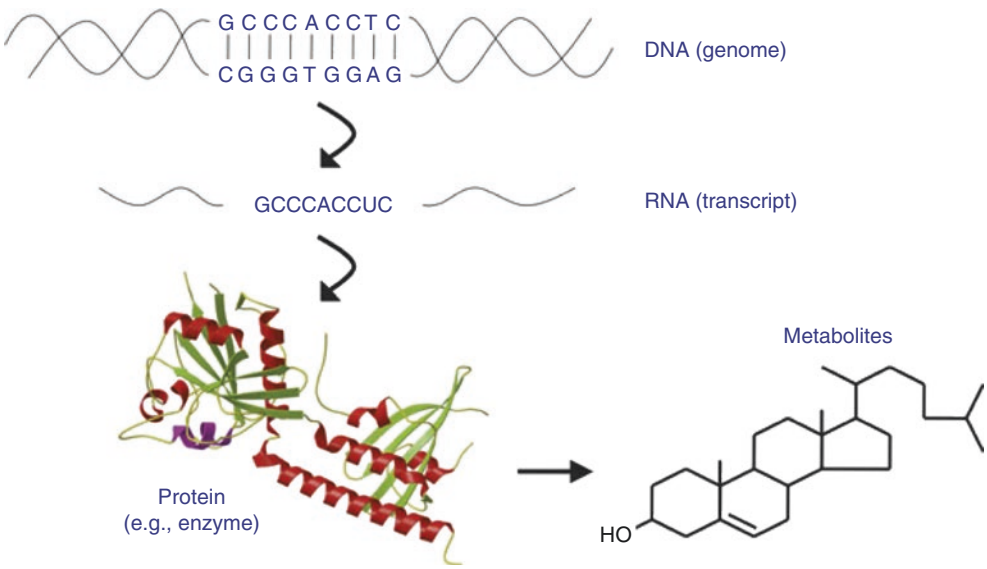

Fig. 6.1 Decoding and implementation of genetic information. Also known as the "central dogma," the cellular pathway begins with deoxyribonucleic acid (DNA) and proceeds with transcription of DNA into ribonucleic acid (RNA) transcripts, followed by translation of RNA into proteins (e.g., enzymes), which in turn produce metabolites

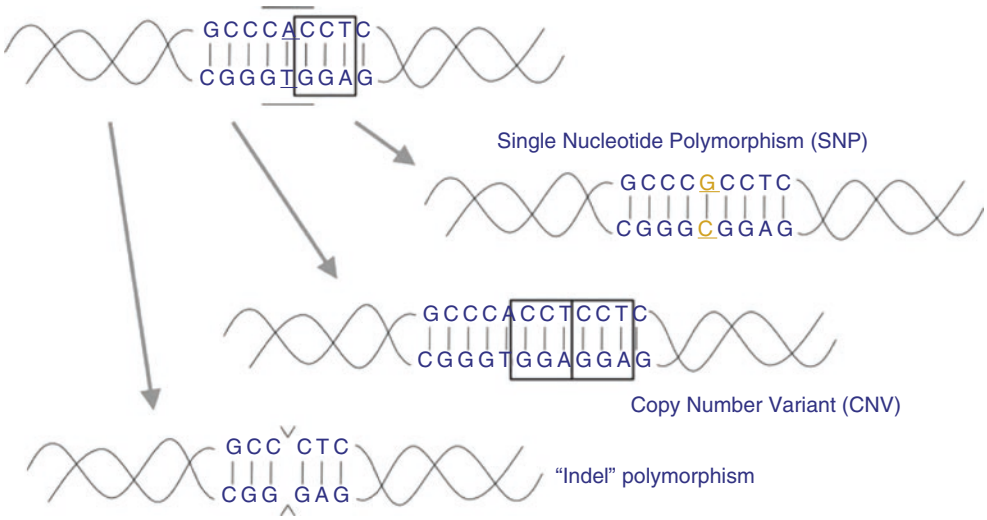

Fig. 6.2 Three types of polymorphisms. Variations in DNA sequence from person to person, or polymorphisms, can take the form of single nucleotide polymorphisms (SNPs), copy number variants (CNVs), and insertion–deletion variants ("indels")

disease to occur. This is the case with most cardiovascular diseases where there are many contributing factors (e.g., hypercholesterolemia, myocardial infarction). Conversely, there are common variants that have the opposite effect – they offer modest protection against disease.

All of these differences at the DNA level are called "polymorphisms," of which there are several types (Fig. 6.2). The best characterized to date are single nucleotide polymorphisms (SNPs) in which a single base in the DNA differs from the usual base at that position. A copy number variant (CNV) is a polymorphism in which the number of repeats of a DNA sequence at a location varies from person to person. An "indel" (short for insertion–deletion) is a polymorphism in which a DNA sequence is either present or absent at a location, varying from person to person. SNPs are the most common and best understood of the polymorphisms, with tens of millions of SNPs having been identified across the human genome.

"Locus" is one of the several terms used to describe a local area on a chromosome around an SNP. In most cases, each person has two copies of each locus because of the pairing of chromosomes; the exceptions are loci on the X or Y chromosome in men, who have only one of each. A person's "genotype" at an SNP is the identity of the base position for each of the two copies – also called "alleles" – of the SNP on paired chromosomes; thus, a genotype is typically two letters. A "haplotype" is a combination of SNPs at multiple linked loci – often adjacent to each other – that are usually transmitted as a group from parent to child (Fig. 6.3).

Some SNPs lie in genes and affect the genes' function. Most SNPs lie outside genes, in the large stretches of noncoding DNA between genes, and do not directly affect the genes. Groups of SNPs near genes tend to stay together with the genes from generation to generation, over thousands of years, in what are called "linkage disequilibrium" blocks that

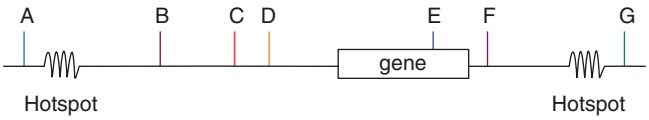

Fig. 6.3 Linkage disequilibrium. SNPs in proximity to a gene tend to stay together with that gene through many generations, a phenomenon known as linkage disequilibrium. In this example, only E is in the gene and directly affects its function. Genotypes at B, C, D, E, and F will stay together on a chromosome as it is passed from parents to offspring. In contrast, A and G are separated from the gene and the other SNPs by recombination hotspots, and thus they may not stay together on a chromosome through many generations – they will not be in linkage disequilibrium. Being linked, B through F make up a haplotype. Knowledge of any one of the five SNPs gives information on – acts as a "tag" for – the other four SNPs. Thus, genotyping B (or C or D or F) will indirectly yield information about the gene, even though the SNP is not in the gene

are separated by chromosomal recombination hotspots (for a more detailed explanation of this phenomenon, please see [1]). Thus, even if it is not known which polymorphism in a gene causes a disease (which is usually the case), one can use a SNP that is not in the gene but is in linkage disequilibrium with the gene – as a "tag" for that disease-causing variant of the gene (Fig. 6.3).

The technology is now available to decode millions of "tag" SNPs in a person's DNA all at once using "gene chips" or "arrays" or "panels." By applying the gene chips to thousands of individuals, some with a disease and some without the disease, researchers are able to identify tag SNPs that are associated with disease (though the association is typically not perfect nor do associations imply causality). These studies are termed "genome-wide association studies" or "GWAS."

As an example of how this technology might be used, consider GWAS performed for myocardial infarction. The study design would entail collecting DNA samples from

thousands of patients who have suffered heart attacks and thousands of control individuals (who have not have had heart attacks but are otherwise similar to the patients). A gene chip is used to determine the genotype for more than 1 million SNPs in each of the study subjects. Despite having a massive amount of information (1 million genotypes for several thousand people or billions of pieces of data), the statistical methods to analyze the information are relatively simple. The investigators set up computer software to analyze each SNP and ask: Does allele "A" versus allele "B" of this SNP occur in equal proportions in the myocardial infarction patients and the control individuals? In the vast majority of cases, there will be no difference in proportions; for a particular SNP, however, there may be a significant difference in the proportions (Fig. 6.4). Because the SNP "tags" any nearby genes, the implication is that there is a variant affecting the function of one of the nearby genes in such a way as to modify the risk of myocardial infarction (presumably through involvement in a pathophysiological process).

Several GWAS with precisely this design have been performed for myocardial infarction and coronary artery disease. These studies all found SNPs in a locus on chromosome 9p21 to be highly associated with coronary disease, with weaker associations seen for SNPs in other chromosomes [2–9]. (At the time of this writing, it remains unclear which gene near the 9p21 locus contributes to myocardial infarction.) Other studies have identified SNPs associated with atrial fibrillation [10–16], lipid levels [17–25], diabetes mellitus [26–41], electrocardiographic QT interval [42–46], abdominal aortic aneurysm [47–52], and statin-induced myopathy [53–56].

Recently, genome-wide approaches have been expanded to also study the relationship of physical modifications to the structure of chromosomes (epigenome-wide association studies) [57] and gene expression levels (transcriptome-wide association studies) [58] in relevant tissues to cardiovascular traits. Such studies are still in their early phases and have been applied to some of the traits mentioned above, but they have the potential to further establish the relationship of common DNA compositional and expression differences to disease when applied to larger populations, tissue types, and specific disorders and clinical outcomes.

In parallel with GWAS, which rely on testing the association of *common* variants one-by-one with a trait or disease being considered, great progress has been made in methods to discover *rare* variants as they relate to cardiovascular diseases and traits. Among these approaches are deep medical resequencing of candidate genes, whole-exome sequencing (WES), and exome-wide genotyping. All of these approaches rely on the notion that (1) the genetic variation that is most likely to significantly impact the function of a gene is that which disrupts the protein encoded by the gene and thus may exist in the coding regions of the gene ("exons") and (2) such variation underlying an extreme trait or disease may be rare in the population but enriched in subsets with a high burden of disease.

Deep medical resequencing involves choosing candidate genes for sequencing on the basis of their known role in a particular trait or disease. The exons of an entire gene or set of genes are resequenced. Variants identified in the candidate genes can then be ascertained for their functional

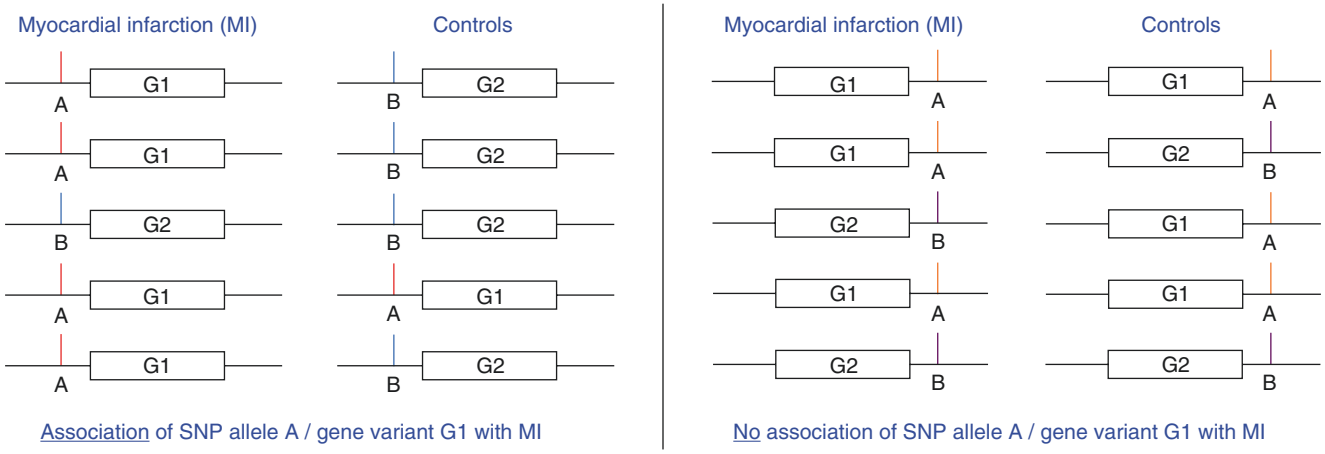

Fig. 6.4 General strategy for genome-wide association studies. For each of millions of SNPs distributed across the genome, the genotypes at the SNP are determined for both cases (myocardial infarction in this example) and controls. As shown on the *left*, an allele of the SNP may be seen in higher proportions in cases than controls. This SNP is therefore associated with the disease, and the strength of the association (*P* value) and exact increase in disease risk can be calculated using biostatistics. Even if this SNP is not in the causal gene (as in this example), it may be in linkage disequilibrium with a polymorphism in the gene, explaining the association with disease. On the *right*, the SNP alleles are present in the same proportions in cases and controls; this SNP is not associated with disease. Typically, out of hundreds of thousands of SNPs, only a few (if any) show a statistically robust association with disease

effects on the encoded proteins as well as their potential to cause the observed trait or disease. Such variants are notable when they are identified in multiple individuals harboring the trait or disease but absent in those who are unaffected. Similarly, when candidate mutations are identified in families and are present in affected members but not in unaffected members, this supports the possibility that the mutation is directly causing the trait or disease. Targeted sequencing gene panels are currently being developed, primarily for research purposes, to identify variants in genes known to contribute to cardiovascular traits and diseases [59–67]; however, their applicability for clinical diagnostics and risk prediction are still limited because it is challenging to interpret whether the identified rare variants are "neutral" (i.e., are of no consequence) or pathogenic [68].

WES applies the principle described for deep medical resequencing across all the regions of the genome that encode proteins (the "exome"). In addition to having applications similar to those for candidate gene deep resequencing, WES allows the ability to identify novel heritable causes underlying traits and diseases. As an example, the first application of WES to a clinical cardiovascular phenotype was its use to identify the underlying cause of a newly identified syndrome of low plasma levels of all the major lipid traits (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides), a disorder called familial combined hypolipidemia [69]. The authors performed WES in two siblings with this disorder and found that both harbored two novel protein-truncating variants in the *ANGPTL3* gene, which encodes a protein that delays the turnover of triglycerides and HDL in experimental models. The authors found no other mutations in other genes that could account for the condition and that were present in both of the affected siblings, and they were thus able to conclude that loss of *ANGPTL3* function was the cause of the dyslipidemia. This example highlights the potential power of WES in identifying new heritable causes of rare or poorly understood clinical traits. Additional potential clinical applications of WES will be discussed further below.

Exome-wide genotyping combines approaches similar to GWAS and WES together to assess protein-coding variation in the genome as it relates to traits and diseases. This method uses SNP panels similar to those used in GWAS but that cover only protein-coding variants for genotyping. These panels include both common and rare coding variants to allow for their combined assessment for association with traits of interest [70–72]. The utility of this approach may be in its ability to capture known rare variants and to assess their burden in particular populations [73] and test their associations with a broad range of traits across large cohorts of patients [74, 75] in a less expensive and more scalable manner than current WES approaches allow.

6.4 Practical Uses of Genomics Studies

GWAS allow for the mapping of diseases (e.g., myocardial infarction) and clinical traits (e.g., cholesterol levels) to specific regions on chromosomes. They narrow the resolution from 3 billion bases (the entire human genome) to around 100,000 bases (chromosomal locus) surrounding a tag SNP. In principle, the tag SNP can then be used for disease risk prediction or for pharmacogenomics (see below). The tag SNP can also be used to pinpoint causal genes underlying the disease or trait or response to therapy. Subsequent studies on those genes can give important insights into basic biology as well as facilitate the development of new therapies that target the genes (Fig. 6.5).

Similarly, sequencing to uncover rare variants has identified multiple putative targets for drug therapies for cardiovascular diseases. A notable example is the discovery of both loss-of-function and gain-of-function protein-coding variants in the *PCSK9* gene. In 2003, rare variants in the *PCSK9* gene were identified that caused extremely high LDL cholesterol levels [76]. Subsequent studies in humans confirmed that these variants were likely gain-of-function mutations that increased *PCSK9* function [77–79], and additional work in mice demonstrated that indeed *PCSK9* increased LDL cholesterol levels [80, 81]. Following this work, sequencing of human subjects with extremely low LDL cholesterol levels identified common loss-of-function *PCSK9* mutations [82]. These mutations result in up to 88% reduction of risk for coronary disease [82, 83]. Additional studies further established the causal and direct relationship of LDL cholesterol levels to coronary disease [84, 85] and paved the way for the development of therapies targeting PCSK9 [86–94]. In 2015, two PCSK9-inhibiting monoclonal antibodies were approved for clinical use to treat extreme forms of hypercholesterolemia [95]. This marked the success of a bench-to-bedside journey that had started only 12 years earlier.

Subsequent large-scale WES efforts in patients with coronary artery disease or early-onset myocardial infarction have also identified cholesterol-related targets of therapeutic rele-

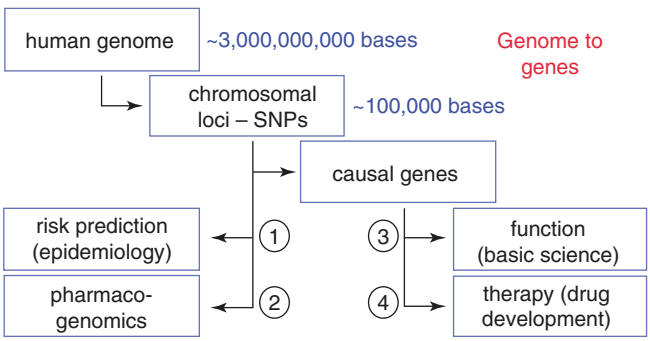

Fig. 6.5 Potential uses of information learned from genome-wide association studies

vance. These include the *LDLR* gene, the indirect target of statin therapy and also the gene responsible for many cases of familial hypercholesterolemia [96]; the *NPC1L1* gene, the target of the cholesterol absorption antagonist ezetimibe [97]; and the *LPA* gene, which encodes the defining protein component of lipoprotein(a) [Lp(a)], a strong coronary disease risk factor [98].

Genomics has also been useful in assessing whether biomarkers for coronary disease are truly causal for disease. In this regard, the recent application of genomics to study the impact of HDL cholesterol and triglycerides to cardiovascular risk has been particularly informative. In the case of HDL cholesterol, the failure of several HDL-raising therapies such as nicotinic acid [99–103] and CETP inhibitors [99, 100, 104–106] was almost simultaneous with the finding that genetic variants that raise HDL cholesterol do not reduce the risk of coronary disease [99, 100, 107–109]. For example, exome-wide genotyping and deep resequencing of the *SCARB1* gene identified carriers of a protein-coding loss-of-function variant in this gene who had extremely high levels of HDL cholesterol but, unexpectedly, had a moderately increased risk of disease, casting doubt on the "protective" role of HDL cholesterol [110]. These and other studies have fueled interest in identifying the physiological functions of HDL beyond their cholesterol content as possible mechanisms by which HDL may still confer protection from cardiovascular diseases [99, 100, 102, 111–113].

In contrast, GWAS and other approaches to studying common variants affecting triglyceride levels have shown that variants associated with decreased triglycerides are also associated with decreased risk of coronary disease [25, 114]. Additional studies of rare protein-coding variants have further established that the lipoprotein lipase (LPL) pathway of circulating triglyceride clearance is protective against coronary disease [115–120]. In particular, loss-of-function mutations in two genes encoding inhibitors of LPL, the *APOC3* gene [116–118, 120] and the *ANGPTL4* gene [115, 119], are protective against coronary disease, making them prime targets for the development of novel therapies to reduce cardiovascular risk [119, 121–123]. A third inhibitor of this pathway, *ANGPTL3*, is also being explored as a therapeutic target [124, 125].

6.5 Genetic Testing and Disease Risk Prediction

After identifying a number of SNPs – in different chromosomal loci across the genome – that are associated with a disease of interest, one can use these SNPs to calculate a genetic risk score for the disease (Fig. 6.6). One simple example entails cataloging for each SNP: Does the patient have two copies of the lower-risk variant of the SNP, two

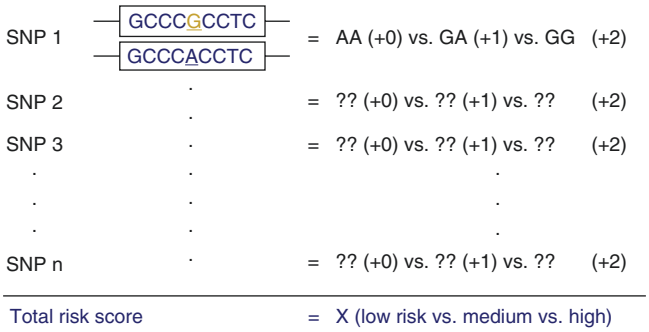

Fig. 6.6 Calculation of a genetic risk score

copies of the higher-risk variant of the SNP, or one copy each of the lower-risk and the higher-risk variant? Risk "points" are assigned depending on the genotype at the SNP. These points are added up for all of the SNPs, yielding a total risk score. This risk score, especially when combined with a traditional risk score (e.g., Framingham risk estimate) that accounts for endogenous (blood pressure, serum lipids, age) and environmental factors (e.g., cigarette smoking), might be useful in predicting the likelihood of developing the disease. Eventually, clinicians would be able to order this panel of SNPs as a blood test and get back a risk score that would help guide patient management.

One of the first published reports of a genetic risk score for cardiovascular disease, in early 2008, demonstrates the potential usefulness of a risk score [126]. The investigators calculated a lipid-based genetic risk score using nine SNPs associated with LDL cholesterol or HDL cholesterol (score from 0 to 18) and found that the score is associated with cardiovascular disease. The higher the risk score, the more likelihood the individual had of developing cardiovascular disease during the study period. However, when this particular genetic risk score was added to a traditional risk prediction model, it did not improve overall risk prediction. After adjustment for traditional risk factors, the relative risk between individuals with high genetic risk scores and those with low genetic risk scores was 1.63, a modest difference [126]. Although the degree of risk discrimination is likely to improve as additional SNPs discovered to be associated with cardiovascular disease are added to the genetic risk score, it remains to be seen whether it will be enough to significantly improve on current risk prediction strategies.

For a healthcare provider presented with this type of genetic information, it will be a challenge to meaningfully integrate it into clinical practice. This is especially true when the relative risks associated with SNP variants are in the 1.0–2.0 range – i.e., the at-risk genotype confers between one and two times the risk of developing the disease – as seems to be the case with most disease-associated genotypes. Providers must already ponder the utility of novel biomarkers, such as high-sensitivity C-reactive protein, that are only modestly

predictive of cardiovascular disease and do not reclassify large proportions of patients into new risk categories [127]. To date, genetic risk scores do not appear to be any more predictive than these biomarkers. Indeed, it remains unclear in the absence of any clinical trials whether a genetic risk score will prove more useful than simply asking the question: "Do you have a family history of heart disease?"

Nevertheless, several companies see significant commercial potential in these types of risk scores and have already started marketing SNP panels to the general public, charging hundreds to thousands of US dollars. The implication of the advertising for these panels is that they will let patients know if they are at higher risk for particular diseases. None of these panels has yet been shown to add value to traditional risk factor algorithms, and they should not be recommended to patients at this time for that purpose.

There are other important limitations of these SNP panels. They do not include rare variants that cause disease (these include the mutations that are unique to one person, or to one family, and so are not going to be found on the SNP panels). So while the patient may learn from an SNP panel that she has a variant of a common SNP that modestly decreases the risk of a particular disease, e.g., breast cancer, she may unknowingly harbor a mutation – not found by the SNP panel – that dramatically increases her breast cancer risk. In this case, having only partial genetic information would give false reassurance and may even be harmful if the patient chooses to forego screening with mammography.

Furthermore, because the initial series of GWAS were performed in Caucasian populations of European ancestry, the first generation of SNP panels may not be relevant to individuals of other ethnic or racial backgrounds. For now, non-Caucasian individuals will benefit less than Caucasians from the recent advances in genomics, although this situation should change as more GWAS are performed in a wider variety of racial and ethnic groups.

When asked about SNP panels by patients, it is appropriate to say that the tests are experimental – they may eventually prove to be useful, but they may also prove to be a waste of money. It is also appropriate to point out that many old-fashioned preventative health practices – good diet, weight control, exercise, and smoking cessation – can have a far larger impact on one's risk of getting a disease than any genetic influences that one may learn about from genetic testing.

6.6 Pharmacogenomics

The field of pharmacogenomics – the use of human genomic variation to predict efficacy and toxicity of drug therapy – is a promising area for the clinical application of genomic information. Commonly used medications such as lipid-lowering therapy, antihypertensive drugs, antiarrhythmic drugs, and anticoagulants have differential effects depending on variation in certain genes. The ultimate objective of pharmacogenomics is to deliver the "right drug for the right patient" by accurately predicting both therapeutic response and safety before a drug is prescribed.

One scenario for the practical application for pharmacogenomics is the use of a screening test to identify patients who are at risk for adverse side effects from medications or who are unlikely to respond to a therapy (Fig. 6.7). A patient presenting to medical attention with a particular condition would undergo the screening test, which would identify the genotype of a relevant polymorphism or set of polymorphisms. The genotype information would be used to determine whether the patient's condition is likely to improve from the treatment, whether the treatment poses a risk and should be avoided altogether, or how much of the treatment should be given – i.e., tailoring the dose to the patient.

When associations between genotype and drug sensitivity have been identified, as in the case of INR response to warfarin therapy on the basis of *CYP2C9* genotypes and *VKORC1* haplotypes, trials must be conducted to evaluate the clinical efficacy of the gene-based prescribing strategy and determine whether the increment in efficacy or safety warrants the cost of genetic testing [128]. An initial trial reported in 2007 assessed an algorithm that used a patient's specific *CYP2C9* and *VKORC1* SNPs to calculate an ideal starting warfarin dose for anticoagulation. When compared to the usual practice (i.e., providers picking a starting dose using best judgment), this specific algorithm did not improve the safety of warfarin initiation (out-of-range INR measurements were not reduced compared to traditional dosing), although it did reduce the number of dosing changes needed [128]. A subsequent study using six additional algorithms for calculating warfarin dose based on *CYP2C9* genotype versus a nongenetically determined dosing strategy found a significantly higher percentage of genotype-dosed patients with INR >2 5 days after initiation relative to the non-genotype-based dosing cohort [129]. More research studies are underway to see whether genetic dosing of warfarin will be clinically useful in broader practice.

Just as GWAS are being used to characterize disease risk, a similar strategy can be used to characterize appropriate or

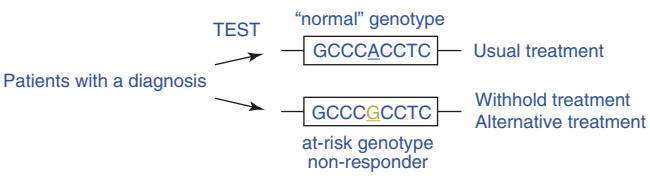

Fig. 6.7 The general strategy of pharmacogenomics

adverse responses to therapy. A GWAS published in 2008 showed that individuals with one genotype at an SNP in the *SLCO1B1* gene have 17 times the risk of statin-induced myopathy than individuals with another genotype [53]. This dramatic difference in relative risk (though not absolute risk, given the overall rarity of statin-induced myopathy) suggests that a genetic test for this SNP could be helpful in predicting which patients are at risk of getting myopathy before they are started on statins. A *SLCO1B1* SNP test might be particularly useful for patients in whom there is already a clinical suspicion for risk of myopathy (e.g., family history, history of myalgias on statin therapy). As with all genetic findings to date, however, this strategy needs to be tested in a clinical trial before it can be recommended for general use.

Another potential application of genetics to predicting response to therapy involves the antiplatelet agent clopidogrel, which has become a mainstay of post-acute coronary syndrome (ACS) patient management, particularly after percutaneous coronary intervention (PCI). Clopidogrel is converted into its active metabolite in the liver by the cytochrome P-450 2C19 enzyme. In three large studies of post-ACS patients on clopidogrel therapy (TRITON-TIMI 38, FAST-MI, and AFIJI), the *CYP2C19* gene encoding this enzyme was genotyped, with identification of at least one reduced-function allele in ~30% of individuals. In all of the three studies, carriers of reduced-function *CYP2C19* alleles suffered significantly higher rates of cardiovascular death, myocardial infarction, and stroke [130–132]. This is consistent with the finding in TRITON-TIMI 38 that reduced-function allele carriers had lower plasma levels of the active metabolite of clopidogrel [131].

However, further studies have called into question the value of using *CYP2C19* genotype to guide post-ACS clopidogrel dosing. One study compared data from clinical trials examining effects of clopidogrel vs. placebo on outcomes and observed a comparable impact on risk between the two groups [133]. Another study in patients who largely underwent PCI with stenting found that carriers of reduced-function *CYP2C19* alleles had a higher rate of adverse events within 30 days of initiating treatment [134]. Larger meta-analyses of patients undergoing PCI have had mixed findings, with one study finding that reduced-function allele carriers had a higher rate of in-stent thrombosis and other adverse cardiovascular events than non-carriers [135]; however, these conclusions were not supported by other meta-analyses in lower-risk patients [136–138]. To date, there are still no published reports from large clinical trials assessing the utility of prospective *CYP2C19* genotyping in improving clinical outcomes. Such studies will be needed to determine whether routine post-ACS genotyping of *CYP2C19* will be of any merit in reducing poor outcomes.

6.7 Risks of Genetic Testing

Although some "early adopter" patients may take the initiative to avail themselves of commercial SNP genotyping services and then bring genetic information to providers for interpretation, others will approach their providers first and ask whether genetic testing is advisable. It may seem harmless for a patient to undergo SNP genotyping – typically involving only a swabbing of the inside of a cheek or a drawing of a blood sample – but there are important potential consequences to consider. As mentioned above, it is not yet clear how physicians should best interpret the results of genetic testing, since few clinical trials have been done. Furthermore, in the "Google era," there is the danger of patients overinterpreting the results of their tests based on misleading information available on the Internet.

One worrisome possibility is that a patient may be falsely reassured by hearing that his genetic risk score is low. He may not be vigorous about lifestyle changes that, if enacted, would reduce his risk of disease even more than the protection offered by his favorable genetic profile. Conversely, a high genetic risk score may cause undue worry and even strain family relations. For example, a person may learn that the spouse is more likely to develop a serious illness, and this may impact their relationship as well as relationships with parents and potential offspring. Arranging for a patient and family members to meet a genetic counselor is recommended if this type of situation should arise.

Finally, privacy issues should be seriously considered prior to the use of genetic tests. It remains to be seen what insurance companies will do if they obtain access to genetic data. The US Congress has acted to prohibit discrimination by employers and health insurers on the basis of genetic testing with the Genetic Information Nondiscrimination Act (GINA), but further ethical safeguards will undoubtedly be needed as the social implications of genomics become clearer.

6.8 Conclusion

Although genomics offers great promise for the improvement of cardiovascular medicine, applications of the technology are still being demonstrated and validated, and the clinical utility of genomics for diagnosis and intervention is in its infancy. Yet with the enormous publicity surrounding genomics discoveries, it will be natural for patients to seek advice about genetic testing from their providers. These inquiries should be welcomed, since they reflect patients taking an active interest in their own health, and they are opportunities for providers not only to educate patients about genomics – to highlight the present uncertainty of the clinical

usefulness of the tests, as well as the potential hazards of obtaining the information – but also to reinforce old-fashioned preventive messages, good diet, weight control, exercise, and smoking cessation, as well.

6.9 Case Study 1

A 57-year-old Caucasian man presents to your clinic for the first time. He is eager to talk to you about the results of his "gene tests." Upon hearing about a commercial "personal genome service" that reads more than 500,000 locations in the genome and offers information on more than 100 diseases, he immediately signed up for the service. He has printed out all the results of the tests and brought them to you so you can read them and keep them in his medical record. He is particularly concerned because the tests reveal that he has an increased risk of having a heart attack. When you look at the specific information in the printouts, you see that on the basis of several SNP genotypes, his relative risk of myocardial infarction is estimated to be 1.6 times that of the general population.

On physical examination, the patient is overweight and moderately hypertensive. He admits that he does not regularly exercise, smokes half a pack of cigarettes a day, and has not been taking the cholesterol medication prescribed to him by a physician 3 years ago. He asks how concerned he should be about the results of his genetic testing.

Answer: You can advise the patient that although his genetic testing may suggest a modestly increased risk of heart attack, the information is not useful at the present time because there have been no clinical trials testing whether this type of information is valid. You should point out that he has several traditional risk factors for myocardial infarction – high blood pressure, high cholesterol, and tobacco use – all of which make it much more likely that he will get a heart attack in comparison to his putative 1.6-fold risk from his SNP genotypes. Importantly, he can do something about those risk factors – improve his diet, exercise regularly, take his prescribed medications, and stop smoking – while he cannot do anything about his genetics.

Given the potential privacy issues, keeping the results of nonclinical genetic testing in the medical record is not advisable at this time.

6.10 Case Study 2

You are seeing in your clinic a 63-year-old woman whom you have been following for several years. She suffered a myocardial infarction 2 years ago, after which she was appropriately prescribed a statin drug for secondary prevention. She stopped taking the statin because she developed severe muscle aches, and she was switched to ezetimibe instead. On a fasting lipid profile taken several weeks ago in anticipation of today's visit, her LDL cholesterol remains quite elevated – 135 mg/dL – far above the optimal goal of 70 mg/dL. You advise her that she really should be on a statin drug, and you can prescribe her a different statin than the one she took before in the hope of avoiding her prior symptoms. She is hesitant to proceed; she has learned that her father developed bad "muscle disease" when he was taking a statin 10 years ago, requiring hospitalization, and both her brother and sister have experienced muscle aches when taking statins.

Is there a role for genetic testing in this patient's management?

Answer: A SNP in the *SLCO1B1* gene has recently been reported to be strongly associated with myopathy [53]. Individuals with the at-risk genotype have 17 times the risk of developing myopathy compared to other individuals. There is now a commercial test for this *SLCO1B1* variant available. Given this patient's prior symptoms and her strong family history, she appears to be at increased risk of statin-induced myopathy. Determining if she has the at-risk *SLCO1B1* genotype could be helpful in her management; if she does have the genotype, it would be prudent to avoid statin therapy altogether. If she does not have the genotype, one might be encouraged to cautiously start her on a different statin.

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Management of Diabetes Mellitus

7

Alicia J. Jenkins, Emma Scott, Jordan Fulcher, Gary Kilov, and Andrzej S. Januszewski

Abbreviations

4S	Scandinavian Simvastatin Survival Study
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	Angiotensin-converting enzyme
ACR	Albumin–creatinine ratio
ADA	American Diabetes Association
ADS	Australian Diabetes Society
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation
AGEs	Advanced glycation end-products
Apo	Apolipoprotein
ARB	Angiotensin receptor blocker
ARIC	Atherosclerosis Risk in Communities
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
BP	Blood pressure
CAC	Coronary artery calcium
CACTI	Coronary Artery Calcification in Type 1 Diabetes study
CAD	Coronary artery disease
CARDS	Collaborative Atorvastatin Diabetes Study
CARE	Cholesterol and Recurrent Events
CKD	Chronic kidney disease
COX-1	Cyclooxygenase-1
CTTC	Cholesterol Treatment Trialists' Collaboration
CVD	Cardiovascular disease
DASH	Dietary Approaches to Stop Hypertension
DCCT	Diabetes Control and Complications Trial
DPP	Diabetes Prevention Program
EASD	European Association for the Study of Diabetes
EDIC	Epidemiology of Diabetes Intervention and Complications
eGFR	estimated glomerular filtration rate
EKG	Electrocardiogram
ESRD	End-stage renal disease
ET-1	Endothelin-1
ETDRS	Early Treatment Diabetic Retinopathy Study
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes
FMD	Flow-mediated dilation
GFR	Glomerular filtration rate
HDL-C	High-density lipoprotein cholesterol
HMG-CoA	Hydroxymethylglutaroyl coenzyme A
HPS	Heart Protection Study
IDF	International Diabetes Federation
IMT	Intima-media thickness
JPAD	Japanese Prevention of Atherosclerosis with Aspirin for Diabetes
LDL-C	Low-density lipoprotein cholesterol
MI	Myocardial infarction
PKC	Protein kinase C
POPADAD	Prevention of progression of arterial disease and diabetes

A. J. Jenkins (✉)
NHMRC Clinical Trials Centre, University of Sydney, Camperdown, Sydney, Australia

University of Melbourne, Department of Medicine, Melbourne, VIC, Australia

Department of Diabetes and Endocrinology, St. Vincent's Hospital, Fitzroy, Melbourne, Australia
e-mail: alicia.jenkins@ctc.usyd.edu.au

E. Scott · J. Fulcher
NHMRC Clinical Trials Centre, University of Sydney, Camperdown, Sydney, Australia

G. Kilov
University of Melbourne, Department of General Practice, Melbourne, VIC, Australia

A. S. Januszewski
NHMRC Clinical Trials Centre, University of Sydney, Camperdown, Sydney, Australia

University of Melbourne, Department of Medicine, Melbourne, VIC, Australia

P. P. Toth, C. P. Cannon (eds.), *Comprehensive Cardiovascular Medicine in the Primary Care Setting*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-319-97622-8_7

PPAR	Peroxisome proliferator-activated receptor
PWV	Pulse wave velocity
RAAS	Renin-angiotensin-aldosterone system
RACGP	Royal Australian College of General Practitioners
SLE	Systemic lupus erythematosus
UKPDS	UK Prospective Diabetes Study
VADT	Veterans Affairs Diabetes Trial
VEGF	Vascular endothelial growth factor
VLDL	Very low-density lipoprotein

7.1 Introduction

Diabetes mellitus is an increasingly common chronic condition characterized by an absolute or relative lack of insulin, hyperglycemia, dyslipoproteinemia, and vascular damage that can affect every organ system in an individual, which impacts their family, friends, colleagues, and the local and global community and economy [1]. There is an epidemic of diabetes, in both advantaged and disadvantaged countries, and by 2030 it is predicted that over 80% of people with diabetes will be in disadvantaged countries. The prevalence of diabetes in most Western countries is estimated at ≈8.8%, and in some high-risk regions such as North Africa, the Middle East, and Pacific Islands, it is estimated at 15–30% [2]. The majority of people with diabetes (85–95%) have Type 2 diabetes, which can be asymptomatic and remain undiagnosed for years, during which time chronic diabetes complications may develop. People with diabetes, and even with prediabetes (in which glucose levels are above normal but not sufficiently high to meet diagnostic cut-points for diabetes), have at least a two-fold higher risk of cardiovascular disease (CVD) than their non-diabetic peers. CVD is the cause of death in approximately 60% of people with diabetes; hence the primary care physician must remain well-informed and diligent regarding the primary and secondary prevention of CVD in diabetes.

The primary care physician is ideally placed to screen for, diagnose, and manage people with diabetes, particularly given the need for diabetes education and support, regular screening for complications, control of multiple vascular risk factors, potentially multiple long-term medications and vaccinations, involvement of several other healthcare professionals, management of coexisting and often associated health issues, and diabetes-related regulatory paperwork such as for driving, travel, or life insurance. While an endocrinologist can perform many of these tasks for people with diabetes, there are simply too few endocrinologists available to provide this care alone. Furthermore, these specialists tend to be concentrated in larger cities, with decreasing accessibility in regional towns, or rural and remote areas where many people with diabetes live. Diabetes crosses all geographic, as well as ethnic, age, gender, religious, political, and socioeconomic boundaries.

In this chapter we will review the diagnosis and management of diabetes and its associated complications, including CVD and its microvascular complications. We will discuss types of diabetes, related health conditions, recommended screening and treatment targets, and evidence-based approaches, suggest useful resources for knowledge updates, and describe an illustrative patient.

7.2 Types of Diabetes Mellitus

Diabetes is categorized into several subtypes, among which the three most common are Type 2 diabetes, Type 1 diabetes, and gestational diabetes (Table 7.1) [3]. Based on a Swedish study, a new classification into five diabetes subtypes has recently been suggested [4]. In most countries, about 90–95% of people with diabetes have Type 2 diabetes, and about 5–10% have Type 1 diabetes, which often commences in childhood or adolescence [2]. Rates of Type 1 diabetes are lower in many non-Caucasian countries [5]. Historically Type 2 diabetes was regarded as a condition of the middle-aged or elderly, but due to the much higher rates of obesity and sedentary lifestyles, the onset of Type 2 diabetes is now not uncommon in young adults or even in children. Young people from high-risk ethnic groups (e.g., Native American Indians, African Americans, Pacific Islanders, and Indigenous Australians), those with a family history of Type 2 diabetes, and those who are obese are at particularly high risk [6]. In the SEARCH study (US), 11% of those aged <20 years diagnosed with diabetes had Type 2 diabetes [7]. Hence, the primary practitioner should not exclude a differential diagnosis of Type 2 diabetes based on youth. Young people who develop Type 2 diabetes accumulate an even higher risk of diabetes complications, including CVD and premature death, than people with a similar duration of Type 1 diabetes [8, 9]. This likely relates to typically higher rates of vascular risk factors (e.g., obesity, hypertension, dyslipidemia, and insulin resistance) in youth with Type 2 diabetes. However, paralleling

Table 7.1 Types of diabetes mellitus

Type 2 diabetes
Type 1 diabetes
Gestational diabetes mellitus (GDM)
Latent autoimmune diabetes of adults (LADA)
Monogenic forms of diabetes (e.g., MODY)
Related to genetic syndromes (e.g., DIDMOAD)
Secondary to (acute or chronic) pancreatitis
Related to other endocrine disorders (e.g., acromegaly, Cushing's disease)
Drug-induced diabetes (e.g., corticosteroids, some antipsychotic drugs, hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, some anti-HIV drugs)

increasing obesity rates in general society, more people with Type 1 diabetes are now overweight or obese than in the past and have features of the metabolic syndrome (sometimes called "double diabetes"), which is associated with increased vascular complication risk [10–12].

Another common form of diabetes is gestational diabetes [13–15], which usually develops in the second or third trimester and affects approximately 4–8% of pregnant women in Western countries, and is usually screened for by an *oral glucose tolerance test* (oGTT) during pregnancy. As gestational diabetes affects young women and usually resolves post-pregnancy, the diabetes duration is too short to lead to CVD. However, around 60% of these women will develop Type 2 diabetes later in life and so require diabetes prevention advice and ongoing screening for diabetes beyond their pregnancies [16].

Prediabetes or Type 2 diabetes may also be drug-induced, which often resolves with drug cessation or the use of non-diabetogenic alternates if possible. Diabetogenic drugs in common use are immunosuppressive, anti-inflammatory corticosteroids, such as those used in severe asthma exacerbations, post-organ transplantation, and connective tissue diseases (e.g., rheumatoid arthritis and systemic lupus erythematosus (SLE), both of which are associated with increased CVD risk [17–19]). Some antidepressant and antipsychotic drugs and protease inhibitors for HIV treatment also have significant diabetogenic effects. Other commonly used cardiovascular drugs, including thiazide diuretics used for blood pressure (BP) control or fluid retention, and low-density lipoprotein cholesterol (LDL-C)-lowering HMG-CoA reductase inhibitors ("statins") have proven, but weaker, effects on worsening hyperglycemia, increasing the risk of prediabetes and Type 2 diabetes [20–22].

Meta-analyses suggest that statins are associated with a ≈ 9% increased risk of the development of Type 2 diabetes [23, 24], but since those most at risk have prediabetes and are at high CVD risk, the benefits of statin therapy (reducing the risk of major vascular events by 22% per each 1 mmol/L LDL-C reduction [25]) outweigh the risks. Henriksbo *et al.* suggest that the link between statins and hyperglycemia is via activation of an immune response which impairs insulin action and is suppressed if the sulfonylurea glyburide is taken with a statin [26], though this is not yet recommended in clinical practice. Alternate hypotheses are that increased risk of diabetes relates to LDL-C lowering *per se*. In support, several studies have identified associations between alleles associated with lower LDL-C levels and higher risk of Type 2 diabetes [27, 28].

In all forms of diabetes, there are both genetic and environmental risk factors contributing to its onset, abnormal insulin secretion and action, and abnormalities of carbohydrate, protein, and fat metabolism. We have previously reviewed the pathophysiology of diabetes [29].

People with other chronic forms of diabetes mellitus, such as that due to chronic pancreatitis, hemochromatosis, cystic fibrosis, or post-transplantation, are also at risk of CVD and diabetic microvascular complications.

7.3 Diagnostic Criteria and Screening for Diabetes

The American Diabetes Association (ADA) diagnostic criteria for diabetes in the non-pregnant state [30] are shown in Table 7.2, which also includes the normal reference range and levels for intermediate levels of elevated glucose (sometimes called prediabetes). Prediabetes itself is a risk factor for CVD, as well as for Type 2 diabetes. A diagnostic test should be repeated on a separate day, so there are at least two tests meeting the diagnostic criteria.

If a patient has typical symptoms of diabetes (e.g., polyuria, polydipsia, weight loss), an oGTT often need not be performed. For example, an elevated random blood glucose and an elevated fasting blood glucose will suffice for diabetes diagnosis in such a setting.

If needed for diagnosis, such as in an asymptomatic subject with borderline random blood glucose levels, an oGTT should be performed. For three days beforehand, smoking and caffeine should be avoided (as these impair glucose tolerance), and daily carbohydrate intake should be at least 150 g. The test is performed after fasting (water permitted) for at least 8 h. A 75 g glucose load dissolved in water is consumed within 20 min., and the patient remains sedentary during the testing period, with venous blood tested at baseline and 2 h. after the glucose load [31].

Advantages of an HbA1c test are that it is less time-consuming for the subject, does not require fasting, reflects glycemia over the preceding 2–3 months, and has greater pre-analytic stability than plasma glucose (which can fall

Table 7.2 Biochemical diagnostic criteria for diabetes mellitus

FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h[a]
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during an oGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water[a]
OR
HbA1c ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay[a]
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L)

[a]In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing

with prolonged time between blood sampling and testing, particularly if the blood is not taken in a sodium fluoride tube [31]). The HbA1c test should be performed in an accredited laboratory participating in a national quality control program and aligned with the Diabetes Control and Complications Trial (DCCT) HbA1c assay. The HbA1c test is not reliable in patients with hemoglobinopathies, anemia, iron deficiency, or recent blood loss or transfusion, or those on erythropoietin treatment. Some HbA1c test types are also adversely affected by renal failure and elevated bilirubin levels, and the pathology laboratory performing the HbA1c test should be able to provide such information. HbA1c tests performed by point-of-care test devices are not sufficiently reliable for diabetes diagnosis, as is the diagnosis or exclusion of diabetes by finger-prick blood glucose levels.

Diagnostic criteria for diabetes from the European Association for the Study of Diabetes (EASD) [32], the International Diabetes Federation (IDF) [33], and the Australian Diabetes Society (ADS) [34] are similar. Criteria for diabetes in pregnancy diagnosis are more controversial [35].

National diabetes associations usually recommend screening asymptomatic overweight (BMI >25 kg/m^2) adults for Type 2 diabetes if they have one or more of the other diabetes risk factors in Table 7.3 and screening all asymptomatic adults over the age of 45 years or younger (e.g. ≥40 years) if from a high-risk ethnic group [36]. Screening by (laboratory-based) fasting blood glucose, HbA1c, or 2-h. glucose after an oGTT is recommended every 3 years thereafter if all tests are normal or sooner if symptoms arise or risk profiles increase. Whole-population screening is not recommended. The primary care provider is well-placed to screen for diabetes. Many diabetes associations, such as the ADA, provide a risk assessment questionnaire [3], which usually includes age, ethnicity, weight, and family history of diabetes to help target those for screening by blood tests.

Table 7.3 Diabetes risk factors

Type 1
Family history of diabetes
Diseases of the pancreas
Infection or illness that can damage the pancreas
Type 2
Obesity or being overweight
Impaired glucose tolerance
Insulin resistance
Ethnic background (Hispanic/Latino Americans, African Americans, Native Americans, Asian Americans, Pacific Islanders, and Alaska natives)
Gestational diabetes
Sedentary lifestyle
Family history
Polycystic ovarian syndrome
Age

The rationale for targeted screening for Type 2 diabetes is that many people (an estimated one in three Americans and higher rates in other countries [2]) have Type 2 diabetes but are asymptomatic or attribute their symptoms to other conditions (e.g., prostatomegaly, aging); that prediabetes is associated with increased CVD risk; and that based on observational studies, people diagnosed via screening have a lower HbA1c level and fare better clinically than those diagnosed later [37].

Due to the recent increase in Type 2 diabetes in youth and their particularly poor long-term prognosis, screening for Type 2 diabetes by the above criteria is recommended for children aged 10 years (or at onset of puberty if that occurs <10 years of age) if they are overweight (defined as ≥85 percentile for age and sex, weight >120 percentile for height, or weight for height above 85th percentile) *AND* if they have at least two of the following risk factors: (i) are from a high-risk ethnic group (e.g., Hispanic, Pacific Islander); (ii) have a first- or second-degree relative with Type 2 diabetes; (iii) if their mother had diabetes (including gestational diabetes) during their gestation; (iv) have polycystic ovary syndrome; and (v) have signs of insulin resistance (e.g., acanthosis nigricans, a black velvety skin rash in skin folds, particularly the neck and axillae – Fig. 7.1) or insulin resistance-associated features such as hypertension or dyslipidemia. As for high-risk adults, rescreening is recommended every 3 years.

Type 1 diabetes usually has an acute clinical onset with marked thirst, frequent urination, and weight loss, so routine screening is not recommended in the clinical setting.

7.3.1 Prevention and Reversal of Diabetes

Currently there are no clinically effective methods recognized to prevent or retard Type 1 diabetes onset, though many clinical trials have been, and are being, conducted. These typically involve screening individuals with a positive family history of Type 1 diabetes and usually test relevant antibody and gene status. Available trials are usually listed at TrialNet (www.trialnet.org).

Type 2 diabetes onset can be prevented or at least delayed [38–42] and, as shown by bariatric surgery for morbidly obese diabetic patients, can sometimes be reversed [43–45]. The Diabetes Prevention Program (DPP) randomized trial [46] showed that lifestyle modification, including weight loss of at least 7% of body weight in the first 6 months and at least 150 min. per week of exercise similar to brisk walking, could lower Type 2 diabetes incidence over 3 years by 58%. Three lifestyle intervention studies confirm even longer sustained reductions in Type 2 diabetes: the US Diabetes Prevention Program Outcomes Study, 34% reduction at 10 years [38, 41]; the Finnish Diabetes Prevention Study, 43%

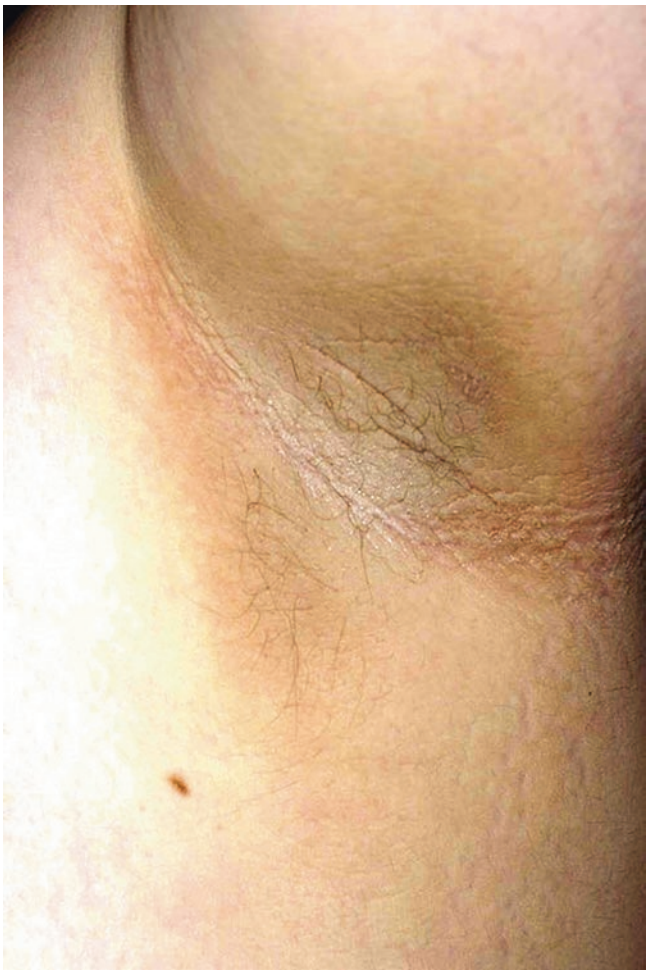

Fig. 7.1 Acanthosis nigricans (Thomas Habif own work http://www.dermnet.com/Acanthosis-Nigricans/picture/22985 under Creative Commons Attribution-Share Alike 3.0 Unported license)

at 7 years [39, 40]; and the Chinese Da Qing Study, 43% reduction at 20 years [42].

The DPP also demonstrated a delay in onset of Type 2 diabetes with insulin sensitizers, though to a lesser extent than with lifestyle changes. The tolerability, proven long safety track record, and low cost of metformin make it the preferred pharmacologic agent for Type 2 diabetes prevention [46]. In the DPP, metformin reduced Type 2 diabetes development by 31%. About 7.8% of the metformin group developed diabetes each year, compared with 11% of the placebo group. Metformin was particularly effective in those with a BMI ≥35 kg/m^2 and in the 25–44-year-old group. Another class of insulin sensitizers are the thiazolidinediones, which improve both glucose and lipids, though these are not widely used due to side-effects such as fluid retention, exacerbation of heart failure, increased fracture risk, and increased risk of bladder cancer [47].

Major weight loss following the development of Type 2 diabetes, such as that achieved by bariatric surgery in those with morbid obesity, can usually improve glycemic control, lessen the amount of glucose control medications needed, and even reverse diabetes [48]. Five-year benefits of bariatric surgery with lapbands have been shown to include improvements in weight, glycemia, and vascular risk factors [49].

7.4 Complications of Diabetes and Comorbidities

The acute and chronic complications of diabetes are summarized in Table 7.4, and health problems that are more common in, but not exclusive to diabetes, are listed in Table 7.5. Many of the conditions that are more common in diabetes, such as obesity, hypertension, and poor mental health, also contribute to a more adverse cardiometabolic risk factor profile and increase the risk of the development and progression of the vascular complications of diabetes. The chronic complications of diabetes are typically divided into microvascular and macrovascular complications, though damage usually occurs not just to blood vessels but to the nerves, connective tissues, and extravascular cells.

Many laypeople, including those with diabetes, and even some clinicians and allied healthcare professionals regard Type 2 diabetes as "mild" diabetes. This statement is usually because, unlike Type 1 diabetes, the glucose fluctuations are not as great and insulin injections are not essential for life. This ignores the facts that the acute and chronic complications of diabetes can also greatly affect people with Type 2 diabetes, even if needing only lifestyle measures for glycemic control. Diabetes is the commonest cause of working-age adult-onset blindness and a leading cause of end-stage renal disease (ESRD) necessitating

Table 7.4 Complication of diabetes mellitus

Acute complications
Dehydration and electrolyte imbalance
Hyperglycemia, including diabetic ketoacidosis and hyperosmolar non-ketotic coma
Increased risk of sepsis
Poor wound healing
Mental health issues, e.g., diabetes distress, anxiety, depression, eating disorders
Chronic complications
Microvascular complications
Diabetic retinopathy
Diabetic nephropathy
Diabetic neuropathy – peripheral neuropathy, autonomic neuropathy
Macrovascular complications
Coronary artery disease (CAD)
Cerebrovascular disease
Peripheral vascular disease
Others
Diabetic cardiomyopathy (independent of hypertension and/or CAD)
Diabetes dementia

Table 7.5 Health problems more common in diabetes

Cardiovascular disease
Hypertension
Congestive cardiac failure
Sudden death, most likely cardiac arrhythmia or CAD-related
Transient ischemic attacks and cerebrovascular events
Peripheral vascular disease
Cardiomyopathy (due to hypertension, CAD, and diabetes *per se*)
Central nervous system
Dementia
Mononeuritis, e.g., III and VI cranial nerve, ulnar nerve
Optic neuritis
Entrapment neuropathy, e.g., carpal tunnel syndrome
Eye
Glaucoma
Cataracts
Optic neuritis and optic atrophy
Adiposity: Overweight or obesity
Dyslipidemia including severe hypertriglyceridemia
Gastrointestinal tract
Non-alcoholic fatty liver disease
Peptic ulcer disease
Cancer often increased risk, decreased risk of prostate cancer
Bone
Osteoarthritis
Osteoporosis
Other autoimmune disease if Type 1 diabetes For example, celiac disease, thyroid disease, pernicious anemia, Addison's disease
Increased risk infections including bacterial, TB, and fungal infections
Periodontal disease
Hearing loss - mild
Pregnancy related
Reduced fertility
Increased miscarriage
Pre-eclampsia and eclampsia
Fetal growth retardation or macrosomia
Congenital malformations in offspring
Increased risk of metabolic syndrome, prediabetes, diabetes, and CVD in offspring
Polycystic ovarian syndrome
Mental health issues
Anxiety, depression, eating disorders

renal dialysis or transplant. Diabetes also increases the risk of heart disease 2–7-fold relative to their non-diabetic peers and increases the risk of non-traumatic lower limb amputations 15-fold [50, 51]. A misconception of Type 2 diabetes being "mild" or "a touch of diabetes" can lead to inertia by the patient, their family, and their clinicians, which may increase the patient's risk of adverse clinical outcomes. As for women in general, those with diabetes, and their clinicians, often also perceive their risk of vascular disease as low. This is not the case. CVD is still a major killer of women in the general population [52], and the relative CVD risk of women with vs. without diabetes is even greater than that of men with diabetes [53, 54]. Women with diabetes lose the female cardioprotection associated with pre-menopausal status [53, 54].

We will now briefly overview the macrovascular, cardiac, and microvascular complications of diabetes and the underlying pathophysiology.

7.4.1 Macrovascular Complications: Accelerated Atherosclerosis in Diabetes

The macrovascular complications of diabetes include CAD, cerebrovascular disease, and peripheral vascular disease. Not only is there more severe arterial disease in people with diabetes; the clinical outcomes are usually worse than that of their non-diabetic counterparts [55].

Evidence from many post-mortem studies [56–63] has demonstrated that the underlying process of atherosclerosis begins in childhood, particularly in Westernized countries, even though vascular disease does not usually become clinically evident until middle-age or later. In people with diabetes or with prediabetes, the underlying process of atherosclerosis is accelerated. Atherosclerosis not only begins earlier; it progresses faster and extends more distally into the arterial tree than in those without diabetes. This more severe atherosclerosis, including its extension into smaller vessels and less arterial collateral formation than in non-diabetic subjects, can make vascular bypass procedures, such as for CAD or peripheral vascular disease, difficult or even impossible due to there being inadequate distal "runoff" [64]. While there are many similarities in the pathology of atheroma in diabetic and non-diabetic subjects, in diabetes, the plaques tend to be more lipid-rich and with more inflammation and hence can be more unstable and prone to rupture, which often triggers a clinical event such as a myocardial infarction (MI) [65]. There is also often a greater level of calcification in both plaque and in the arterial media in people with diabetes [66].

Diabetes has long been recognized to confer a significantly increased cardiovascular risk, both independently and in association with its direct effects on major cardiovascular risk factors. Previous research suggested people with Type 2 diabetes without MI have an equivalent risk of coronary events as those without diabetes who have had a previous MI, supporting the notion that Type 2 diabetes was a coronary disease risk equivalent [67]. This was later shown in a large meta-analysis to be an overestimation, with a population-wide 43% lower risk of a coronary event with Type 2 diabetes alone compared to people with previous MI [68]. Current estimates place the increased risk among middle-aged adults to be about twice that of those without diabetes [69], noting that a patient's age and the duration of their diabetes will influence the magnitude of this risk, and that a given patient's absolute risk will be also influenced by

the presence and control of other cardiovascular risk factors in combination.

In spite of these differences in atherosclerosis prevalence and characteristics, people with diabetes usually respond to the same primary and secondary prevention measures as people without diabetes. For example, the Cholesterol Treatment Trialists' Collaboration (CTTC) individual patient data meta-analyses of outcomes from statin trials have demonstrated the LDL-C-lowering effect of statins and proportional reduction in cardiovascular events are similar in diabetic and non-diabetic subjects. Greater absolute risk reductions from statin therapy will therefore be achieved among those at higher absolute risk, as most people with diabetes are [70].

7.4.2 Peripheral Vascular Disease

Every 30 seconds, somewhere in the world, a leg is lost due to diabetes [71]. Often a lower limb amputation in a person with diabetes is due to a combination of macrovascular and microvascular damage, neuropathy, tissue infection, and impaired wound healing. Due to the more severe and distal disease associated with diabetes, peripheral vascular bypass procedures may not be possible, and a limb amputation is required. Macrovascular disease usually leads to a major above- or below-knee amputation, while microvascular disease usually leads to a non-healing foot ulcer and/or amputation of a toe or forefoot. Smoking is a major contributor to peripheral vascular disease in people with diabetes; hence non-smoking should be strongly promoted and supported. The lipid-lowering drug fenofibrate, unlike statins, has been shown in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial to significantly reduce the risk of lower limb amputation in people with Type 2 diabetes by 37% [72]. This benefit was driven by a 47% reduction in microvascular disease-related amputations, while there was no significant reduction in amputations due to macrovascular disease [72]. The mechanism is suspected to relate to favorable pleiotropic effects on peripheral blood flow and angiogenesis [73].

7.4.3 Microvascular Complications

The microvascular complications of diabetic retinopathy, nephropathy, and neuropathy develop over several years of having diabetes. While rarely seen within the first 5 years of diagnosis of Type 1 diabetes, due to the more insidious onset of Type 2 diabetes, chronic complications can often be present at the time of diagnosis. Of the 51,526 newly diagnosed Type 2 patients in Scotland, 19.3% [74] had diabetic retinopathy at diagnosis, which can coexist with other complications. Hence, a thorough physical examination, ocular screening, renal function testing, and an electrocardiogram (EKG; e.g., to screen for a silent infarct) are prudent at Type 2 diabetes diagnosis.

People with diabetes who develop diabetic retinopathy or nephropathy also have a high risk of other complications (both microvascular and macrovascular) and premature death [75–77]. Their coexistence may relate to a common pathophysiology (discussed below) and common risk factors. Many risk factors associated with the development and progression of renal damage are also risk factors for CVD, including hypertension, dyslipidemia, obesity (particularly central obesity), and smoking, as well as novel risk factors relating to inflammation, a prothrombotic/anti-fibrinolytic state, increased oxidative stress, advanced glycation end-products (AGEs), and alterations in angiogenesis-related factors [78–80].

7.4.3.1 Diabetic Retinopathy

There are both vascular and neural damage components in the retina [81, 82]. Diabetic retinopathy is typically divided into background diabetic retinopathy (further subdivided into mild, moderate, and severe background retinopathy) and proliferative retinopathy. Figure 7.2 shows the various clinical stages of diabetic retinopathy. Non-proliferative retinop-

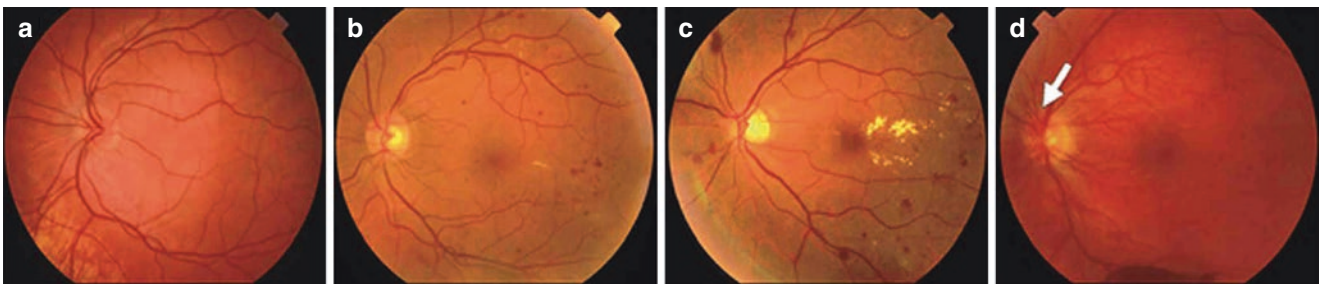

Fig. 7.2 Normal retina and stages of diabetic retinopathy. Fundus photographs showing the clinical stages of diabetic retinopathy: (**a**) a normal retina; (**b**) mild non-proliferative diabetic retinopathy, with hemorrhages, microaneurysms, and hard exudates; (**c**) non-proliferative retinopathy; (**d**) proliferative diabetic retinopathy, with the optic disc (white arrow) and preretinal hemorrhage in the inferior retina [550] (Licensed under CC BY 4.0 via: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4649912/figure/f3/)

athy includes microaneurysms, (dot and blot) hemorrhages, soft exudates (retinal infarcts), and hard exudates, which consist of lipid deposits. The advanced stage, proliferative retinopathy, involves formation of new fragile vessels that are prone to leaking and bleeding, and such a bleed can cause sudden severe vision loss, which may be the first symptom for the patient. Contraction of the resultant fibrous tissue post-bleed can also cause retinal detachment. Figure 7.3 shows the appearance of typical retinal lesions in diagram format.

While clinically the first evident ocular lesions are usually microaneurysms or hemorrhages, there is thought to be a pre-clinical stage of retinal damage; hence, there may be even earlier markers of diabetic retinopathy suitable for clinical use. An exciting potential early marker may be retinal vessel calibers, which we [83–85] and others [86–88] have found in cross-sectional and some longitudinal studies to be associated with and, more importantly, predictive of, subsequently more advanced diabetic retinopathy and also other systemic diabetes complications, including nephropathy and lower limb amputations [86, 89–98]. An advantage of this approach is that these analyses can be performed on retinal photos that are commonly taken for diabetic retinopathy screening. Further evidence must be provided yet as to the power of this approach at the individual patient level.

People with diabetes are 25-fold more likely to go blind than people without diabetes [99], and globally diabetes is the commonest cause of working-age adult-onset blindness [100]. With better risk factor control and regular screening programs, the risk of vision loss due to diabetic retinopathy has declined in affluent countries, such that the lifetime risk of vision loss due to diabetes in Australia is estimated at ≈10%. Regular screening, preferably by an ocular clinician (optometrist or ophthalmologist), and systemic risk factor control, discussed later in this chapter, are important components to prevent or retard diabetic retinopathy. The primary care physician is well-placed to manage this process, including the prescription of angiotensin-converting enzyme (ACE) inhibitors, which have been shown to protect against the development of diabetic retinopathy [101], and fenofibrate, which retards the progression of diabetic retinopathy in Type 2 diabetes [102]. For late-stage diabetic retinopathy, local ocular care by an ophthalmologist, preferably with expertise in diabetic retinopathy, is desirable, to assess need for and administer ocular laser therapy or anti-vascular endothelial growith factor (VEGF) or corticosteroid injections, to surgically remove coexistent cataracts, and to advise re-treatment of any coexistent glaucoma or other ocular disorders. Screening and treatment are discussed further later in this chapter.

7.4.3.2 Diabetic Nephropathy

There are two major aspects to renal function: glomerular filtration and the leakage and non-reabsorption of albumin (and other proteins) into urine. One or both can become abnormal in diabetes, and it is of course the former that in its late stages leads to need for peritoneal dialysis or hemodialysis or kidney transplantation. Diabetic kidney disease (related to increased albumin excretion rate (AER) and reduced glomerular filtration rate (GFR) occurs in 20–40% of people with diabetes and is a leading cause of ESRD [103]. Both albuminuria and GFR loss are risk factors for CVD. Albuminuria, even at low levels (termed microalbuminuria), is already a risk factor for CVD, which may be related to its association and likely contribution to an adverse vascular risk factor profile, including dyslipoproteinemia, inflammation, and a pro-thrombotic state [78, 104–106]. With more severe proteinuria, apolipoprotein (Apo) A1, a major constituent of high-density lipoproteins (HDL), and lipoprotein metabolism-related enzymes are also lost in the

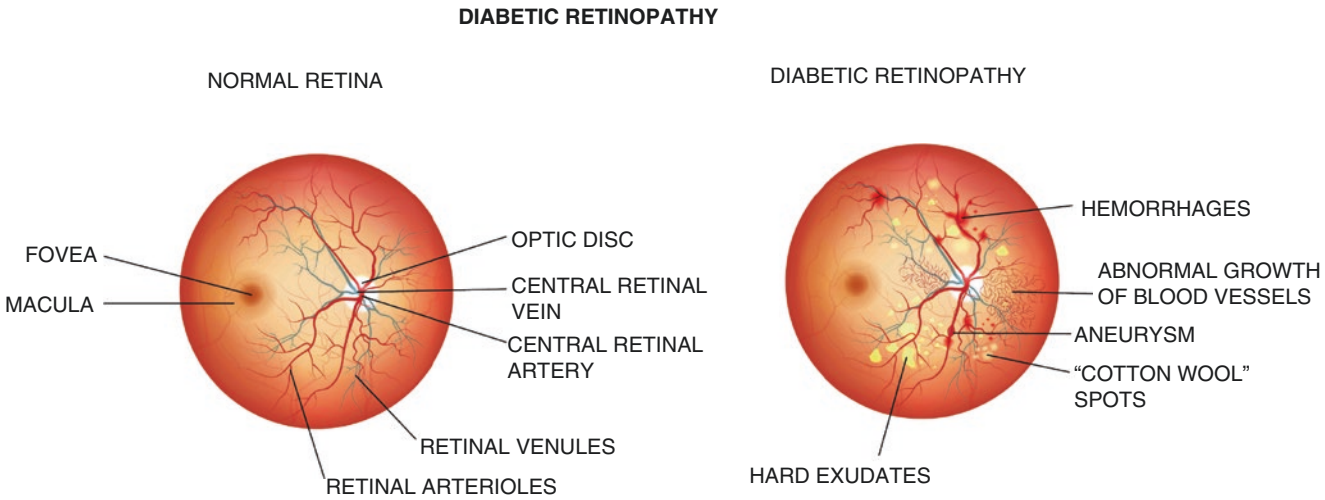

Fig. 7.3 Retinal lesions: (Tefi's Portfolio). Diabetic retinopathy and normal eye retina. Shutterstock. Web. 05 May 2017

Table 7.6 Stages of diabetic nephropathy

Stage	eGFR (ml/min/1.73m^2)	Urinary albumin or protein
1 (pre-nephropathy)	≥30	Normal (<30 mg/g Cr)
2 (incipient nephropathy)	≥30	Microalbuminuria (30–299 mg/g Cr)
3 (overt nephropathy)	≥30	Macroalbuminuria (≥300 mg/g Cr) or persistent proteinuria (≥0.5 g/g Cr)
4 (kidney failure)	<30	Any albuminuria or proteinuria
5 (dialysis therapy)	<30	Any

urine [1, 107], contributing to low HDL levels, which are already common in Type 2 diabetes, and are associated with increased CVD risk.

Diabetic nephropathy is usually divided into five stages (Table 7.6), as recognized by the Joint Committee on Diabetic Nephropathy [108].

In periods of poor glucose control, particularly in youth and at Type 1 diabetes diagnosis, the GFR is above normal (termed hyperfiltration). With progressive renal impairment, the GFR returns to within "the normal range" and then declines. Diabetic nephropathy does not always progress from one stage to the next. The rate of progression of renal dysfunction can be modulated by multiple factors, which the primary care physician can address, including poor glycemic control, hypertension, obesity, smoking, dyslipidemia, and diet.

Stage 1 Diabetic nephropathy (pre-nephropathy) is characterized by renal hypertrophy, hyperfiltration, normal serum creatinine levels, normal urinary albumin and protein levels, and normal BP. It is asymptomatic.

Stage 2 Diabetic nephropathy (incipient nephropathy, which is also silent) is characterized by microalbuminuria. GFR is not decreased, being normal or elevated. There is usually abnormal renal morphology (though renal biopsies are usually not done unless there are atypical features, such as hematuria). Albuminuria is often episodic, being normal during good glycemic control and at rest and increased with exercise or poor glycemic control. This stage may regress spontaneously or by risk factor and ACE inhibitor treatment. BP is often normal.

Stage 3 Diabetic nephropathy (overt nephropathy) has macroalbuminuria or proteinuria as its main manifestation. It is usually associated with hypertension, rising serum creatinine levels and declining GFR. In the absence of antihypertensive agents (usually an ACE inhibitor first), GFR declines at a mean rate of about 1 ml/min/month. Long-term antihypertensive treatment substantially reduces the fall rate by about 60%.

Stage 4 Diabetic nephropathy (kidney failure) is defined as very low GFR (<30 ml/min/1.73 m^2) irrespective of urinary albumin or protein loss. Hypertension is usually present.

Stage 5 Diabetic nephropathy is end-stage renal failure (GFR <30 ml/min/1.73m^2) requiring renal replacement therapy by peritoneal or hemodialysis or kidney transplant [109].

7.4.3.3 Diabetic Neuropathy

Neuropathy in diabetes is thought to have both a vascular and a metabolic etiology. Several types of neuropathy may occur in diabetes: peripheral neuropathy, autonomic neuropathy, mononeuritis, and plexopathy. Diabetes is a risk factor for dementia which, like cardiomyopathy, can be multifactorial. More recently a specific, likely microvascular-based dementia has been suggested – "diabetes dementia" [110].

Both Type 1 and Type 2 diabetes are common causes of a *peripheral neuropathy*, which usually leads to bilateral and fairly symmetrical sensory loss affecting the feet and hands in a "glove and stocking" distribution. Over time it may progress proximally. The major loss is usually sensory, but motor loss and muscle wasting can also occur. A peripheral neuropathy may be present at Type 2 diabetes diagnosis or be the presenting problem leading to its diagnosis.

Diabetes may also affect the *autonomic nervous system*, affecting the cardiovascular system, gastrointestinal tract, genitourinary system, perspiration, and pupil reactions. In the cardiovascular system, autonomic neuropathy can cause postural hypotension (which can range from asymptomatic to debilitating). Postural hypotension due to neuropathy may be further exacerbated by dehydration due to hyperglycemia, diuretics, other antihypertensive agents, and the relatively new sodium-glucose cotransporter 2 (SGLT2) inhibitors [111]. Autonomic neuropathy may also lead to silent or atypical pain myocardial ischemia. Silent MIs are more common in diabetic than in non-diabetic subjects, accounting for approximately one third of infarcts [112].

Autonomic neuropathy can also lead to erectile dysfunction [113, 114], which may also be contributed to by vascular disease, low testosterone levels, psychosocial factors, and drug (e.g., beta blocker) side effects. Neural damage can also lead to incomplete bladder emptying (which can promote urinary tract infections) [113]. In the gut autonomic neuropathy can cause delayed gastric emptying and alternating diarrhea and constipation. The abnormal intestinal motility can lead to bacterial overgrowth, which can cause diarrhea and can also reduce vitamin B12 levels. Perspiration can also be abnormal, such as in response to eating – gustatory sweating [115].

Diabetes, like connective tissue disorders, can also cause a *mononeuritis*, whereby decreased blood flow to a nerve,

perhaps via a vasculitis, results in a nerve palsy. Common sites are the third cranial nerve, the sixth cranial nerve, the facial nerve, the ulnar nerve, or the lateral popliteal nerve. Onset is usually sudden and recovery to a variable extent.

An uncommon neuropathic condition in diabetes is *diabetic amyotrophy*, also known as proximal diabetic neuropathy, diabetic lumbosacral plexopathy, or diabetic polyradiculopathy [116]. This condition, due to a lumbosacral plexus neuropathy, is a painful, often sudden onset of wasting and weakness of the quadriceps and/or hip and/or buttock muscles. It may even be the presentation of Type 2 diabetes. Recovery is usually over 1–2 years.

Pupillary reaction responses can change early in the course of diabetes, even in a pediatric Type 1 diabetes setting [83, 85, 117]. Pupil responses can be measured non-invasively by pupillometry as a clinical research tool. Donaghue et al. [117] have demonstrated that small pupil size at baseline (when subjects were complication-free) was independently associated with the development of microalbuminuria (odds ratio, 4.36 [95% CI, 1.32–14.42]; $p = 0.016$) and retinopathy (4.83 [1.3–17.98], $p = 0.019$), but not with the development of hypoglycemia unawareness. In contrast, there was no association between baseline cardiac reflex function tests and complications 12 years later [83, 117, 118].

Cardiac Autonomic Neuropathy, QT Prolongation, and Arrhythmias

Cardiac cell pacemaking activity is a neural function which can be impaired by diabetes. Cardiac autonomic neuropathy can manifest as reduced heart rate variability and a prolonged QTc interval on the EKG. The QT interval quantifies the time for ventricular depolarization and repolarization.

A prolonged QT interval corrected for heart rate (QTc) is a risk factor for ventricular arrhythmias, vascular disease, and mortality (especially sudden cardiac death) in the general and (Type 1 and Type 2) diabetic populations [119–125]. In a cross-sectional study of Type 1 diabetic and non-diabetic youth, despite similar mean group QTc intervals, we found that a longer QTc interval in people with diabetes was associated with abnormalities of heart rate variability and pupillometry [84].

The incidence of sudden unexplained death in childhood-onset Type 1 diabetes cohorts has been estimated to be 45–48 per 100,000 patient-years [126], 5–6% of all deaths below 40 years old [127] and 10% of all deaths in Type 1 diabetes [128]. An event occurring overnight in a previously well, typically complication-free, young person with diabetes is known as the "dead in bed" syndrome [129, 130]. The underlying cause is thought to relate to a cardiac arrhythmia triggered by hypoglycemia [131]. Hypoglycemia is associated with high levels of (proarrhythmogenic) stress hormones, such as catecholamines, with hypokalemia due to a relative excess of insulin, and with an acute (and reversible) prolonged QTc interval [129]. In studies of free-living people with Type 1 and with Type 2 diabetes simultaneously wearing a Holter cardiac monitor and continuous glucose monitor (CGM), even mild and asymptomatic hypoglycemia was associated with QT prolongation and atrial and ventricular arrhythmias [129, 132, 133].

7.4.4 Diabetic Cardiomyopathy

In addition to damage to the large and small vasculature supplying the myocardium, the myocardium itself can be damaged by the diabetic milieu. Subclinical myocardial dysfunction is common in both Type 1 and Type 2 diabetes [134, 135], requiring detailed cardiac imaging, mostly by echocardiography including tissue Doppler and strain imaging, for its detection [136]. Signs include increased atrial volume, eccentric hypertrophy, diastolic dysfunction, a low to low normal ejection fraction (45–50%), and a dilated inferior vena cava [136].

Congestive cardiac failure is also several-fold more common in people with vs. without diabetes and often has a worse prognosis. Clinical symptoms include dyspnea, orthopnea, peripheral edema, and fatigue. People with diabetes are more likely to develop diastolic than systolic heart failure, which is associated with similar 5-year mortality rates of ≈50–60% [137]. Independent of CAD, coronary microvascular disease, hypertension, and renal failure, it is thought, though still somewhat debated [138], that diabetes can cause a diabetic cardiomyopathy [139–141]. Several factors may be contributory to myocardial dysfunction and heart failure in an individual patient. In diabetic cardiomyopathy, there are abnormal myocardial contraction and abnormal relaxation, increased fibrosis, AGEs, inflammation, altered cell/molecular signaling [136, 142–145], and potentially a contributing role of dietary fructose toxicity [142]. Diabetic cardiomyopathy has been reported to be more common in women than in men; hence a hormonal contribution may be involved [146].

7.5 Pathophysiology of Diabetic Vascular Damage

Diabetes is characterized by endothelial dysfunction in both large and small blood vessels [147]. The vascular endothelium is a large dynamic organ distributed throughout the body and in contact with almost all organs. There are few avascular structures in the body, such as the cornea, cartilage, hair, and nails. While only one cell thick, there are over a trillion endothelial cells in the adult human body, covering a surface area of over 3000 square meters and weighing over 100 g [148, 149]. The vascular endothe-

lium is not just an inert structural lining to the blood vessels, but a dynamic multifunctional organ [150, 151]. The vascular endothelium mediates blood clotting (with procoagulant and anticoagulant actions), inflammation, blood flow, blood vessel repair, and new blood vessel formation; participates in lipoprotein metabolism (in particular the catabolism of triglyceride-rich lipoproteins which are precursors to LDL), and regulates nutrient flow. Many endothelial functions are disturbed in diabetes (Table 7.7). The barrier is leaky, as reflected by albuminuria and retinal lipid exudates. Furthermore, its pro-inflammatory, prothrombotic state with impaired vasodilation and abnormal angiogenesis (e.g., increased in the retina and impaired in wound healing and collateral formation) predisposes to CVD and the microvascular complications.

Table 7.7 Endothelial dysfunction and changes in diabetes

Endothelial function	Feature in diabetes
Structural	Thick basement membranes
Barrier	↑ permeability
Modulate thrombosis/fibrinolysis, platelet activation	↑ thrombosis, ↓ tPA, ↑ PAI-1, ↑ glycoproteins
Influences inflammation	↑ CAMs/monocyte adhesion
Modulate vascular tone (ET-1, NO, ACE)	Altered blood flow/↑ BP and capillary pressure
Lipid metabolism (LPL)	Dyslipidemia
Cell growth/angiogenesis (VEGF)	Cell proliferation/death/ angiogenesis

ACE angiotensin-converting enzyme, *BP* blood pressure, *CAMs* cell adhesion molecules, *ET-1* endothelin-1, *LPL* lipoprotein lipase, *NO* nitric oxide, *PAI-1* platelet activator inhibitor 1, *tPA* tissue plasminogen activator, *VEGF* vascular endothelial growth factor

7.5.1 Common Mediators of Vascular Endothelial Damage Stemming from Hyperglycemia

Dysglycemia, encompassing high glucose, fluctuating glucose, and hypoglycemia, often exacerbated by other traditional and novel risk factors (such as dyslipidemia and high BP, discussed further later in this chapter) can promote an adverse (e.g., pro-inflammatory and prothrombotic, prooxidant) milieu and alter cell signaling and cell behavior that adversely impacts tissue structure and function, ultimately leading to the microvascular, macrovascular, and other cardiac complications of diabetes. A schema is suggested in Fig. 7.4.

Dr. Michael Brownlee has suggested a common intracellular pathway within vascular endothelial cells that

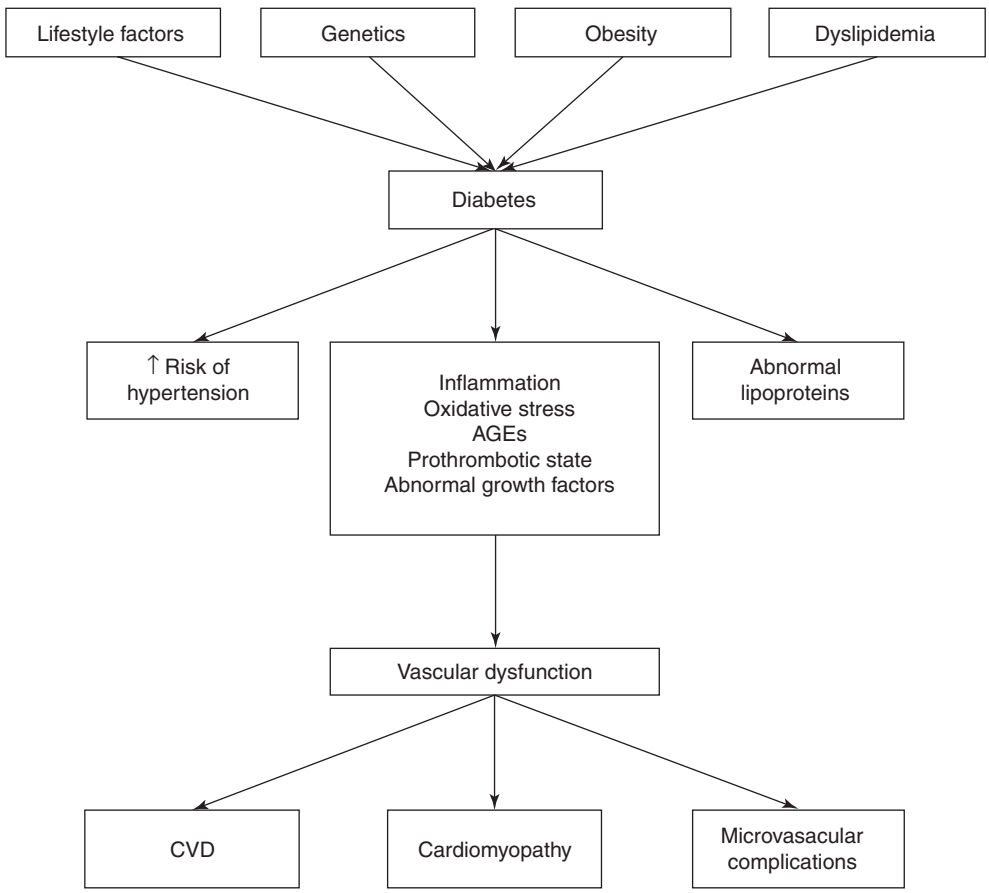

Fig. 7.4 Mediators of vascular complications of diabetes

links hyperglycemia and the vascular complications of diabetes. He suggests, with much supportive preclinical research, that hyperglycemia induces increased mitochondrial oxidative stress, which then activates four pathways implicated in the pathogenesis of diabetic vascular damage: the polyol, hexosamine, protein kinase C (PKC), and methylglyoxal/AGE pathways [152]. This "unifying hypothesis" explains why inhibition of single pathways, such as the PKC-beta pathway [153] and AGE formation [154], which have reached human clinical trials, is not as effective at reducing vascular complications as hoped, as glucose still activates the other non-suppressed pathways. Hence, inhibition of common proximal modulators, such as reduced hyperglycemia, and/or of common distal mediators, such as of increased mitochondrial oxidative stress, is required. Brownlee's team has provided laboratory-based science support of these approaches. There are major clinical trials in both Type 1 and Type 2 diabetes that prove the efficacy of improving glucose control from levels of poor glycemic control for reducing the vascular complications of diabetes: For Type 1 diabetes, the DCCT demonstrated that intensive vs. standard diabetes therapy (with HbA1c levels of approximately 7 vs. 9% (53 vs. 74.9 mmol/mol), respectively) significantly reduced microvascular complications by 26–63% [155]. The relative youth of the DCCT cohort meant macrovascular event rates were low, but they decreased by 42%, which did not reach statistical significance during DCCT, but did so in the observational follow-up – the Epidemiology of Diabetes Control and Complications (EDIC) study [156]. In Type 2 diabetes, the UK Prevention of Diabetes Study (UKPDS) demonstrated vasoprotection of both the macrovascular and microvascular beds [157, 158]. These (DCCT/EDIC and UKPDS) studies have also demonstrated that the vascular (and neural) beds have memory of previous glycemia (discussed in the next section).

In contrast, more recent Type 2 diabetes trials, such as Action to Control Cardiovascular Risk in Diabetes (ACCORD) [159], Action in Diabetes and Vascular Disease (ADVANCE) [160], and the Veterans Affairs Diabetes Trial (VADT) [161], aiming for even tighter glucose control (HbA1c below 6.5% (47.5 mmol/mol) or 6.0% (42.1 mmol/mol)) did not show macrovascular disease benefit of improved glycemia. Potential explanations may be different patient characteristics, the generally tight control of other major risk factors (e.g., BP and lipids) and pleiotropic benefits of the related drugs (e.g., statins), shorter trial duration, confounding effects of metabolic memory, and adverse effects of weight gain and of hypoglycemia. Furthermore, there may be less benefit in lowering HbA1c from moderate to even lower levels compared to lowering HbA1c from high to moderate levels as in the earlier trials.

7.6 Metabolic Memory for Glucose Control

Metabolic memory and the legacy effect are comparable terms that were coined based on post-trial follow-up of the DCCT and UKPDS studies [162–164]. These terms refer to the phenomenon by which the body's tissues continue to respond to poor or good glycemic control for years after the glucose control has improved or worsened. Susceptible tissues include retinae, kidneys, nerves, and arteries. Some non-glucose-related examples of metabolic memory are the persistence of smoking-related increase in CVD and cancer risk years after smoking cessation and of skin cancer risk years after sunburn.

How long can metabolic memory for glycemic control last? The UKPDS data from Type 2 diabetic patients demonstrates a legacy effect of glycemia for 10 years after 10 years with a HbA1c ≈7.0% (53 mmol/mol) [163]. In the Type 1 diabetes DCCT/EDIC study, ≈5.9 years of intensive vs. conventional diabetes management (HbA1c 7 vs. 9% (53 vs. 74.9 mmol/mol)) lowered vascular complication rates for at least 8–12 years [164] and for the eye up to 25 years [165]. It is not yet clear if there is a threshold HbA1c or duration level for metabolic memory and differences in duration of persistence across the full HbA1c spectrum. Some of this clinically important information could be gleaned from ongoing analyses of the UKPDS and DCCT/EDIC trials.

This aspect of metabolic memory should be borne in mind in the interpretation of clinical trials and also in clinical practice. Anecdotally, in clinical practice, patients can become upset that their diabetes complication, such as retinopathy, progresses after much effort on their part to substantially improve their HbA1c levels. They should be counselled that, as shown in the DCCT for retinopathy, there may even be an initial worsening of retinopathy [166] with improved control prior to long-term to very long-term benefit [155]. Metabolic memory may also be a confounder in clinical trial interpretation, particularly in shorter clinical trials.

Potential mediators of glucose metabolic memory are epigenetic changes [167], which are acquired changes in DNA function without changes in DNA sequence, such as DNA and histone methylation, histone acetylation, and telomere shortening, and microRNAs (non-coding RNAs which regulate gene expression at the translational level) [168]. Other potential, not mutually exclusive, mediators of glucose metabolic memory are glucose and AGE-induced modifications of long-lived tissues such as vascular basement membranes, and these may also be a therapeutic target. Some currently used drugs, such as ACE inhibitors, statins, and metformin, also have anti-AGE and DNA protective effects, as well as their primary

actions related to BP and renoprotection, lipid, and glucose lowering, respectively [169–171]. Novel drugs, such as histone deacetylase inhibitors, which reduce epigenetic damage, are currently in human cancer clinical trials and protect against diabetic nephropathy in an animal model [172].

Metabolic memory by the vasculature has also been demonstrated, predominantly in non-diabetic subjects, for lipid and BP control [173]. Recently, metabolic memory for CVD benefit of exposure to fenofibrate by dyslipidemic (defined as triglyceride levels >204 mg/dL and HDL-C levels <34 mg/dL) Type 2 diabetic patients was demonstrated in the 5-year post-trial follow-up of the ACCORD Lipid trial [174]. In the ACCORD Lipid trial, fenofibrate or placebo was added to a statin background in Type 2 diabetic patients and either CVD or CVD risk factors and low HDL-C <50 mg/dL (<55 mg/dL for women and African Americans). While the trial's primary endpoint for all subjects was not positive, the prespecified secondary endpoint of reduced CVD events in dyslipidemic patients was [175]. After the trial less than 5% of participants continued fenofibrate. In the observational follow-up study of 4644 participants, the risk of cardiovascular outcomes among participants previously randomized to fenofibrate vs. placebo was comparable to that originally observed in ACCORD study (HR 0.93 vs. 0.92), but they continued to find evidence that prior fenofibrate therapy effectively reduced CVD in study participants with dyslipidemia (HR, 0.73; 95% CI, 0.56–0.95) [174]. This supports the existence of "metabolic memory" or a "legacy effect" for fenofibrate and/or lipid levels.

7.7 Risk Factors and Biomarkers for the Vascular Complications of Diabetes

7.7.1 Definitions

The terms of risk factors and biomarkers are often used interchangeably. As defined by the World Health Organization (WHO), a risk factor is any attribute, characteristic, or exposure of an individual that increases their likelihood of developing a disease or injury [176]. Some clinicians include in their definition of a risk factor that its attenuation or removal (e.g., smoking, hyperglycemia) is associated with reduction of disease risk or severity, yet not all "risk factors," such as increasing age or diabetes duration, can be altered.

A biomarker can be defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention [176].

7.7.2 Multiple Risk Factors for Diabetes Complications Are Common

The vascular complications of diabetes have multiple risk factors, and each person with diabetes usually has several risk factors. In the 2011–2012 Australian Health Survey of Australian adults with diabetes, over 94% had three or more vascular risk factors concurrently, 25% had three concurrent risk factors, 41% had four concurrent risk factors, and 28% had five or six concurrent risk factors [177]. Many people, with and without diabetes, who develop vascular disease do not have extreme adverse values for an individual risk factor; rather, mild to moderate perturbations in multiple risk factors. The presence of several risk factors at low level, e.g., mildly elevated BP, weight, or LDL-C, which can often be disregarded by the patient or their clinician, can place a person at moderate or high vascular risk. This has led to the recommendations to use absolute cardiovascular risk calculators to quantify and manage cardiovascular risk in primary prevention, which is discussed later in this chapter.

7.7.3 Traditional and Novel Risk Factors

Vascular risk factors, which are often interrelated, are usually divided into traditional and novel risk factors, as summarized in Table 7.8. Risk factors may also be subdivided into those that are unmodifiable and modifiable. Some risk factors reflect the presence of vascular disease; for example, albuminuria, or subclinical disease such as a wide pulse pressure, left ventricular hypertrophy, or increased carotid intima-media thickness (IMT).

Traditional risk factors which are unmodifiable include age, longer diabetes duration, gender, and an adverse family history. With regard to gender, both men and women are at high risk of macrovascular disease. Men usually tend to be at higher risk of microvascular complications, though females with prepubertal onset of Type 1 diabetes tend to be at higher risk than their male counterparts [178, 179]. The reasons for this are not fully elucidated. With regard to family history, the risk of diabetes complications is higher in subjects with other family members with diabetes complications or in Type 1 diabetic patients with non-diabetic family members with hypertension or Type 2 diabetes [180].

Modifiable traditional risk factors, which are also influenced by genetic and environmental factors, include hypertension, dyslipidemia, and obesity. Obesity, in particular central obesity, or an increased waist circumference, may compound hypertension, dyslipidemia, and insulin resistance, but is also thought to act independently. This may be via increased levels of inflammation and increased insulin resistance and perhaps by adipokines, which also modulate

Table 7.8 Risk factors for CVD

Traditional risk factors
Increasing age (including age of diabetes onset)
Diabetes (and for T2D prediabetes) duration
Glycemic control – hyperglycemia
Obesity
Increased waist circumference
Smoking
Hypertension
Dyslipidemia
High triglycerides
High LDL-C
Low HDL-C
Family history of T2D, hypertension, or chronic complications
Novel and emerging risk factors
Glycemic-related
Glycemic variability
Hypoglycemia
Lipoprotein-related
Qualitative and quantitative changes in lipoproteins
For example, small dense LDL (pro-atherogenic/prothombogenic)
For example, lipoprotein glycation and/or oxidation
For example, altered enzyme activities, e.g., paraoxonase
Inflammation, e.g., CRP
Oxidative stress/AGEs, e.g., CML, RAGE, isoprostanes
Insulin resistance, e.g., HOMA
Uric acid
Prothrombotic/antifibrinolytic factors
For example, ↑ PAI-1 activity, ↑ fibrinogen, ↓ tPA activity
For example, microparticles
Platelet activation
Angiogenesis-related growth factor disturbances
For example, PEDF, VEGF levels
Adipokines
Molecular markers
Genetics, e.g., GWAS sNPs
Epigenetics
For example, shorter telomeres/altered telomerase activity
For example, histone modification: methylation, acetylation
For example, microRNA profiles
Evidence of vascular disease
Albuminuria (>30 mg/24 h) or ↑urinary albumin–creatinine ratio (ACR)
Chronic kidney disease (CKD) with reduced GFR <60 ml/min/1.73^2
Diabetic retinopathy
Pulse pressure ≥60 mmHg
Increased carotid IMT (>0.9 mm) or plaque
Ankle-brachial index, 0.9
Left ventricular hypertrophy on echocardiography or EKG
Prior CVD event, even if silent
Cerebrovascular disease
Peripheral vascular disease
Coronary artery calcium (CAC) scores on CT angiogram

insulin resistance and vascular risk [181]. Renal disease progression, even in non-diabetic subjects, is hastened both by obesity [182, 183] and by dyslipidemia [184]. Smoking is a major risk factor for vascular complications, and is discussed in more detail later in this chapter.

7.7.3.1 Lipoproteins

There are many epidemiologic studies showing that an adverse lipid profile, in particular high LDL-C and total cholesterol and low HDL-C levels, is associated with, and predictive of, CVD and the microvascular complications in Type 1 diabetes (in both pediatric and adult age groups) and in Type 2 diabetes [78].

Dyslipidemia is common, particularly in people with Type 2 diabetes. In 2011–2012 in Australia, 86% of adults with diabetes had dyslipidemia, with two thirds having uncontrolled dyslipidemia, compared with 67% and 56%, respectively, in non-diabetic subjects [185].

The lipid profile in people with Type 2 diabetes is typically one of the elevated triglycerides, lower HDL-C levels, and normal or increased total and LDL-C levels. In people with Type 1 diabetes and good HbA1c, renal function, and a healthy BMI, the conventional lipid profile is normal – indeed, triglyceride levels may be slightly lower and HDL-C levels higher than non-diabetic subjects, due to the effects of high circulating levels of insulin on lipoprotein metabolism. In both types of diabetic people with obesity, high HbA1c levels, or renal disease, the triglyceride levels increase, and HDL-C levels fall, and the LDL becomes a more atherogenic phenotype of small dense LDL. Higher triglycerides (>1.7 mmol/L (151 mg/dL)) are associated with a preponderance of small dense LDL [1, 78]. Contributors to dyslipidemia in diabetes include diabetes per se, hyperglycemia, and insulin resistance, which leads to high free fatty acid levels, that together with hyperglycemia drive hepatic production of triglyceride-rich very low-density lipoprotein (VLDL), which is catabolized to low-density lipoprotein (LDL). Poor diet, lack of exercise, smoking, obesity, renal impairment, fatty liver, and some drugs (such as beta blockers, thiazide diuretics, estrogen), infections (including periodontal disease), and unfavorable lipoprotein-related genetics may also be contributory [186, 187].

In addition to quantitative changes in lipid levels, there are qualitative changes in lipoproteins in diabetes, such as by non-enzymatic glycation, oxidation, and glycoxidation (AGEs), and immune complex formation, which enhance lipoprotein pathogenicity in both macrovascular and microvascular systems [1, 78, 188]. For detailed information on lipoproteins in diabetes, there is a textbook on "Lipoproteins in Diabetes" [1], which includes many relevant chapters.

To reach lipid levels associated with lower CVD risk, most people with diabetes, in particular with Type 2 diabetes in Western countries, will require lipid-lowering drugs in addition to lifestyle modifications.

7.7.3.2 Hypertension

Hypertension is common in the general population, and people with diabetes have at least double the risk of hyperten-

sion [189]. Hypertension in people with diabetes is a risk factor both for accelerated atherosclerosis and for the microvascular complications of diabetes, and it is important to treat it with lifestyle changes and with drugs (discussed later in this chapter) to recommended targets. High BP is contributed to by obesity, physical inactivity, smoking, a high-salt diet, hyperinsulinemia, and any renal damage. Family history, likely reflecting genetic factors, and also intrauterine factors are also likely contributory. In diabetes increased sympathetic tone and activation of the renin-angiotensin-aldosterone system (RAAS) are additional features promoting hypertension [190].

Because of the lability of BP, repeated measures, including at each diabetes clinic visit, are desirable. Both supine and erect BP should be measured to assess postural drop. An early feature of hypertension is loss of the normal nocturnal drop in BP. Ambulatory BP monitoring is helpful in diagnosing and also in assessing the adequacy of BP control. Where available, this is recommended by many relevant national bodies, such as the ADA [3].

It is not uncommon for people with diabetes to need two or more BP-lowering drugs from different classes of antihypertension agents to reach optimal BP targets.

Novel risk factors There are many other clinical, biochemical, and molecular markers that are of interest in relation to diabetes These include subclinical disease markers such as coronary artery calcification, carotid IMT, and biochemical measures of inflammation, oxidative stress, and insulin resistance and an array of molecular and "omics" markers. We now briefly comment on some of them.

Subclinical vascular disease detected by imaging (arterial wall thickness or vascular calcification) or vascular function studies such as pulse wave velocity (PWV), pulse wave analysis, or flow-mediated dilation (FMD) are increasingly used clinically and in clinical research as a surrogate endpoint in clinical trials. *Carotid IMT,* a measure that is non-invasive, does not involve radiation and is relatively low cost, is generally increased in people with diabetes, and can help guide individual decisions regarding risk factor interventions [191]. *Coronary artery calcification,* a clinically available but costly test involving a CAT scan and radiation exposure, has been found useful in predicting vascular events in high-risk diabetic patients [192, 193].

Hyperglycemia increases *inflammation*, *oxidative stress*, and *AGE formation*, in addition to *non-enzymatic glycation* of many short-lived proteins (e.g., lipoproteins and albumin) and long-lived proteins (including basement membranes and skin collagen). We have previously reviewed the adverse effects of hyperglycemia-induced modifications of protein, including lipoproteins [1, 78].

Insulin resistance, while commonly associated with Type 2 diabetes, is also a feature of non-diabetic subjects [194, 195] and in people with Type 1 diabetes [196, 197]. Insulin resistance has been associated with increased risk of macrovascular disease in non-diabetic subjects, where it has been observed in multiple trials to be an independent CVD risk factor [198], and of vascular complications in people with Type 1 diabetes [199]. Pathways involved in vascular insulin resistance include toll-like receptors, inflammation-related NFκB and TNF-alpha, insulin receptor substrate 1, glucose transporters (GLUT-4), and nitric oxide (NO)-related pathways [200]. In keeping, insulin-sensitizing drugs, in particular metformin, which is often used in prediabetes, Type 2 diabetes, and gestational diabetes, and sometimes as an insulin adjunct in Type 1 diabetes [201], improve vascular function as reflected by FMD [202, 203].

Molecular markers: Emerging biomarkers of vascular disease include molecular factors, such as genes and more recently epigenetic factors. Epigenetics is the study of potentially heritable changes in gene expression that do not involve changes to the underlying DNA sequence but alter gene activation. Epigenetics is the interface of the environment with our genetics, and includes the subfields of telomeres, DNA methylation, and microRNAs. Genetic studies, such as by *genome-wide association studies* (GWAS) using "chip-based" analyses, ideally require very large studies (tens of thousands of subjects) and linkage with well-characterized subject data. *Telomeres* are protective caps on the ends of chromosome that modulate cell life-span, and white blood cell (WBC) telomere length has been associated (positively) with longevity. Circulating WBC telomeres have been shown to be shorter in diabetic vs. non-diabetic subjects and to be associated with vascular dysfunction and risk factors [204] and in several small longitudinal studies to predict adverse renal and CVD outcomes or mortality [205–208].

DNA methylation modulates gene expression, and people with the metabolic syndrome or Type 2 diabetes have been shown to have DNA hypomethylation [209], which is associated with upregulation of genes involved in inflammation, oxidative vascular damage, adiposity, and dysfunctional beta cells [210].

MicroRNAs are small (~22-nucleotide) single-stranded RNA molecules that do not code for any protein but act post-transcriptionally to inhibit protein expression by interfering with mRNA translation and stability. MicroRNAs have been identified that modulate genes involved in physiological and disease processes relevant to diabetes-related tissue damage, including angiogenesis, blood flow, neural dysfunction, tissue-specific inflammation, and glucose metabolism [211]. microRNAs can cross cellular boundaries and communicate with other cells via gap junctions and hence exist outside

cells and in the circulation (free or associated with proteins) or in membrane-bound particles [212] and in ocular fluids [213, 214]. Their value as biomarkers is increased as they are resistant to degradation by endogenous nucleases and by repeated freeze-thawing and also have a long half-life (days–weeks) in serum. Recently, three miRNAs in the serum of patients with diabetic retinopathy have been reported as potential biomarkers of disease [211, 215, 216]. As well as their clinical potential for diagnosis and prognosis and for identifying potential drug targets, miRNAs may be therapeutic agents themselves.

Other novel biomarkers, such as from "omics" studies such as lipidomics, proteomics, and metabolomics have potential to enhance our understanding of vascular damage (and protection) in diabetes. A combination of preclinical and human studies and application of these techniques to clinical trials are of relevance to advancing medical knowledge, and findings should always be validated in independent subject groups.

As yet, no molecular or advanced biochemical or "omics" biomarkers are used in clinical practice, but they are an interesting area of research which may improve the understanding of disease mechanisms, guide the development of novel treatments, improve risk stratification, and with sophisticated risk algorithms in the future enhance the delivery of personalized medicine.

7.8 Risk Stratification: Absolute Cardiovascular Risk and Risk Calculators

As mentioned previously, vascular damage, even in the non-diabetic population, is usually due to the presence of multiple risk factors, which may often be perceived as mildly abnormal and disregarded by the person with diabetes and/or their clinicians. In people with diabetes, particularly with Type 2 diabetes, there are often multiple comorbidities of obesity, hypertension, dyslipidemia, and a sedentary lifestyle. The development of renal damage, albuminuria, or a cardiovascular event (including CAD, cerebrovascular disease, peripheral vascular disease) is, in both the general population and the diabetic population, a major risk factor for the development of CVD and for CVD-related mortality. Based on the recognition that multiple even mildly abnormal risk factors can increase the risk of a CVD event, the emphasis has shifted to treating absolute cardiovascular risk.

Absolute cardiovascular risk is an estimate of the chance that an individual will experience a cardiovascular event, usually reported as within the next 5–10 years. A total CVD risk level of 20% or more over the next 10 years is regarded as high, and that of 10% or less as low, though cut-points differ between various expert groups. Contemporary thresholds for recommending preventative treatments such as aspirin or statins in those without known vascular disease are mostly around 10%. It is recommended that people with diabetes with a prior CVD event (thus needing secondary prevention) or with CKD, severe hypertension (over 160/100 mmHg) and end-organ damage, or marked dyslipidemia or aged 75 years or more be regarded as being at high CVD risk and undergo secondary prevention, which usually includes attention to lifestyle, antiplatelet agents, lipid and BP control agents, and control of glycemia and specific cardiovascular drugs or devices. This is discussed further below. For those with no evident CVD (or other high-risk state), then use of a CVD risk table or online calculator is recommended to gauge their absolute CVD risk.

7.8.1 Cardiovascular Disease Risk Calculators

There are a range of CVD calculators to estimate absolute CVD risk, with most being for the general population or for people with Type 2 diabetes. Examples include the Framingham risk score, UKPDS risk engine, UK QRisk calculators, ADVANCE risk calculator, American College of Cardiology/American Heart Association (AHA) ASCVD risk calculator, and the Australian absolute CVD risk calculator. There are variations in what risk factors are included in the various risk calculators and in what vascular events they predict. Common denominators are age, gender, smoking status, diabetes status, BP status, and lipid levels. In general those developed from large groups of people with Type 2 diabetes are more accurate for people with Type 2 diabetes than those for the general population, and differences may arise due to differences between the ethnicity (and genetics) of the population from which the CVD risk calculator was devised and that of the person(s) whose risk is being calculated. Even within a given population, CVD risk may change over time as major risk factors (e.g., community smoking rates) change; hence a calculator developed decades ago may not reflect an individual's CVD risk well in more recent times. There are several comparative studies of various risk calculators [217, 218].

Framingham Risk Scores: This is a series of calculators based on the Framingham Heart Study in the US which commenced in 1948 and has also evaluated CVD and related conditions in the next two generations. These calculators relate to CAD, heart failure, intermittent claudication, atrial fibrillation, and diabetes. The Framingham risk score predicts coronary heart disease events. A Framingham general cardiovascular risk score is available at www.framingham-heartstudy.org/risk-functions/index.php.

The US-based ASCVD Pooled Cohort Equations calculator http://tools.acc.org/ascvd-risk-estimator/ estimates

the 10-year risk of a first ASCVD (atherosclerotic CVD) event in people aged 40–79 years without preexisting CVD. Elevated risk is taken at a predicted risk of ≥7.5%. This calculator has been proposed to replace the Framingham Risk 10-year CVD calculation, having included Framingham data as well as other US population cohorts in its derivation.

ADVANCE Risk Calculator: This calculator (http://www.advanceriskengine.com) estimates CVD risk over 36 years and includes age at Type 2 diabetes diagnosis, known diabetes duration, sex, pulse pressure, treatment for hypertension, retinopathy, urinary ACR, non-HDL-C levels, and atrial fibrillation.

UKPDS Risk Engine: This risk calculator (https://www.dtu.ox.ac.uk/riskengine/download.php) predicts non-fatal and fatal CAD and non-fatal and fatal cerebrovascular disease (stroke) and was developed from 53,000 patient-years of Type 2 diabetic patients free of CVD at baseline in the UKPDS. The initial CAD risk engine has a sensitivity (true positive rate) of 90%. Factors included in the UKPDS CAD risk engine are age, known Type 2 diabetes duration, sex, ethnicity, smoking status, systolic BP, total and HDL-C levels, and the presence or absence of atrial fibrillation [219, 220].

QRisk Calculators: Developed from a large primary care database (QResearch) across the UK and now in its third iteration (https://qrisk.org/three/index.php), this is the recommended calculator for general use in the UK to predict a 10-year risk of developing fatal or non-fatal coronary heart disease/stroke/TIA [221]. It incorporates many variables which are mostly intended to be imputed directly from existing primary care computer software and is updated annually to reflect contemporary outcome data. The most recent NICE guidelines for CVD prevention (2014) recommended using the now superseded QRisk2 calculator for people with Type 2 diabetes but not Type 1 diabetes [222]. Validation studies of QRisk2 among people with diabetes reported very good discrimination for Type 1 diabetes and good discrimination for Type 2 diabetes with good calibration for both types. No head-to-head comparisons with the UKPDS calculator have yet been performed.

The Australian Absolute Cardiovascular Risk Calculator (May 2012): Developed by the National Vascular Disease Prevention Alliance (NVDPA), it provides an online calculator (http://www.cvdcheck.org.au) and estimates an individual's 5-year risk of a vascular event based on age, sex, systolic BP, smoking status, total and HDL-C levels, diabetes, and left ventricular hypertrophy (LVH). The Australian calculator treatment thresholds are quite conservative; for example, only recommending statins if lifestyle changes have been unsuccessful for those at above a 5- (not 10)-year risk threshold of 15%. Secondly, this calculator uses the Framingham risk equation from 1991, considered more inaccurate than more contemporary equations, particularly among people with Type 2 diabetes.

Age is a powerful driver of CVD risk in many of these CVD risk calculators, and some of these calculators may underestimate risk for young people with Type 2 diabetes, who are at particularly high risk of vascular complications [83, 85, 141]. The calculators are also usually not accurate for people with Type 1 diabetes, though attempts to develop and validate risk calculators from long-term Type 1 diabetes observational studies and trials are ongoing [223, 224]. A risk calculator was developed from a 7-year follow-up of 1973 adults with Type 1 diabetes in the EURODIAB Prospective Complications Study, of whom 95 developed micro- or macrovascular events, and was validated in three other cohorts: the Pittsburgh Epidemiology of Diabetes Complications study (EDC, n = 554), the Finnish Diabetic Nephropathy study (FinnDiane, n = 2999), and the Coronary Artery Calcification in Type 1 Diabetes study (CACTI, n = 580). Strong prognostic factors for a composite endpoint including CVD (including amputations), ESRD, blindness, and (all-cause) death were age, urinary ACR, HbA1c, waist-hip ratio, and HDL-C levels.

Adding novel, predominantly simple biochemical, biomarkers, such as C-reactive protein, to current risk equations does not yet substantially increase their predictive power beyond that of the basic models. For example, the Atherosclerotic Risk in Communities (ARIC) study found that the addition of up to 19 novel biomarkers did not improve CAD event prediction in middle-aged men and women [225]. Nevertheless, these simple CVD risk calculators can be a helpful assessment and educational tool, with patients (without evident CVD) being shown their risk reduction associated with, for example, improved lipids if they were to take a statin. Their use can be complemented and individualized by assessment of subclinical vascular damage, such as by vascular imaging (e.g., carotid IMT) or EKG findings.

7.9 Cardiovascular Disease Detection in Asymptomatic People with Diabetes

The question of whether asymptomatic people with increased cardiovascular risk (e.g., diabetes) should be screened for coronary disease is often raised. Several lines of research have examined this area, both among those with Type 2 diabetes and among people at high cardiovascular risk due to other risk factors. In both settings, to date there is no clear supporting evidence for routine screening of asymptomatic people. Stress tests using either nuclear perfusion imaging or echocardiography have estimated the prevalence of silent ischemia in Type 2 diabetes, based on a positive test, to be

about 20–25% [226–229]. However, the specificity of such a test in ultimately identifying a severe coronary stenosis on invasive coronary angiography is only 50% [230]. Most studies which randomized asymptomatic patients with silent ischemia on stress testing to either further investigation or routine care have shown no difference in clinical outcomes for up to 5 years of follow-up [229, 231, 232]. However, one of these studies demonstrated an increased risk of silent CAD progression (scintigraphic ischemia or new scar on follow-up perfusion stress testing) among those with silent ischemia compared to no ischemia at baseline. In the same study, patients with silent ischemia at baseline were also randomized to medical vs. invasive management, with significantly less progression of silent ischemia in the invasive arm patients [232]. This study was relatively small and short in duration but certainly raises issues around cardiac imaging abnormalities and long-term clinical outcomes that require further investigation.

Studies of asymptomatic people with Type 2 diabetes using *coronary computed tomographic angiography* (*CCTA*) have generally found around one third of patients have no coronary disease, one third have minor or moderate disease, and one third have at least one artery with a stenosis greater than 50%, which would usually prompt invasive angiography [233]. Although there have been major advances in CT imaging, this modality still has limitations. The sensitivity in detecting a lesion with over 50% stenosis is around 90%, and specificity is typically 80–90%, but this has been shown to fall to around 50% in the presence of high CAC scores (>400 Agatston units) [234]. Lesions on CT with a stenosis >50% are typically reported as significant, requiring confirmation with invasive angiography. However, only a third of lesions on invasive angiography which are truly 50–70% stenosed are functionally significant and potentially suitable for revascularization, compared to 80% of those over 70% stenosed [235]. Therefore, in a large number of cases, significant lesions on CT may be subject to further investigation without any change in medical management. The FACTOR-64 trial followed asymptomatic high-risk people with Type 2 diabetes randomized to either standard guideline-based care or CCTA-guided management according to disease severity. There was no difference in clinical outcomes over 4 years of follow-up [236].

Measurement of a CAC score is another increasingly used screening modality, providing an aggregate measure of the quantity of calcium in the major coronary artery walls. Compared to CCTA it is an inexpensive test with much less radiation exposure. The CAC score has been shown to correlate with the severity of atherosclerosis and predicts short- and long-term vascular and mortality outcomes [237–239]. However, it is not specific for the presence of severe or clinically significant lesions [240]. Currently the value of the CAC score is felt to be in providing a means of additional stratification among people at low or borderline intermediate vascular risk – allowing those with a CAC score of 0 (or possibly 0–10) to be potentially reclassified as truly low risk (for up to 15 years), while those with incrementally higher scores may be shifted upward in their risk categorization and treated more aggressively.

The overriding message in this setting is that in most cases, screening asymptomatic people will not prevent major cardiovascular events or reduce mortality, providing that judicious attention to risk factor management and guidelines for primary prevention are being appropriately followed. Meanwhile there are significant costs, as well as small but not negligible risks, associated with subjecting people to these investigations, particularly when additional invasive testing is required for clarification. The ADA 2016 guidelines therefore advise that routine screening of asymptomatic people is **not** recommended as it does not improve outcomes, as long as atherosclerotic CVD (ASCVD) risk factors are appropriately treated [241].

There are some situations, however, where a non-evidence-based specialist consensus exists for consideration of screening. These include (i) people with "atypical" symptoms which might cautiously be considered variant angina (such as shortness of breath or atypical chest pain); (ii) people with signs or confirmation of other vascular diseases such as carotid bruits, TIAs, or claudication (although in this situation, secondary prevention management is empirically indicated); (iii) people with ischemic EKG abnormalities such as Q waves or dynamic EKG changes; or (iv) high-risk people potentially undertaking strenuous physical activity in the absence of regular exercise.

The choice of test in an asymptomatic person typically depends on the specific reasons for deciding to proceed. A resting transthoracic echocardiogram will assess ventricular function and provide signs of previous MI. It will not, however, exclude the presence of existing silent coronary atherosclerosis. A CAC score of 0 would make the likelihood of any significant disease extremely small, but a positive score would only provide a guide to the overall burden of coronary atherosclerosis, rather than any functional information potentially relating to a severe focal coronary stenosis. For stress testing, exercise is generally preferred, but in those who cannot exercise, pharmacological stress is an alternative. Adding an imaging component to the test (echocardiography or nuclear perfusion, noting the latter involves radiation exposure) will improve specificity, particularly when patients have resting EKG abnormalities (e.g., ST-T abnormalities, left bundle branch block, or ventricular pacing) that may limit or preclude interpretation of exercise-induced changes. Women also have a high false-positive rate of EKG changes and should generally not undergo EKG-based stress tests without an imaging component. CCTA is increasingly

being performed in people with indeterminate stress testing results among whom the likelihood of significant CAD is not considered high, as a means of exclusion, to avoid an invasive angiogram.

Given the complexities involved in this decision-making, particularly as increasing modalities are emerging for stress testing and cardiac imaging, referral to a cardiologist to consider the most appropriate and cost-effective investigation and management strategy is generally recommended.

7.10 Cardiovascular Disease Treatment in Diabetes

As for all people with CVD, among those who have diabetes, standard secondary prevention therapies, including antiplatelet agents, beta blockers, renin-angiotensin system antagonists, and statins, provide long-term vascular and mortality reductions. Anti-anginal therapies using nitrates, beta blockers, or calcium channel blockers are also the same.

Regarding revascularization therapies, as diabetic vascular disease is often more diffuse and distal than in non-diabetic subjects, both coronary angioplasty and surgery can be more challenging and sometimes are not possible. Drug-eluting coronary stents have been shown to be superior to bare metal stents in people with diabetes. Most recent long-term outcome studies comparing revascularization strategies among people with diabetes and left main or multivessel coronary disease (particularly more complex disease) have favored bypass graft surgery over coronary angioplasty and stenting, providing patients are fit for anesthesia. This important area was recently reviewed [242]. The pros and cons of such treatment options are appropriate for discussions with diabetic patients with CAD requiring surgical intervention and with the treating cardiologists and cardiothoracic surgeons.

7.11 Vascular Risk Factors and Their Control in Diabetes

7.11.1 General Vascular Risk Factor Targets for People with Diabetes

In keeping with recognition of the multifactorial etiology of atherosclerosis and the related microvascular complications in people with diabetes, most national diabetes bodies recommend at least annual screening for the major risk factors and presence and stage of microvascular complications. Those by the ADA, EASD, ADS, and IDF are summarized in Table 7.9. As shown in Table 7.9, the components vary between groups, but all include the major risk factors of glycemia, BP, and lipid targets. Targets, such as LDL-C targets, may vary as to whether a person is for primary or secondary CVD prevention and based on their individual circumstances. For example, a less tight HbA1c target may be more appropriate for an older person with long Type 2 diabetes duration who lives alone and has impaired hypoglycemia awareness than for a younger person with recent-onset Type 2 diabetes, family living with them, and intact hypoglycemia awareness. Hypoglycemia may predispose to QT interval prolongation, cardiac arrhythmias, and increased risk of mortality [243–248].

An excellent guide to the general treatment targets and/or triggers for clinical action is provided in the annually updated Royal Australian College of General Practitioners (RACGP) General Practice Management of Type 2 diabetes [249]. While individualization of targets is appropriate such as related to age and comorbidities, the general vascular health-related targets or triggers for action are *healthy diet* (perhaps a Mediterranean diet), at least 5–10% *weight loss* for those who are overweight or obese, *non-smoking*, at least 30 min of moderate *physical activity* on most, if not all, days of the week, *HbA1c* ≤7.0% (53 mmol/

Table 7.9 Risk factor targets for diabetic patients

	ADA [548]	EASD [32]	ADS [34]	IDF [33]
HbA1c	<7% or 7–8%	≤6.5%	≤7%	<7%
SBP	<140 mmHg[a]	<130 mmHg[b]	<130 mmHg[b]	≤130 mmHg
DBP	<90 mmHg[a]	<80 mmHg[b]	<80 mmHg[b]	≤80 mmHg
LDL-C	<2.6 mmol/L[c] [549]	≤1.8 mmol/L	???	<2.0 mmol/L
BMI	<25 kg/m^2[d] [3]	<25 kg/m^2	<27.5 kg/m^2 [34]	–
Waist-hip Ratio	–	–	–	–
Waist circumference	–	♂ <94 cm ♀ <80 cm	–	–
eGFR			>60 ml/min/1.73m^2	>60 ml/min/1.73m^2

[a]Target lower by 10 mmHg may be appropriate in younger individuals, people with albuminuria, and/or individuals with hypertension and one or more additional CVD risk factor

[b]Target lower by 5 mmHg in case of renal impairment or proteinuria >1 g / 24 h

[c]<1.8 mmol/L for patients with very high risk for CAD

[d]<23 kg/m^2 for Asian American

mol) (range 6.5–7.5% (47.5–58.5 mmol/mol) due to test accuracy variation), *BP* <130/80 mmHg, and *urine ACR* (screening test) <3.5 and <2.5 mg/mmol for women and men, respectively. General *lipid goals* are total cholesterol <4.0 mmol/L (155 mg/dL), LDL-C <2.0 mmol/L (77 mg/dL), HDL-C ≥1.0 mmol/L (39 mg/dL), and fasting triglycerides <2.0 mmol/L (177 mg/dL), though initiation of lipid pharmacotherapy in primary prevention is usually based on the thresholds according to absolute risk calculator estimates (e.g., the Australian absolute CVD risk calculator discussed above), which consider the contribution of multiple risk factors to guide recommendations for therapy, even in the setting of seemingly reasonable lipid levels. These recommendations are based on the fact that the magnitude of vascular risk reduction is directly proportional to the magnitude of LDL-C lowering, without any currently known lower limit of benefit.

With increasing adiposity, sedentary lifestyles, and more mature ages of childbearing, many women of reproductive age have diabetes, including Type 2 diabetes, and care must be taken to avoid/temporarily replace medications that are contraindicated during pregnancy and breastfeeding, such as ACE inhibitors and statins.

7.11.1.1 A Mnemonic for Vascular Risk Factor Control

We have devised a mnemonic [250] to remind busy clinicians of the vascular risk factors they should check, and where necessary treat, in their diabetic patients. The mnemonic (which is relevant to both CVD and microvascular complications) is GLOBE^{2}S^2, representing **G**lucose, **L**ipid and lipid drugs, **O**besity, **B**P and BP drugs, **E^2** Education and Emotion, and **S^2** for Smoking and screening.

For "lipids" and "BP," the clinician should consider whether the use of lipid and/or BP drugs is appropriate even if the patient's lipid and BP levels are at target. The triglyceride-lowering drug fenofibrate can retard progression of diabetic retinopathy independent of lipid levels [102, 251]. The evidence base around *glucose*, *lipids*, and *BP* and management strategies are discussed later in this chapter.

Obesity. For the overweight or obese person with diabetes, weight loss is very important. In addition to the association between adiposity and several other major vascular risk factors (Type 2 diabetes per se, hypertension, and dyslipidemia), abdominal obesity, which is reflected by an increased waist-hip ratio (WHR), is an independent risk factor for MI, with WHR being stronger than body mass index (BMI) when both are considered [252], Increased waist circumference above normal is linearly associated with an increased risk of all-cause mortality [253]. An initial weight loss goal of 5–10% of body weight is recommended, via a combination of dietary modification and physical exercise [249]. There are also roles for pharmacological therapies, such as orlistat; in some people, and for those with very high BMIs (e.g., BMI >35 kg/m^2) and multiple comorbidities, bariatric surgery may also be considered [249].

Education of patients with diabetes, and as appropriate of their carers, should be provided at the time of diabetes diagnosis and as needed thereafter [3]. Education should include information about diabetes and its complications; lifestyle, including nutrition and exercise, medications, screening, and home- and clinic-based monitoring (such as home glucose monitoring and clinic-based HbA1c testing). An American Association of Diabetes Educators (AADE) systematic review of randomized controlled trials demonstrated that patient education was associated with a HbA1c reduction of 0.56%, with higher HbA1c levels being associated with larger HbA1c benefit [254, 255].

Emotions. Anxiety, depression, and disturbed eating are common in people with diabetes, as in the general population. It has been estimated that one in four Type 2 diabetic patients will experience a clinically significant episode of depression, a prevalence five-fold that in the general population [256]. Comorbid anxiety and depression in people with Type 2 diabetes can increase mortality risk [257].

Weight gain, insulin resistance, and Type 2 diabetes are often also increased in people with major mental health problems such as bipolar disorder, schizophrenia, and major psychosis. Contributing factors are poor nutrition and exercise habits and sometimes antipsychotic medications; in particular, the second-generation antipsychotic drugs [258–261]. The primary care physician can play an important role in screening and managing the cardiometabolic risk factors of their patients requiring such medications.

Specific to the chronic condition of diabetes is a common and often episodic entity called diabetes distress, which includes patient concerns about their diabetes management, prognosis, support, emotional burden, and access to care. It is estimated that 40–45% of people with (Type 2 or Type 1) diabetes will experience diabetes distress [262]. As well as meriting recognition and management in its own right, emotional distress can adversely impact attention to a healthy diet, exercise, and the diabetes treatment regimen [263] and may also contribute to adverse vascular status by neurohumoral effects [264]. There are various formal screening tools to assess mental health in diabetes, including a short (two-item) screening tool (Diabetes Distress Scale 2 (DDS-2)) suitable for use in busy clinical practices [265]. An alternate is to ask a question such as "How is your diabetes being a pain for you at the moment?" [266].

In addition to mental well-being care by the primary care practitioner, input by other clinicians, including diabetes educators, psychologists, and as needed, psychiatrists, can be helpful.

Smoking. Cigarette smoking represents the greatest lifestyle-based risk factor for CVD. Nicotine exposure increases insulin resistance in Type 2 diabetic patients, as shown by glucose clamp studies [267]. Smoking rates in the diabetic population are often similar to or slightly lower than that of non-diabetic subjects in the general population, for example, being 11.4% and 13.3% in Australia in 2013. Many people with diabetes will cease smoking if counselled and supported to do so [268]. Smoking cessation reduces mortality risk by a third over just a few years [269]. As well as individual counselling by their primary care practitioner, consideration should be given to referral to smoking cessation support programs and nicotine replacement therapy.

e-Cigarettes: Electronic or e-cigarettes or "vaping" is a recent and increasingly common practice in many countries. Electronic cigarettes are a handheld battery-operated device that warm and vaporize chemical substances that are inhaled by the user. The inhaled liquids usually contain nicotine (0–20 mg/ml) and variable other substances, commonly propylene glycol, glycerol, and flavorings. By comparison, a cigarette contains ≈10 mg of nicotine, and blood nicotine concentrations achieved via some e-cigarettes can be greater than that achieved by cigarettes [270].

e-Cigarettes may cause vomiting, nausea, cough, local irritation to the mouth and throat [271], increase heart rate and BP [272], and can induce oxidative stress and inflammatory cytokines and reduce nitric oxide levels [271], all of which are thought to promote diabetic vascular complications [78].

The literature surrounding a role for e-cigarettes in smoking cessation is generally not positive. A 2016 meta-analysis of 18 observational studies found that e-cigarette use was associated with a 28% lower odds ratio of smoking cessation compared to those who did not use e-cigarettes. A subanalysis including only e-cigarette users interested in smoking cessation removed the negative effect of e-cigarettes and found no difference between the groups [273]. The AHA does not recommend that e-cigarettes be used as a tool for smoking cessation [19] and advises that clinicians should screen patient e-cigarette use as a component of smoking cessation counselling [272]. Clinicians still recommend traditional smoking cessation aids including support programs and pharmacologic agents such as nicotine (patch or gum) replacement therapy, if needed.

Regular *screening* (such as often covered by government or private health funds) for HbA1c four times a year and at least once a year for lipids, renal function (including albuminuria and serum creatinine), ocular health, and foot care is recommended, with more frequent checks for those with vascular damage or out-of-target risk factors. Measurement of BP and weight at each clinic visit is recommended. A suggested schedule of vascular health (and other diabetes-related screening) is included in the RACGP GP management of Type 2 diabetes care [249].

Allied healthcare professionals, including diabetes educators, podiatrists, optometrists, dietitians, exercise physiologists, psychologists, and other medical and surgical specialists, can be of great assistance in the management of patients with diabetes, especially the particularly complex patient. The primary care physician (general practitioner) is ideally placed to arrange referrals and coordinate and assist with management, including the patient's understanding and adherence to recommendations.

While there are common features in the risk factors for CVD in people with diabetes and for their microvascular complications of retinopathy, nephropathy, and neuropathy, we will now review the evidence base for risk factor control in CVD and then for each of the microvascular complications.

7.12 Evidence-Based Primary and Secondary Prevention of Cardiovascular Disease in Diabetes

While targeting individual CVD risk factors is usually beneficial, there is even greater benefit for simultaneously addressing multiple risk factors. With this multi-risk factor targeting and increasingly potent drugs, such as for LDL-C lowering, the rates of CVD events and CVD death are improving in some countries, such as the US [274].

If a diabetic patient has a history of angina or MI, a cerebrovascular event (transient ischemic attack (TIA) or stroke), peripheral vascular disease (e.g., intermittent claudication or vascular disease-related amputation), or (coronary, carotid, or lower limb) arterial revascularization, they are high risk for future cardiovascular events, and there is a strong evidence base for secondary prevention.

Secondary CVD prevention is multifactorial, incorporating attention to lifestyle factors, such as non-smoking and diet, antiplatelet agents, ACE inhibitors, beta blockers, and lipid drugs, such as "statins" and if dyslipidemia (high triglycerides, low HDL-C) fenofibrate treatment. We and some of our colleagues have recently reviewed the literature and also created two evidence-based mnemonics to guide medical students and clinicians [275, 276]. These are for the general population but are also relevant for people with diabetes.

7.12.1 Evidence-Based Mnemonics for Secondary Cardiovascular Prevention

"**Fairly Fast SAAB Convertible**" for the secondary prevention of CVD disease refers to **F**ish oils, **F**ibrates, **S**tatins, **A**spirin, **A**CE inhibitors or ARB antagonists, **B**eta blockers, and **C**lopidogrel. Definitive evidence supports the use of statins, aspirin, ACE/ARB drugs, and P2Y12 antagonists (clopidogrel, ticagrelor, or prasugrel) for the secondary prevention of CVD. Aldosterone antagonists now have strong evidence in the setting of systolic heart failure, which is common in people with diabetes. There is a weaker evidence base for the routine use of omega-3 fatty acid supplementation (fish oils), although this therapy carries minimal harms and does not worsen glycemia. Fenofibrate reduces cardiovascular (and microvascular) events in dyslipidemic Type 2 patients. Hence, to guide the secondary prevention of CVD, it is suggested to upgrade to a Fairly Fast $SA^{(2)}A^{(2)}B$: **F**ish oils, **F**ibrate, **S**tatin, **A**ntiplatelets (Aspirin+Other), **A**CE/ARB, **A**ldosterone **A**ntagonist, **B**eta blocker.

As covered by the mnemonic [276], following an acute coronary syndrome (ACS) people with (and without) diabetes are recommended to take aspirin. As well as aspirin, a second antiplatelet agent is recommended for at least 1year post-event. This second agent is either ticagrelor, clopidogrel, or, if they had a percutaneous coronary revascularization, prasugrel. (These drugs are discussed shortly.) A beta blocker for at least 2 years is also recommended post-ACS. There is also evidence that adding ezetimibe to moderate-intensity statin therapy following ACS with an LDL-C >1.3 mmol/L (50 mg/dL) reduces cardiovascular events.

The mnemonic **BANDAID(2)** for the treatment of heart failure refers to **B**eta blocker, **A**CE/ARB receptor blocker, **N**itrate-hydralazine (or potentially neprilysin inhibitor), **D**iuretics, **A**ldosterone antagonist, **I**vabradine, **D**evices (automatic implantable cardioverter defibrillator, cardiac resynchronization therapy, or both), and **D**igoxin. As covered in the review [275], these treatments have strong evidence for their use in systolic heart failure. Treatment with fish oils, statins, or antithrombotic therapies has limited benefits in a general heart failure population, but in the setting of heart failure patients with diabetes, it is anticipated that most would have an evidence-based benefit from statins and antithrombotic treatments (e.g., aspirin).

Many secondary CVD prevention targets are also primary CVD prevention targets and targets relevant to the prevention and care of diabetic microvascular complications. The evidence for, and role of, various non-pharmacologic lifestyle factors, antiplatelet agents, lipid, BP, and glycemic control factors in relationship to CVD in diabetes are summarized in Table 7.10 and are now briefly reviewed.

7.12.2 Lifestyle Modification

Non-pharmacological interventions are important in both the primary and secondary preventions of CVD as the major CVD risk factors of adiposity, smoking, dyslipidemia, hypertension, and glycemic control are modulated by lifestyle. In addition, dental health and flu vaccination status have been associated with CVD risk.

Smoking, which is the major lifestyle-based risk factor for MI [252], was discussed earlier in this chapter, and smoking cessation reduces mortality risk by 36% over several years [277].

7.12.2.1 Nutrition and Physical Activity

Weight is impacted by diet and physical activity, and aspects of weight control in diabetes were discussed earlier in this chapter.

Irrespective of their weight status, people with diabetes should be assessed and educated by a dietitian with regard to a *healthy diet*, including aspects related to glucose, weight control, and lipid and sodium control. Various aspects of the standards of care around diet have been provided by the ADA [3]. Major recommendations in the general population are also applicable to people with diabetes [278]. Compared to an average Western diet, recommendations include reducing saturated/trans fat intake, restricting salt, and increasing omega-3 fatty acid and vegetable and fruit intake [279].

The *DASH* (*Dietary Approaches to Stop Hypertension*) *diet* has been found to be effective at reducing the risk of developing Type 2 diabetes [280] and at lowering BP and improving cardiometabolic risk factors in people with Type 2 diabetes [281–283]. In a systematic review and meta-analysis in the non-diabetic population, the DASH diet has been associated with (19–29%) reduced risk of CVD endpoints [284], but has not been studied in people with diabetes.

The *Mediterranean diet* is well-studied in regard to CVD prevention. In 7447 people aged 55–80 years and at high CVD risk over 4.8-year (median) follow-up, the Mediterranean diet with either extra virgin olive oil supplementation or mixed nut supplementation has the strongest randomized trial evidence for the primary prevention of CVD. This diet significantly reduced the risk of a composite CVD endpoint (MI/stroke/cardiovascular death) by 30% compared to a control diet (advice to reduce dietary fat) in [285]. The Mediterranean diet also has proven benefit for the secondary prevention of CVD [286, 287].

Table 7.10 Secondary prevention for CVD in people with Type 2 diabetes [a]

Risk factor	Target	Main agents	Reduces CVD events	Reduces CVD mortality
Lipids				
Elevated LDL-C (treatment initiation according to CVD risk level)	Maximize LDL-C reduction	Statins	Yes	Yes
		Ezetimibe (secondary prevention)	Yes	No
Residual dyslipidemia	↓Triglycerides ↑HDL-C	Fenofibrate	Yes	No
Hypertension	<140/90 mmHg	ACEI/ARBs, diuretics, beta blockers, calcium channel blockers,[c] spironolactone	Yes	Yes
Hyperglycemia	HbA1c <7.0% or as per individualized target	Biguanides, sulfonylureas, DPP-4 inhibitors,[c] thiazolidinediones,[c] GLP-1 analogues, insulin	Yes	conflicting evidence
		Empagliflozin (SGLT2 inhibitor) (secondary prevention)	Yes	Yes
Smoking	Cessation	Nicotine replacement therapy, varenicline, bupropion	Yes	Yes
Obesity [b]	Initial goal: 5–10% weight loss over 6 months. Target: BMI <25 kg/m^2	Orlistat	? insufficient evidence	? insufficient evidence
		Phentermine or Phentermine-topiramate combination	? insufficient evidence	? insufficient evidence
		Bariatric surgery	Yes	Yes

Footnote: Outcomes listed as "No" are for those treatments which yielded negative results in one or more large randomized controlled trials, compared to those marked "Uncertain" on the basis of inconsistent or insufficient evidence

[a]Lifestyle modifications through dietary modification and exercising regularly have positive impacts on all of these risk factors and are recommended first-line

[b]Mild (2–4 kg) weight loss with glucagon-like peptide-1 (GLP-1) analogues (especially liraglutide), SGLT2 inhibitors, and, to a lesser extent, metformin, is well documented

[c]Some agents of these classes may cause adverse cardiovascular outcomes when used in specific settings

There is strong evidence for an inverse relationship between *physical activity* and the risk of a cardiovascular event or all-cause mortality; hence the general recommendations are for at least 30 min of moderate-intensity activity most days of the week [279] and are applicable for people with diabetes. The ADA recommendations are that most adults with (Type 1 or Type 2) diabetes should undertake 150 min or more of moderate to vigorous exercise per week, spread over at least 3 days a week, and also undertake two or three sessions a week of resistance training on non-consecutive days. Reducing sedentary time is also important, with avoidance of prolonged sitting [3].

With regard to the effects of weight loss exercise on CVD and mortality benefits in people with Type 2 diabetes, a long-term prospective intensive lifestyle intervention study (Look AHEAD) in overweight or obese people with Type 2 diabetes did not show any significant cardiovascular or mortality benefits over 10 years. However, between-group differences in weight, physical fitness, waist circumference, and HbA1c levels beyond the first year were minimal [288].

A systematic review and meta-analysis of trials of 8940 acute coronary syndrome patients undertaking an *exercise-based cardiac rehabilitation* program with at least 6-month follow-up found the exercise program was associated with significantly reduced all-cause mortality (20%), cardiovascular mortality (26%), and some vascular risk factors [289]. However, there were no significant differences in the rates of non-fatal MI and revascularization nor of health-related quality of life.

7.12.2.2 Mobile Health and CVD

Increasingly, mobile technology, such as pedometers, glucose control support, nutrition and weight control support, and medication management, is being used in healthy lifestyle promotion and in healthcare, including in diabetes and in CVD. A recent systematic review of articles from 2002 to 2016 demonstrated high rates of effectiveness in improving outcomes. Text messaging, mobile applications, and telemonitoring via mobile phones were effective in improving outcomes [290]. The role of such devices in diabetes and CVD care and the related evidence base are of interest.

7.12.3 Aspirin and Other Antiplatelet Agents

7.12.3.1 Aspirin

Diabetes is often associated with increased risk of thrombosis related to platelet hyper-reactivity and a prothrombotic shift in pro- and anticoagulant factors [291, 292]. Aspirin, a low-cost drug, usually available over the counter (without prescription), irreversibly inactivates cyclooxygenase-1 (COX-1), reducing thromboxane A2 synthesis, leading to inhibition of platelet activation and aggregation.

Dosage and Contraindications

Unless contraindicated, there is clear benefit of aspirin use in adults with (and without) diabetes for the secondary prevention of CVD, but there is less evidence and more debate regarding its use as primary CVD prevention (discussed further below). Standard contraindications to aspirin therapy include aspirin allergy, bleeding tendency, anticoagulant therapy, recent gastrointestinal bleeding, and clinically active liver disease. Severe (e.g., proliferative) diabetic retinopathy is not a contraindication to aspirin use [3]. The Early Treatment of Diabetic Retinopathy Study (ETDRS) demonstrated no increase in vitreous or preretinal hemorrhages or cataracts with aspirin (650 mg daily) vs. placebo in patients with diabetic retinopathy [293].

There is general population evidence that a standard 325 mg dose of aspirin is associated with a higher bleeding risk than a 75 mg dose, while there is no evidence of greater cardiovascular protection at doses higher than 75 mg, suggesting doses of 75–100 mg once daily, usually taken with food (to reduce gastrointestinal upset), are preferable [294].

Interestingly, there is an as yet unanswered question as to whether people with diabetes may be "aspirin resistant" and require higher doses than non-diabetic adults for clinical efficacy. Supporting data are that platelet dysfunction is more evident with worse glycemic control [295, 296], and studies with more frequent dosing (e.g., 75 mg twice a day) compared with standard once-daily dosing have shown improved platelet inhibition in people with diabetes [297, 298]. A similar phenomenon related to more rapid recovery of COX activity has been identified in obese insulin-resistant subjects [299], with improvement with short-term weight loss or pioglitazone [300]. However, platelet function is a surrogate endpoint, and as yet, there are no clinical trials with hard clinical endpoints to support need for a different aspirin dosage or frequency of administration in people with vs. without diabetes.

Aspirin and Secondary Cardiovascular Disease Prevention in the General Population and in Diabetes

Aspirin reduces major CVD events by 22%, strokes by 25% (despite a 22% increase in hemorrhagic strokes), and all-cause and CVD mortality by about 20%. Hence treating 1000 people for 2 years with aspirin would prevent 36 vascular events at a risk of up to two hemorrhagic strokes and about five major extracranial bleeds [301]. Data from the subset of 45,000 people with diabetes in the Antiplatelet Trialists' Collaboration showed that aspirin reduced major vascular events by 25% [302]. Based on this type of evidence, national advisory bodies usually recommend aspirin in doses ranging from 75 to 162 mg daily for all patients for the secondary prevention of CVD, unless contraindicated [303, 304].

In these high-risk diabetic patients, if aspirin is contraindicated (e.g., aspirin allergy), then (provided there is also no contraindication) clopidogrel (75 mg/day) should be considered [303].

Aspirin and Primary Cardiovascular Disease Prevention in the General Population and in Diabetes

An individual patient data meta-analysis (n = 95,000) in the general (non-diabetic and diabetic) population found that aspirin reduces major vascular events by 12% and a combination of non-fatal MI and coronary death by 5% [302]. Subgroup analyses showed no statistical differences in benefit between patients with and without diabetes. However, there was a substantial increase in risk of cerebral bleeds: hemorrhagic stroke was increased by 32% and major extracranial bleeds by 54%. Based on these data, in people with a high 5-year coronary event risk (>10%), aspirin would prevent two major vascular events for every 100 adults treated for 5 years (14.0% vs. 16.0%) but would cause one non-fatal GI or other extracranial bleed (2.7% vs. 1.7%). The net benefit of therapy over 5 years would be very small, about 1%. As these studies did not include patients on other vascular medications, such as statins, which also have antiplatelet effects, the clinical benefit may be even smaller.

Diabetes-Specific Studies: The Prevention Of Progression Of Arterial Disease And Diabetes (POPADAD) trial examined cardiovascular outcomes with aspirin vs. placebo in 1200 patients aged over 40 years of age with (any type) diabetes and asymptomatic peripheral arterial disease and found no differences in the two primary cardiovascular endpoints nor in adverse outcomes [305].

The open-label Japanese Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD trial) compared 2539 Japanese patients with Type 2 diabetes given aspirin 81–100 mg daily for not over 4.4 years. The primary CVD endpoint was non-significantly reduced by 20%, with a significant 90% (95% CI, 21%–99%; p = 0.04) reduction in CVD mortality and a non-significant 10% reduction in all-cause mortality. There was no significant increase in bleeding. In a prespecified subgroup (age >65 years), there was a significant 32% reduction in the primary endpoint, but there was no statistical heterogeneity between results of any subgroup analyses [306].

Table 7.11 ADA/AHA/ACC recommendations 2010 for adults with diabetes and no previous history of CVD

Absolute CVD risk	Recommendation of low-dose aspirin (75–162 mg) for primary prevention	Class of recommendation	Level of evidence
HIGH 10-year risk >10% 5-year risk >5% Annual risk >1%	Reasonable in those who are not at increased risk for bleeding Includes most men >50 and women >60 who have one or more of the following additional major risk factors: smoking, hypertension, dyslipidemia, family history of premature CVD, and albuminuria	ACCF/AHA Class IIa	ACCF/ AHA: B ADA: C
LOW 10-year risk <5% 5-year risk <2.5% Annual risk <0.5%	Not recommended, as the potential adverse effects from bleeding offset the potential benefits. Includes men under age 50 years and women under 60 years with no major additional CVD risk factors	ACCF/AHA Class III	ACCF/ AHA: C ADA: C
INTERMEDIATE 10-year risk 5%–10% 5-year risk 2.5–5% Annual risk 0.5–1%	Might be considered until further research is available	ACCF/AHA Class IIb	ACCF/ AHA: C ADA: E

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Adapted from: Pignone et al. [551]

To help address this important question, in 2010, the ADA, the AHA, and the American College of Cardiology undertook a comprehensive meta-analysis of diabetic patient data (n = 11,787), which also included the POPADAD and JPAD trials. Aspirin therapy resulted in a nonstatistically significant 9% reduction in coronary heart disease events and a 15% reduction in stroke [307]. The authors suggested a modest benefit of primary prevention by aspirin in people with diabetes. Assuming aspirin increased risk of a bleed by 1–5 per 1000 treated per year, they concluded that adults with a 10-year CVD risk of 10% (i.e., 1% risk per year) will have at least the same if not greater number of CVD events prevented as bleeding events caused. Their recommendations for practice, noting that most are not based on rigorous randomized clinical trial evidence, are shown in Table 7.11.

More recently, a Swedish population cohort (primary prevention) study of adults with Type 2 diabetes without CVD compared patients treated with aspirin (n = 4608) to those not treated (n = 14,038) and found no association between aspirin use and CVD risk reduction or mortality over 3.9 years of follow-up [308].

Another meta-analysis (published in 2016) evaluated six studies (n = 10,117 subjects) of aspirin (100 mg second daily to 650 mg daily) in diabetes for the primary prevention of a broad spectrum of CVD events, including revascularization, angina, fatal or non-fatal MI or stroke, or peripheral vascular disease. Follow-up ranged 3.6 to 10.1 years. There was no significant difference between aspirin and placebo with respect to the risk of all-cause mortality (OR, 0.93; 95% CI, 0.81–1.06) or individual atherosclerotic events. There were no significant differences in bleeding or hemorrhagic stroke [309].

Two randomized trials examining aspirin for primary prevention in diabetes (ACCEPT-D and ASCEND) which were still in progress at publication time will help address ongoing uncertainties [310, 311].

7.12.3.2 Other Antiplatelet Agents

$P2Y_1$ and $P2Y_{12}$ are two (G-protein-coupled) receptors on platelets which when bound with ADP (released from platelets and from damaged vascular cells) trigger platelet aggregation, and $P2Y_{12}$ also amplified and stabilizes this ADP-induced platelet aggregation. Several antiplatelet drugs target the $P2Y_{12}$ receptor, with generally favorable results for CVD protection, including in people with diabetes.

Clopidogrel

Clopidogrel is an orally active irreversible inhibitor of P2Y12, which has proven benefits in clinical trials in acute coronary syndromes and stroke [312]. In the Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial in 19,185 CVD (non-diabetic and diabetic) patients with a mean of 1.9-year follow-up, clopidogrel significantly reduced the annual risk of a CVD event by 0.5% [313], with an even larger benefit (2.1% per annum) in the 1952 diabetic subjects [314].

There are also trials of clopidogrel in addition to aspirin. In the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial of 15,603 diabetic and non-diabetic subjects with CVD or at high risk of CVD, there was no additional benefit of clopidogrel for the primary (composite) endpoint of cardiac death, stroke, or MI [315].

In contrast, in the acute coronary syndrome setting of unstable angina in the Clopidogrel in Unstable Angina to

Prevent Recurrent Events (CURE) trial, combination therapy significantly reduced the composite endpoint of non-fatal MI, stroke, and CVD death in both the diabetic and non-diabetic subgroups [316].

Prasugrel

Prasugrel is an oral drug that undergoes activation via hepatic metabolism to generate an irreversible P2Y12 inhibitor.

The TRITON-TIMI-38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38) study compared the benefit of this drug (60 mg loading and 10 mg daily maintenance) versus clopidogrel (300 mg loading and 75 mg daily maintenance). There was clinical benefit over the 15-month follow-up with prasugrel for both diabetic and non-diabetic patients undergoing percutaneous cardiac intervention. Prasugrel was associated with reduced (composite) CVD events (9.9% vs. 12.1%; HR = 0.81; p <0.001) and also reduced stent thrombosis, but with increased risk of major bleeding [317]. The CVD event reduction was significantly greater in the diabetic (12.2% vs. 17%; p <0.001) vs. non-diabetic subgroups (9.2% vs. 10.6%; p <0.001), p = 0.02).

Ticagrelor

Ticagrelor is an orally active reversible P2Y12 inhibitor that has shown greater potency of inhibition of platelet aggregation than clopidogrel in the setting of an acute coronary syndrome. In the PLATO study in 18,624 acute coronary syndrome patients (both with and without ST elevation), both diabetic (n = 4662) and non-diabetic subgroups ticagrelor (180 mg loading dose, 90 mg twice daily maintenance) and clopidogrel (300–600 mg loading dose, 75 mg daily maintenance) were compared with 1-year follow-up. Ticagrelor use was associated with significantly reduced (composite) CVD events (9;8% vs. 11.7%, p <0.001) and also significantly lowers all-cause mortality and stent thrombosis. There was an increase in the rate of non-procedure-related bleeding with ticagrelor [318].

Summary of Antiplatelet Drugs for Cardiovascular Disease in Diabetes

There is strong evidence of benefit for using aspirin in diabetes for the secondary prevention of CVD, but in primary prevention, the benefit is less clear, especially when factored against undisputed bleeding risks. Current international recommendations are to consider a patient's absolute cardiovascular risk in deciding whether to recommend preventative aspirin therapy, preferably using a CVD risk calculator to assess absolute CVD risk. In general, for those at low CVD risk (<1% per annum), such as people with diabetes aged below 50 years and with no major CVD risk factors, aspirin is usually not recommended. For those at high risk (>1% per year), aspirin is generally recommended. For those at intermediate risk (e.g., 0.5–1.0% per year), aspirin should be carefully considered with careful assessment of the patient's clinical status. Likely ongoing trials and research will provide more guidance in the future.

For people allergic to aspirin, clopidogrel (75 mg daily) should be considered. For diabetic patients who have had an acute coronary syndrome, aspirin plus a P2Y12 inhibitor for up to a year should be considered, and in those with an acute coronary syndrome treated with a stent, more potent $P2Y_{12}$ inhibitors such as prasugrel and ticagrelor should be considered, with treatment duration being dependent on the type of stent used [319]. The cardiology team should provide input as to the recommended antiplatelet treatment type and duration.

7.12.4 Systemic Risk Factor Control for Cardiovascular Disease

7.12.4.1 Lipid Control Related

LDL is the major proatherogenic lipoprotein, and LDL-C lowering is associated with reduced CVD risk. HDL is the major vasoprotective lipoprotein for CVD, thought to act via multiple mechanisms including reverse cholesterol transport, anti-inflammatory, antioxidant, antithrombotic, and vasodilatory effects. The triglyceride-rich VLDL particles are thought to be too large to ingress substantially into the arterial wall, but they can trigger endothelial cell prothrombotic cascades, and triglyceride levels reflect other proatherosclerotic factors, such as obesity, hyperglycemia, and insulin resistance.

Predominantly Low-Density Lipoprotein-Lowering

Statins

There is robust evidence that LDL lowering with statins is effective at reducing CVD events in people with diabetes in both the primary and secondary CVD prevention settings. The statin trials are in Type 2 diabetes alone or an admixture of Type 1 and Type 2 diabetes.

Key earlier (secondary prevention) statin trials which demonstrated CVD reduction benefit for adults with diabetes and CVD included the 4S (Scandinavian Simvastatin Survival Study), the Cholesterol and Recurrent Events (CARE), Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)-Lipid-Lowering Arm trial, the Heart Protection Study (HPS), and the first primary prevention study of Collaborative Atorvastatin in Diabetes Study (CARDS).

The diabetic subgroup (n = 483) of the 4S study of simvastatin 20–40 mg vs. placebo over 4 years demonstrated that the statin significantly reduced major coronary events (RR 0.58, p = 0.001) and revascularization procedures (RR 0.52, p = 0.005) and tended to lower all-cause and cardiac mortality [320]. In the CARE second-

ary prevention trial, pravastatin 40 mg daily reduced CVD events in Type 2 diabetic participants by 24% [321]. In the ASCOT-LLA trial in hypertensive patients in the diabetic subgroup (n = 2352), a mean of 3.3 years of atorvastatin vs. placebo significantly reduced fatal and nonfatal MI by 36% [322].

In HPS, 5963 adults (aged 40–80 years) with diabetes were randomized to simvastatin 40 mg daily or placebo. The statin reduced first occurrence of any major vascular events with a 22% reduction with simvastatin (p <0.00). There was also a 27% reduction (p = 0.0007) among the 2426 diabetic participants whose pre-treatment LDL-C was <3.0 mmol/L (116 mg/dL). The proportional reduction in risk was also about a quarter among other subcategories including diabetes duration, type, glycemia, age, hypertension status, or total cholesterol levels. In participants who had a first major vascular event following randomization, simvastatin reduced their risk of subsequent vascular events. In CARDS, the CVD primary prevention study in Type 2 diabetes subjects aged 40–75 years with an LDL-C of 4.1 mmol/L or lower (n = 2838) subjects received atorvastatin 10 mg daily or placebo. The trial was stopped early (after a mean of 3.9 years) as the statin significantly reduced cardiac events by 36%, revascularization procedures by 31%, and stroke by 48% [323].

After deciding to commence statin therapy, the next decision is to how large a dose to give: moderate- or high-dose statin. The starting dose of most statins lowers LDL-C levels by 25–50%, and each doubling of the dose usually only lowers LDL-C by an additional 6%. This is known as "the rule of six" [324]. Moderate-dose statin therapy is usually defined as that lowering LDL-C by 30% to ≤50%, and high-dose statin therapy lowers LDL-C by 50% or more from its pre-treatment level [319].

The Treating to New Targets (TNT) study of 1501 patients with diabetes and stable CAD addressed the CVD protection of higher vs. lower atorvastatin (80 mg vs. 10 mg daily) and demonstrated (over a 4.9-year follow-up) a 25% lower rate of major CVD events [325].

While higher-dose statins are associated with greater reductions in LDL-C levels and in CVD risk, they may also be associated with a higher risk of side effects and higher financial costs.

The CTTC meta-analysis of 14 statin trials including over 18,000 diabetic subjects demonstrates broad benefit of statins for CVD prevention in people with diabetes, including by gender, by diabetes type, by prior CVD history, and by smoking status, independent of lipid levels. Statins reduced the risk of CVD events by 25%, all-cause mortality by 9%, and CVD death by 13% per 1 mmol/L (39 mg/dL) LDL-C reduction, over a mean of 4.3-year follow-up, with comparable benefit in people with diabetes as without diabetes [326]. In this meta-analysis, the magnitude of CVD benefit was associated with the magnitude of LDL-C reduction.

Assessment tools and guidelines for statin therapy vary between countries.

US guidelines recommend moderate- to high-dose statin therapy for nearly all individuals with diabetes over the age of 40 with a predicted 10-year risk of a cardiovascular event of ≥7.5%, using their ASCVD Pooled Cohort Equations calculator [327]. The ADA recommends statin therapy in all diabetic patients aged over 40 years, including in those aged over 75 years. Moderate-dose statin therapy is recommended in those with no other CVD risk factors other than diabetes. High-dose statin therapy is recommended for those with CVD or with CVD risk factors. For those with CVD who cannot tolerate high-dose statin, moderate-dose statin and ezetimibe could be tried. For diabetic patients <40 years old with CVD, high-dose statins are recommended, and moderate- or high-dose statins are recommended for those aged <40 years and other CVD risk factors (LDL ≥100 mg/dL or 2.6 mmol/L, smoking, hypertension, renal disease, albuminuria, or a family history of premature CVD). Statins are not usually recommended for diabetic patients <40 years old with no CVD risk factors [319].

The UK uses the QRisk2 calculator and recommends statins for individuals over age 35 years with a predicted 10-year risk of a vascular event >10% [328]. The UK guidelines do not make separate recommendations for people with diabetes per se, but the calculator assigns a 10% or greater risk to all white males with Type 2 diabetes aged over 50 years and for females over the age of 57 years, in the absence of any other risk factors. People with diabetes and albuminuria are automatically considered to be at an elevated cardiovascular risk and recommended statin treatment.

The Australian guidelines are much more conservative, recommending statins if lifestyle changes have been unsuccessful above a 5- (not 10)-year risk threshold of 15%, using the National Vascular Disease Prevention Alliance (NVDPA) risk calculator. This calculator uses the Framingham risk equation from 1991, which is felt to be more inaccurate than more contemporary equations, particularly among people with Type 2 diabetes [329, 330].

Statin intolerance is common in primary practice, but due to the major CVD benefits of statins in people with diabetes, the exclusion of other potential causes of the symptoms (e.g., hypothyroidism, low vitamin D levels, viral- or alcohol-related hepatitis, non-alcoholic fatty liver disease, connective tissue disorders, or an inherited myopathy) should be considered. A trial of statin withdrawal to see if symptoms and/or abnormal biochemistry resolves and (ideally if the patient is agreeable) reoccurs with statin rechallenge is worthwhile. Trying alternate statin drugs and starting from a low dose with slow titration can often result in tolerability of statin therapy. Even low-dose statins several times a week can be

effective [331]. Several guidelines to the diagnosis and management of statin intolerance are available [332–336].

Triglyceride and High-Density Lipoprotein-Related

Fibrates

In Type 2 diabetes, the FIELD and the ACCORD Lipid studies of the peroxisome proliferator-activated receptor-alpha (PPAR-alpha) agonist fenofibrate (alone in FIELD), or on a statin background in the ACCORD Lipid study, demonstrated fenofibrate benefits for CVD reduction in those with high triglycerides/low HDL-C levels [337, 338]. Long-term follow-up of the ACCORD Lipid study confirmed metabolic memory for CVD benefit in those exposed to fenofibrate vs. placebo in the intervention phase [174]. The active metabolite of fenofibrate is fenofibric acid, which is now also available for clinical use in the US [339], but as yet there are no major CVD endpoint trials of fenofibric acid, including in diabetes.

There are other fibrates, such as gemfibrozil and bezafibrate, but as statins are of major benefit for CVD reduction, it is anticipated that many people with diabetes will merit statin treatment, and fenofibrate is the only fibrate recommended by the FDA for combination therapy with a statin due to very low rates of rhabdomyolysis [340].

The HPS and CARE (statin) trials demonstrated links between low HDL and CVD events [39, 321], and the TG/HDL ratio does predict CVD events [341], yet there is little trial evidence that pharmacologic modulation (elevations) of HDL levels improves CVD outcomes. While epidemiologic studies support an inverse relationship between HDL and ApoA1 levels and CVD in the general population and in diabetes and HDL-C and ApoA1 levels are usually lower in people with Type 2 diabetes than in the general population, there is as yet no pharmacologic drug that substantially raises HDL levels that has proven (by trial) benefit to reduce CVD in people with diabetes. Powerful HDL-elevating drugs are cholesteryl ester transfer protein (CETP) inhibitors.

Cholesteryl Ester Transfer Protein Inhibitors

CETP inhibitors (e.g., torcetrapib) substantially increase HDL. In the ILLUMINATE trial of torcetrapib plus atorvastatin vs. atorvastatin alone in 15,067 high CVD risk patients (including people with diabetes), torcetrapib significantly increased HDL-C levels and lowered LDL-C levels but was associated with significantly increased risk of CVD events (HR, 1.25; 95% CI, 1.09–1.44; $p = 0.001$) and death from any cause (HR, 1.58; 95% CI, 1.14–2.19; $p = 0.006$) [342]. Off-label effects of hypertension were implicated.

In another CETP inhibitor trial, dal-OUTCOMES trial, in 15,871 (non-diabetic and diabetic) subjects with a recent acute coronary syndrome which tested dalcetrapib vs. placebo added to best available clinical practice, HDL-C (but not LDL-C) levels were significantly increased, but there was no significant effect on the primary composite CVD endpoint, nor on any component thereof, nor on all-cause mortality [343]. There are currently no CETP inhibitors available for clinical practice.

Drug Combinations

No more than one drug from each lipid drug class should be used simultaneously, but drugs from different classes can be combined for additional LDL-C lowering (statin plus ezetimibe or statin plus resin or statin plus PCSK9 inhibitor) or for a statin plus a fibrate for triglyceride lowering ± HDL elevating and a shift to larger less dense LDL. Apart from the FIELD and ACCORD Lipid trials of fenofibrate, there are very limited trial data on such lipid drug combination therapies for people with diabetes.

Statin and Ezetimibe

The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) [344] evaluated simvastatin with 10 mg ezetimibe or placebo in adults aged 50 years or more with a recent (10 days or less) acute coronary syndrome and an LDL-C≥50 mg/dL (1.3 mmol/L). In the subgroup (27%) with diabetes, those given simvastatin 40 mg and ezetimibe derived significant benefit with an absolute risk reduction of 5% and relative risk reduction of 14%.

The combination of a simvastatin (20 mg daily) and ezetimibe (10 mg daily) or placebo was also studied in the Study of Heart and Renal Protection (SHARP) trial of 9270 CKD patients (including 3023 on dialysis) with no known MI or revascularization. Over a mean 4.9-year follow-up, allocation to ezetimibe was associated with a significant 17% reduction in first major CVD event but no reduction in (all-cause) death. Twenty-three percent of the participants had diabetes. Their results were not reported separately, but there was no heterogeneity between the diabetic and non-diabetic subjects [345].

Statin and Niacin

Nicotinic acid (niacin) is a lipid drug class that predominantly lowers triglycerides and also increases HDL-C levels and shifts LDL toward a larger less dense phenotype. Unfortunately, tolerability is often problematic due to flushing and sweating and worsening of glucose tolerance. In the AIM-HIGH study of 3414 people (with and without diabetes), given niacin vs. placebo on statin background did not significantly reduce coronary events (HR 1.02) in the whole study or in the subgroup with diabetes [346]. Furthermore, in AIM-HIGH, there was a trend toward increased stroke with combination therapy [346]. Hence this combination is not recommended for people with diabetes.

Statin and Proprotein Convertase Sublislin-Kexin Type 9 Inhibitors

Proprotein convertase subtilisin-kexin type 9 (PCSK9) is a proprotein convertase which is involved in the degradation of LDL receptors in the liver. Certain mutations in the PCSK9 gene cause familial hypercholesterolemia via reduced LDL receptor numbers on hepatocytes limiting LDL clearance from the circulation in a subset of patients by reducing the number of LDL receptors on the surface of hepatocytes. This decreases their ability to clear LDL from plasma. Other types of PCSK9 mutations lead to very low plasma LDL levels and reduced CVD risk. Blocking the activity of PCSK9 with antibodies reduces the degradation of LDL receptors and increases the clearance of LDL, lowering LDL levels for several weeks at a time [347].

PCSK9 inhibitors (e.g., evolocumab) are a relatively new class of injectable inhibitory antibodies to PCSK9 which can lower LDL-C by approximately 60%. The recently completed FOURIER trial [347] was a randomized, double-blind, placebo-controlled trial of the monoclonal antibody drug evolocumab. The study included 27,564 patients with CVD and LDL-C ≥70 mg/dL (1.8 mmol/L) who were on a statin. Patients were randomly assigned to receive subcutaneous injections of evolocumab (either 140 mg every 2 weeks or 420 mg monthly) or placebo. Their primary endpoint was a composite of CVD death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. After a median 2.2-year follow-up, the PCSK9 inhibitor reduced LDL-C by 59% to a median of 30 mg per deciliter (0.78 mmol/L) and significantly reduced risk of the primary endpoint (1344 patients [9.8%] vs. 1563 patients [11.3%]; hazard ratio, 0.85; 95% confidence interval [CI], 0.79 to 0.92; p <0.001). The results were consistent across diabetic subgroups. There was no significant difference between groups for adverse events, including new onset diabetes, except for injection site reactions with active drug. Hence people with diabetes may benefit from this drug combination and from very low LDL-C levels. Detailed analysis of the diabetic subgroup, long-term follow-up, and further PCSK9 trials in diabetes and CVD are merited. Cost may be a limiting factor.

7.12.4.2 Specific Drugs for Lipid Treatment

Predominantly Low-Density Lipoprotein-Lowering Drugs

Hydroxymethylglutaroyl Coenzyme A Reductase inhibitors: Statins

Examples: Rosuvastatin, atorvastatin, pravastatin, simvastatin.

Mechanisms of action: Statins partly inhibit the intracellular enzyme HMG-CoA reductase, which is the rate-limiting step in cholesterol biosynthesis. This depletes intracellular cholesterol and increases LDL receptor activity, the majority of which are located in the liver, and increases LDL uptake from the blood by the liver.

In addition to their main LDL-lowering effects, there are many pleiotropic effects of statins, likely by a range of mechanisms not yet fully elucidated related to antioxidant, anti-inflammatory, antithrombotic, and vasoactive effects and effects on angiogenesis and endothelial progenitor cells [348–350]. The clinical relevance of each of these pleiotropic effects and at what statin dosage they become evident are still unanswered questions.

Dose range:

Moderate intensity:

Atorvastatin 10–20 mg/day, rosuvastatin 5–10 mg/day, simvastatin 20–40 mg/day, pravastatin 40–80 mg/day, lovastatin 40 mg/day, fluvastatin XL 80 mg/day, pitavastatin 2–4 mg/day.

High intensity:

Atorvastatin 40–80 mg/day, rosuvastatin 20–40 mg/day.

Expected lipid changes: ↓ *LDL-C 20–60%; HDL-C* ↑ *5–15%; triglycerides* ↓ *7–30%*

Side effects and contraindications:

Side effects: Elevated CK, myalgia, and uncommonly rhabdomyolysis (the risk of muscle side effects is increased with hypothyroidism); abnormal LFT (increased ALT and AST), hepatitis (which usually resolves with drug withdrawal); arthralgia, rash, headache, sleep disturbance, increased risk Type 2 diabetes (see below).

Contraindications: pregnancy and breastfeeding.

Avoid use in combination with any non-fenofibrate fibrate drug due to high risk of myositis.

In non-diabetic subjects, statins increase risk of Type 2 diabetes by 9%. On average for every 255 people treated for 4 years with a statin, one person will develop diabetes, but a mean of 5.4 CVD events will be prevented [24]. Given that most people prescribed a statin have high CVD risk, the relative benefit versus risk ratio is perceived to be favorable for statin commencement. The underlying mechanism is thought to relate to effects of statins on inflammation, immune function, and insulin section by the islet beta cells [351].

Importantly, much-publicized concerns about statins and dementia or cognitive impairment are NOT supported by a systematic review by the US FDA databases, trials, cohort, and cross-sectional studies.

Ezetimibe

Mechanism of action: Acts at the brush border of the small intestine to inhibit an enzyme key to cholesterol absorption, reducing cholesterol delivery to the liver.

Dose: 10 mg oral daily.

Can be used alone or in combination with a statin (and combination drugs are available).

Absorption can be impaired if used in combination with a resin; hence separate dosage by at least 2 h.

Expected lipid changes: ↓ *LDL-C 18%; HDL-C 0–1.3%; triglycerides ↓ 6%*

Side effects and contraindications:

Side effects: Gastrointestinal upset, myalgia, arthralgia, fatigue, upper respiratory tract upset (nasopharyngitis, sinusitis) fatigue, rash.

Contraindications: Pregnancy, breastfeeding, moderate to severe liver disease, allergy to ezetimibe.

Bile acid-binding resins

Examples: Cholestyramine, colestipol, colesvelam.

Mechanism of action: Binds cholesterol-rich bile acids in the intestine, and removes them via the bowel, reducing their availability for recycling by the enterohepatic circulation, necessitating (cholesterol-requiring) synthesis of new bile acids by the liver.

Dose range:

Cholestyramine: 1 (5 g) – six packs per day with meals. Gradual increase (one pack/month).

Colestipol: 1 (5 g) – six packs per day with meals. Gradual increase (one pack/month).

Colesvelam: 625 mg tablets – two tablets three times a day with meals. Maximum seven tablets/day.

Expected lipid changes: ↓ LDL-C 15–30%; ↑ HDL-C 3–5%; triglycerides 0 or possible ↑

Colesvelam also has HbA1c lowering effects (≈0.5%) – the only one of the class to do so.

Side effects and contraindications:

Side effects: Gastrointestinal upset, e.g., constipation, bloating; interference with drug absorption; can increase triglyceride levels.

Contraindications: High triglycerides (>4 mmol/L), as can lead to marked hypertriglyceridemia.

PCSK-9 inhibitors

Example: Evolocumab injection.

Mechanism of action: *Inhibitor of PCSK9 which degrades LDL receptors in the liver and hence increases hepatic clearance of LDL.*

Dose range: 140 mg s.c. every 2 weeks or 420 mg s.c. monthly.

Expected lipid effect: ↓ LDL 55%

Side effects and contraindications:

Side effects: Injection site reactions; potential antibody development which may reduce effectiveness; nasopharyngitis, rash, flu-like symptoms.

Contraindications: Allergy to drug, pregnancy (as unknown effects).

Predominantly Triglyceride/Very Low-Density Lipoprotein-Lowering Drugs

Fibrates

Examples: Fenofibrate, fenofibric acid, bezafibrate, gemfibrozil.

Mechanism of action: PPAR-alpha agonist, which activates vascular endothelial cell lipoprotein lipase and reduces apoprotein CIII, increasing lipolysis and elimination of triglyceride-rich particles from plasma.

Dose ranges:

Fenofibrate: 45–145 mg daily. Standard dose with normal renal function is 145 mg, reducing with progressive renal impairment, but not using it in ESRD.

Fenofibric acid: 45–135 mg daily. Standard dose with normal renal function is 145 mg, reducing with progressive renal impairment, but not using it in ESRD.

Gemfibrozil: 600 mg b.d.

Expected lipid changes: *LDL ↔ or ↓5–20%*, *HDL ↑ 10–20%*, *triglycerides ↓ 20–50%*

Side effects and contraindications:

Side effects: Myalgia, CK rise, myositis, rarely rhabdomyolysis (increased risk if elderly, hypothyroidism or renal impairment), rash, pancreatitis, and DVT/PE (rare, reported in FIELD but not ACCORD).

Interference (prolonging) anticoagulants; hence anticoagulation monitoring and dosage adjust is needed.

Contraindications: Severe renal impairment; active liver disease, including primary biliary cirrhosis and unexplained persistent liver function test abnormalities; known gallbladder disease; previous pancreatitis and DVT/embolus (based on FIELD); pregnancy and breastfeeding; allergy to fenofibrate or fenofibric acid.

Fish Oils

Fish oils in high enough doses mainly lower triglycerides. They also have some mild BP lowering and anticlotting and anti-arrhythmia effects.

Examples: Omacor (by script); many over-the-counter fish oil preparations (usually labelled as 1000 IU, but with varying doses of PUFAs (EPA and DHA)).

Mechanism of action: Lipid effect mechanisms not completely understood. Potential mechanisms include inhibition of lipogenesis-related enzymes in the liver (acyl CoA: 1,2-diacylglycerol acyltransferase) and increased fatty acid oxidation in the liver.

Dose range: Omacor/Lovaza 2–4 g/day. Fish oil capsules: up to 4 g/day.

Expected lipid changes: Triglycerides ↓ up to 50%, ↔ or ↑ LDL-C, HDL-C ↔ or ↑

Sides effects and contraindications:

Side effects: Gastrointestinal upset, fishy breath.

Inhibits platelet aggregation, hence increased bruising and bleeding (hence should be stopped 10 days pre-surgery); care with anticoagulant use.

Anti-arrhythmic post-AMI at high dose (beneficial).

Contraindications: Allergy to fish oils; pregnancy (unknown effects).

Combination Tablets

A statin and ezetimibe which would lower LDL-C predominantly and a statin and fenofibrate which would lower LDL-C and triglycerides with a mild HDL-C rise are available in some countries.

7.12.4.3 Blood Pressure Related

Lifestyle

BP may be improved by lifestyle measures such as a low-salt diet, no excess alcohol, weight loss if required, exercise, and non-smoking. For many people with diabetes with moderate or severe hypertension, in addition to lifestyle, several (even four or five) BP drugs from different classes will be required to reach and maintain optimal BP targets.

General Hypertension Treatment Principles

The BP-lowering effects among individual drugs are very similar, with an average reduction for the major classes of BP drug monotherapy of 9.1/5.5 mmHg. Common recommendations for initial BP therapy in the general population include an ACE inhibitor, angiotensin receptor blocker (ARB), calcium channel blocker, or thiazide diuretic in the non-black population. Blacks and older patients in general appear to have better BP responses to a thiazide or calcium channel blocker. In diabetes a thiazide is often avoided due to adverse effects on lipids and uric acid. In diabetes, there may also be renal or retinal protective effects from ACE inhibitors or ARBs. For most drugs, increasing dosage from half to full standard dose lowers BP by about 20% for most drugs. A more graded dose response exists for hydrochlorothiazide (but not other thiazides), for aliskiren and, to a lesser extent, for calcium channel blockers. About 30–50% of patients achieve satisfactory BP control on a single BP agent, but there is wide interpatient variability, and in diabetes it is not uncommon for more than one drug to be required. It is generally recommended that when BP is over 20/10 mmHg above goal, two drugs should be considered as initial therapy. In general the BP-lowering effects of combination therapies are additive: the effects of one, two, or three drugs at half standard dose are 6.7/3.7 vs. 13.3/7.3 vs. 19.9/10.7 mmHg.

Major high BP management society guidelines worldwide conclude that the magnitude of BP lowering is the major determinant of CVD risk reduction, not the choice of BP-lowering drug. Compared to other antihypertensive drugs, beta blockers provide additional CVD risk reductions beyond their BP benefits in people (in the general population) with coronary heart disease in the early years following a MI (29% vs. 15%). Thiazide-like diuretics (e.g., indapamide) are preferred over thiazide-type diuretics (e.g., hydrochlorothiazide) based on large network meta-analyses suggesting that after controlling for BP differences, thiazide-like diuretics additionally reduced the risk of CVD events and heart failure. For all other agents and patient classes, there are a 22% reduction in coronary heart disease events and 41% reduction in stroke per reduction of 10/5 mmHg [352–364].

Drug Treatment Targets in Diabetes

After deciding that hypertension is present, based on multiple BP measurements on different days and ideally using 24-h ambulatory BP monitoring, then the two major issues related to BP care are what BP target to treat to and what drugs to use.

If the BP is only mildly elevated (e.g., 130–140/80–90 mmHg), then several months of lifestyle treatment alone can be used, but with more marked elevations (e.g., >140/90 mmHg), concurrent commencement of a single BP drug and lifestyle changes is recommended. With even more severe hypertension (e.g., over 160/100 mmHg), the concurrent uptake of lifestyle and two BP-lowering drugs (which could be given as a single-pill combination) is recommended [3]. Should the BP fall well into the treatment target range on follow-up, then drug down-titration or cessation can be trialed, with careful monitoring.

There is clear clinical trial evidence that BP control reduces the risk of CVD events (in addition to microvascular complications, discussed later in this chapter) [365]. A reasonable target for most people with diabetes and hypertension is below 140/90 mmHg, with lower targets for high CVD risk diabetic patients (e.g., 130/80 mmHg) if they can be readily achieved [3].

Early diabetes trials showing benefit of BP lowering included the UKPDS and Appropriate Blood Pressure Control in Diabetes (ABCD). In the UKPDS (which was planned in the 1970s) in a group of 1148 hypertensive Type 2 diabetic subjects, the "less tight" BP control target was <180/105 mmHg, and the "tight" target was <150/85 mmHg, with targets achieved being 154/87 vs. 144/82 mmHg, respectively. The less elevated BP target reduced total CVD events significantly by 34%, with a non-significant 18% reduction in death [366]. In the ABCD study (in the 1990s), targeting a diastolic BP of 75 mmHg vs. 80–89 mmHg and achieving mean BP levels of 132/78 vs. 138/86 mmHg significantly reduced total mortality by 49% [367].

A meta-analysis of 40 trials between 1966 and 2014 of BP-lowering drugs and vascular disease in Type 2 diabetes (n = 100,354) showed that each 10 mmHg lower systolic BP

was associated with a significantly lower risk of mortality (relative risk [RR], 0.87; 95% CI, 0.78–0.96) and absolute risk reduction (ARR) in events per 1000 patient-years (3.2; 95% CI, 0.9–5.2), CVD events (RR, 0.89 [95% CI, 0.83–0.95]; ARR, 3.90 [95% CI, 1.57–6.06]), coronary heart disease (RR, 0.88 [95% CI, 0.80–0.98]; ARR, 1.81 [95% CI, 0.35–3.11]), and stroke (RR, 0.73 [95% CI, 0.64–0.83]; ARR, 4.06 [95% CI, 2.53–5.40]). For microvascular complications, there was also benefit for every 10 mmHg lower systolic BP: albuminuria (RR, 0.83 [95% CI, 0.79–0.87]; ARR, 9.33 [95% CI, 7.1–11.7]) and retinopathy (RR, 0.87 [95% CI, 0.76–0.99]; ARR, 2.23 [95% CI, 0.1–4.0]).

When trials were stratified by mean baseline systolic BP above or below 140 mmHg, RRs for outcomes other than stroke, retinopathy, and renal failure were lower in studies with greater baseline systolic BP (p interaction <0.1). The associations between BP-lowering treatments and outcomes were not significantly different, irrespective of drug class, except for stroke and heart failure.

Hence in Type 2 diabetic patients with hypertension (BP >140 mmHg), BP lowering does improve mortality and other clinical CVD (and microvascular) outcomes [365].

More recent trials, such as the ACCORD trial that targeted even lower BP targets (e.g., systolic BP <120 or <130 mmHg vs. <140 mmHg), have not demonstrated convincing net benefits (apart from a small reduction in stroke risk), which was supported by a recent meta-analysis [368]. In ACCORD 4733 participants with Type 2 diabetes and high BP were randomized to intensive vs. standard treatment (systolic BP <120 vs. <140 mmHg). The primary endpoint was a composite of CVD events. After 4.7 years of treatment, a mean BP of 134 vs. 119 mmHg was not associated with significantly lower CVD events but conversely was associated with increased serious adverse events of hypotension and renal dysfunction (3.3% vs. 1.3%, p <0.001) [369].

While the Systolic Blood Pressure Intervention Trial (SPRINT) did show benefit of a more intensive BP target (<120 mmHg), people with diabetes were excluded from this trial [370].

Another area of controversy is what drug or drug combinations to use in order to achieve the desired BP targets.

BP Drug Choices in Diabetes

Early studies of RAAS blockers in patients with diabetes and microalbuminuria showed a significant "renoprotective" effect (mainly by slowing progression to proteinuria), leading to the recommendation of RAAS blockers for this indication, which was then extended to all people with diabetes. However, for CVD protection, these RAAS drugs may not be superior.

A recent meta-analysis evaluated RAAS blockers versus other antihypertensive agents in 19 randomized controlled trials of at least 1-year duration, including 25,414 people with diabetes over 95,910 patient-years. All 19 trials studied people with Type 2 diabetes, and in 17 trials the subjects also had diagnosed hypertension. Endpoints were death, CVD death, MI, angina, stroke, heart failure, revascularization, and ESRD. RAAS blockers were associated with a similar risk of death (RR, 0.99; 95% CI, 0.93–1.05), CVD (1.02; 95% CI, 0.83–1.24), MI (0.87; 95% CI, 0.64 to 1.18), angina (0.80; 95% CI, 0.58 to 1.11), stroke (1.04; 95% CI, 0.92–1.17), heart failure (0.90; 95% CI, 0.76–1.07), and revascularization (0.97; 95% CI, 0.77–1.22). There was also no difference in ESRD by RAAS vs. non-RAAS drug type. Hence in people with diabetes, RAAS blockers were not found to be superior to other classes of BP drugs (e.g., thiazides, calcium channel blockers, and beta blockers) at reducing the risk of hard CVD and renal endpoints. These findings support recommendations of the European Society of Cardiology/European Society of Hypertension and 8th Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure to also use other antihypertensive agents in people with diabetes but without kidney disease [371].

Benefits of Nocturnal Blood Pressure Drug Dosing

The time of day of BP drug administration has been found to be important in people with diabetes [372] and in the general population [373]. As mentioned previously, the earliest manifestation of elevated BP is the loss of nocturnal dipping in BP levels, and studies support there being lower CVD risk associated with lower sleep-time BP levels, which can be achieved with at least one BP medication being taken at bedtime. A prospective, open-label, masked endpoint trial on 448 hypertensive patients with Type 2 diabetes randomized participants to taking all their BP tablets on waking vs. one or more at bedtime, and BP was monitored by ambulatory BP. After a median follow-up of 5.4 years, those with at least one BP drug being taken at bedtime had significantly lower CVD risk with a 12% reduction for each 5 mmHg fall in sleep BP (HR, 0.33 [95% CI, 0.21–0.54]; p <0.001), with cardiovascular death, MI, and stroke being reduced HR 0.25 [0.10–0.61]; p = 0.003). Bedtime dosing was associated with lower sleep-time BP and better-controlled BP [372].

Drug Classes and Combination Therapies

There are currently eight broad classes of antihypertension agents that may be used for CVD risk control: (i) RAAS drugs, including subclasses of (a) ACE inhibitors and (b) ARB blockers and (c) a renin inhibitor (aliskiren); (ii) calcium channel blockers, (iii) beta blockers, (iv) diuretics (including loop diuretics, thiazide diuretics, and potassium-sparing diuretics), (v) aldosterone receptor antagonists (e.g., spironolactone, eplerenone), (vi) alpha adrenergic receptor blockers (e.g., prazosin, doxazosin),

(vii) centrally acting alpha adrenergic agonists (sympatholytics), and (viii) vasodilators (such as hydralazine and minoxidil) [374].

Combination therapies are often needed to control BP and related CVD risk in people with diabetes as; as with LDL-lowering statin drugs, less treatment effects are gained with higher doses of a BP drug; hence adding a low dose of another drug usually has a greater BP-lowering effect than high dose of a single agent. Use of multiple drugs also reduces the risk of side effects. The combination of an ACE and ARB drug should not be used due to adverse effects on renal function.

A common approach (as well as lifestyle measures) is to use an ACE or ARB drug first. A diuretic is a common second-line drug, and many combination tablets are available to reduce pill burden, increase adherence, and reduce cost to the patient. Calcium channel blockers are often third-line drugs. In general dosage, titration can be assessed after 4 weeks of treatment.

Some of the major drug classes commonly used in people with diabetes are described briefly below.

ACE Inhibitors

As well as lowering BP, ACE inhibitors lower intraglomerular pressure and have favorable effects in heart failure and on cardiac remodeling post-AMI.

Examples: Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril.

Mechanisms of action: Blocks conversion of angiotensin I to angiotensin II and the degradation of bradykinin and reduces aldosterone secretion.

Dose range (examples with starting and maximum daily dose): Enalapril 10–40 mg, ramipril 1.25–20 mg, perindopril 4–8 mg, benazepril 10–80 mg, quinapril 10–80 mg, lisinopril 10–40 mg.

Side effects and contraindications:

Side effects: Persistent dry cough (in 5–20% of users, thought to be due to bradykinin accumulation); elevated serum potassium, mild decrease in renal function, gastrointestinal upset, hypotension, rash, headache, fatigue; rarely (<1%) angioneurotic edema.

Contraindications: Pregnancy, renal artery stenosis (as can cause marked renal impairment), prior angioedema, hypersensitivity to the drug.

Precautions with dehydration and hypovolemia and dialysis and aortic stenosis or other cardiac outflow obstruction.

Angiotensin Receptor Blockers

Examples: Candesartan, irbesartan, losartan, olmesartan, telmisartan, valsartan.

Mechanisms of action: Competitively antagonize interactions between angiotensin II and angiotensin receptors and reduce aldosterone levels.

Dose range examples with typical daily start and maximum doses:

Losartan 50–100 mg, candesartan 4–32 mg, irbesartan 150–300 mg, olmesartan 10–40 mg, valsartan 80–320 mg.

Side effects and contraindications:

Side effects: Hyperkalemia, mild decrease in renal function, dizziness, headache; gastrointestinal upsets, abnormal liver function, myalgia, low blood counts; rarely angioneurotic edema.

Contraindications: Pregnancy, angioedema, drug hypersensitivity.

Beta Blockers

Examples: Atenolol, labetalol, metoprolol, propranolol, timolol.

Mechanisms of action: Decrease heart rate and cardiac output, inhibit renin release, peripheral vasodilation, central effects.

Dose range examples (start to usual maximum daily): Atenolol 25–100 mg daily, labetalol 100 mg twice daily to 400 mg twice daily.

Side effects and contraindications:

Side effects: Gastrointestinal upset, bronchospasm, cold extremities, exacerbation of Raynaud's syndrome, bradycardia, hypotension/postural hypotension, heart failure, heart block, fatigue, dizziness, hallucinations, insomnia, nightmares, erectile dysfunction, increased glucose levels with potential to reduce hypoglycemia awareness, dyslipidemia.

In practice impairment of hypoglycemia detection is not usually an issue.

Contraindications: Asthma, COPD, second- or third-degree heart block, sick sinus syndrome, cocaine use; use of non-dihydropyridine calcium channel blockers as may lead to atrioventricular block.

Calcium Channel Blockers

Examples: Amlodipine, diltiazem, felodipine, nifedipine, verapamil.

Mechanisms of action: Inhibition of the influx of calcium through slow channels in the vascular smooth muscle and myocardial tissue during depolarization causing vasodilation, decreased myocardial contractility, and sinoatrial and atrioventricular nodal depression. Decreased aldosterone production.

Dose range examples with typical starting dose and maximum dose:

Amlodipine 5–10 mg once daily, felodipine 2.5–10 mg once daily, nifedipine.

(modified release) 20–90 mg once daily.

Side effects and contraindications:

Side effects: Headache, flushing, dizziness, tachycardia, constipation, edema, palpitations, gingival overgrowth.

Rapid withdrawal can cause coronary spasm and angina in patients with ischemic heart disease.

Avoid use of non-hydropyridine calcium channel blockers (verapamil and diltiazem) with beta blockers due to risk of inducing heart block.

Contraindications: Hypersensitivity to the particular drug, second- or third-degree heart block, Wolfe-Parkinson-White syndrome, or sick sinus syndrome. Symptomatic hypotension, heart failure.

Diuretics

Examples:

Thiazide diuretics: Indapamide, hydrochlorothiazide, chlorothiazide.

Potassium-sparing diuretic: Amiloride, triamterene.

Loop diuretic: Frusemide, etacrynic acid.

Mechanisms of action: Inhibit sodium and water retention in renal tubules.

Dose range examples:

Thiazide diuretic: Indapamide 2.5 mg once daily or indapamide SR 1.5 mg once daily, hydrochlorothiazide 12.5–25 mg daily.

Potassium-sparing diuretic: Amiloride.

Loop diuretic: Frusemide 20 mg once daily – 80 mg divided twice daily.

Side effects and contraindications:

Side effects: Hypotension, dehydration, hypokalemia, increased uric acid levels, gout, low magnesium levels, hyponatremia, muscle cramps, worsen glycemia, and lipid control (thiazides).

Contraindications: Renal impairment – estimated GRF (eGFR)<50 ml/min, pregnancy, breastfeeding.

Aldosterone Antagonists

Examples: Spironolactone, eplerenone.

Mechanisms of action: Blocks aldosterone effects in renal tubules, hence causes renal sodium (and water) loss and potassium retention.

Dose ranges with typical starting and maximum doses:

Spironolactone 25–100 mg.

Eplerenone 25–50 mg.

Side effects and contraindications:

Side effects: Hyperkalemia.

Spironolactone is non-selective, so it also binds to progesterone and androgen receptors, which can lead to menstrual irregularities and breast pain in women and gynecomastia, breast pain, and impotence in men.

Contraindications: Renal impairment, Addison's disease, concomitant use of another aldosterone antagonist.

Renin Inhibitor

Example: Aliskiren.

Mechanism of action: Binds to the active site of renin and inhibits binding of renin to angiotensinogen.

Dose range: 150–300 mg once daily.

Side effects and contraindications:

Side effects: Hyperkalemia (especially if combined with an ACE inhibitor), hypotension, gastrointestinal upset, rash, elevated uric acid, rarely angioedema, headache, dizziness, fatigue, gastrointestinal upset.

Contraindications:

Use with an ACE inhibitor or ARB in patients in patients with diabetes or decreased kidney function (CrCl <60 ml/min). There are no studies of the drug with CrCl <30 ml/min; pregnancy; concomitant itraconazole and cyclosporine

Other drug classes such as alpha blockers and centrally acting drugs (e.g., methyldopa) are relatively infrequently used. Drug combinations in a single pill, particularly including a diuretic are common.

7.12.4.4 Glycemic Control Related

Relationships Between Glucose Control and Cardiovascular Disease

While there is a continuous relationship between glucose levels and CVD in both the non-diabetic and diabetic populations [375], better glycemic control in people with diabetes is associated with less cardiovascular event protection than for the microvascular complications of diabetes. Of concern, as evidenced by recent Type 2 diabetes trials (ACCORD, ADVANCE), intensive glucose control has been associated with no change in, or even increased, cardiovascular event rates, with potential modulating factors being age, diabetes duration, the intensity of glucose control, glucose control drugs used, and more recently genetic factors [376].

Since the Type 2 diabetes trials demonstrate an association of intensive glucose control with harm, several major regulatory bodies have mandated that the cardiovascular safety of new glucose control agents must be demonstrated. In its 2008 Guidance for Industry publication, the US Food and Drug Administration (FDA) issued detailed recommendations to the pharmaceutical industry for demonstrating that new and existing glucose control therapies will not result in an unacceptable increase in CV risk [377]. Similarly, in 2012, The European Medicines Agency (EMA) issued guidelines for drug developers to explore and exclude potentially harmful drug interactions [378].

Despite epidemiological evidence supporting an increased cardiovascular and total mortality risk with poor glycemic control in people with diabetes [379], a reduction in cardiovascular risk with intensive glycemic treatment has not consistently been demonstrated at a randomized control trial level. Favorable results are from the UKPDS and the Veterans Affairs Diabetes Trial (VADT). The UK Prospective Diabetes Study (UKPDS) randomized individuals with Type 2 diabetes to intensive relative to conventional control (median HbA1c, 7.0% vs. 7.9% (53 vs. 62.8 mmol/mol)) [157], and

follow-up studies found an association between lower median on-study HbA1c and long-term reduction in cardiovascular events [163]. In the VADT, 1791 subjects with Type 2 diabetes were randomized to intensive or conventional glycemic management, achieving a median HbA1c of 6.9% (51.9 mmol/mol) and 8.5% (69.4 mmol/mol) at 12 months, respectively. Although there was no difference in cardiovascular events between the two arms on trial, over 10 years of follow-up, the long-term risk of cardiovascular events was reduced in the intensively treated group [380]. The UKPDS and VADT trials in Type 2 diabetes and the DCCT/EDIC study in Type 1 diabetes support a role of "metabolic memory" or a "legacy effect" of lowering HbA1c and the resultant long-term reduction in cardiovascular mortality.

However, other studies (ADVANCE and ACCORD) have not shown such a positive effect of intensive glucose control-related therapy. The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) study involved 11,140 subjects with Type 2 diabetes randomized to intensive (target HbA1c ≤ 6.5% (47.5 mmol/mol)) or standard therapies; however there was no resultant change in cardiovascular mortality between the two groups [160].

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study randomized 10,251 individuals with Type 2 diabetes to intensive or conventional glycemic control targets, with median HbA1c of 6.4% (46.4 mmol/mol) and 7.5% (58.5 mmol/mol) achieved in each group, respectively, after 12 months of therapy [159]. The trial was ceased due to an unexpected 22% increased mortality risk in the intensive group. An increased risk of severe hypoglycemia was thought to be the mechanism behind this increase in adverse outcomes; however it was subsequently disproved [381] in extensive *post hoc* investigations. Indeed, individuals on the ACCORD study with higher HbA1c were found to have the greater mortality risk [382]. The increased mortality may be attributed to individuals in the intensive group who did not achieve the tight glycemic target [383].

ACCORD participants experiencing severe hypoglycemia (regardless of treatment arm) had higher rates of cardiovascular events, microvascular complications, cardiovascular mortality, and all-cause mortality. No consistent temporal or dose-response relationship has been shown between known severe hypoglycemic events and mortality; nor was the magnitude of HbA1c reduction correlated with the risk of severe hypoglycemia [338, 384, 385]. Indeed, study participants with higher HbA1c levels were found to be at greater risk of severe hypoglycemia, which may reflect impairment of counter-regulatory defenses [384].

It has been speculated that people with diabetes who have episodes of severe hypoglycemia are manifesting a more vulnerable health state with an overall worse prognosis [385]. It is possible that in comparison to Type 1 diabetes, other risks play a stronger role in the development of CVD in Type 2 diabetes, and therefore benefits of intensive glycemic management are more difficult to prove in a clinical trial setting.

There is less trial evidence for CVD benefit of glycemic control in Type 1 diabetes. In Type 1 diabetes, intensive glucose control in the DCCT was associated with non-statistically significant lower rates of cardiovascular events in their relatively young study group, but statistically significant reductions in CVD events with prior intensive glucose control were demonstrated in the observational follow-up EDIC stage, during which merging of HbA1c levels between the prior intensive and conventional therapy group (metabolic memory) was observed. During the 30 years of follow-up of the DCCT/EDIC, 149 CVD events occurred in 82 former intensive treatment group subjects versus 217 events in 102 former conventional treatment group subjects; hence intensive therapy reduced the incidence of any CVD by 30% (95% CI, 7, 48; $p = 0.016$) and the incidence of major cardiovascular events (non-fatal MI, stroke, or cardiovascular death) by 32% (95% CI, −3, 56; $p = 0.07$). All of the observed treatment effects on CVD events were accounted for statistically by the lower HbA1c levels [386].

Customized HbA1c Targets in Diabetes

The HbA1c target in people with diabetes should be individualized to the patient and their comorbidities and reviewed in relationship to other clinical factors. Many recommendations suggest that a general target should be ≤7.0% in the majority of individuals [387, 388]. However a more stringent glycemic target of ≤6.0% and ≤6.5% should be considered in some subgroups, such as those with shorter Type 2 diabetes duration and those with Type 2 diabetes treated with lifestyle/metformin or any other oral hypoglycemic and with few adverse side effects of treatment. Prepregnancy the HbA1c target should be ≤6.0% (42.1 mmol/mol). In individuals with a history of severe hypoglycemia or hypoglycemia unawareness, multiple comorbidities of limited life expectancy less stringent targets, such as ≤8.0%, are reasonable.

More recently, in 2018, based on review of recent international guidelines and of trials (including ACCORD, ADVANCE, UKPDS, and VADT), the American College of Physicians recommended less stringent HbA1c targets (of 7–8%) for most non-pregnant adults with Type 2 diabetes [389]. There are four guidance statements:

1. Clinicians should personalize glucose control goals considering benefits and harms of pharmacotherapy, patient preferences, general health, life expectancy, treatment burden, and care costs.
2. A HbA1c between 7% and 8% is appropriate for most (non-pregnant adult) patients with Type 2 diabetes. They

cited the reason as inconsistent results in clinical microvascular benefits.
3. Consider deintensification of drug therapy for those with HbA1c levels <6.5%. This was based on the adverse cardiovascular, mortality, severe hypoglycemia events, other side effects, and costs in the ACCORD and ADVANCE trials.
4. Treatment strategies should minimize hyperglycemia-related symptoms and avoid targeting a HbA1c level in patients in whom harms outweigh benefits such as people with a limited life expectancy (<10 years) and advanced age (≥80 years), nursing home residents, and those with chronic conditions (e.g., dementia, cancer, renal failure, severe chronic obstructive pulmonary disease, or heart failure).

It is important for the clinician to consider and discuss the changing glycemic goals over the course of their patient's life with diabetes.

Does Glucose Control Medication Choice Matter for Cardiovascular Disease?

Many drugs have off-target or pleiotropic effects, which may modulate cardiovascular health; hence glucose control drug choice may have implications beyond the HbA1c level achieved.

Metformin (summarized in the next section) is considered generally safe from the CVD viewpoint, including in heart failure patients except during hospitalizations with acute cardiac decompensation or acute renal failure [390]. While there has not previously been convincing evidence of specific cardiovascular outcome advantages using particular diabetes medications, recent results of two studies (using members of two recently available drug classes – a SGLT2 inhibitors and GLP-1 agonists) are of great interest.

The EMPA-REG OUTCOME trial evaluated an oral SGLT2 inhibitor, empagliflozin, vs. placebo on cardiovascular outcomes in high-risk Type 2 diabetic participants and demonstrated a 14% risk reduction for major cardiovascular events, with reductions in cardiovascular and all-cause mortality of 38% and 32%, respectively [391]. While multiple mechanisms have been proposed, these effects appear most likely to be related to significant reductions in heart failure hospitalizations. The results of similar trials with other SGLT2 inhibitors (canagliflozin (CANVAS) [392] and dapagliflozin (DECLARE-TIMI58) [393] when available will be of interest.

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial randomized high CVD risk participants with Type 2 diabetes to the injectable GLP-1 analogue or placebo and found a 13% reduction in their composite CVD primary outcome, with significant mortality reductions (CVD death (22%) and all-cause mortality (15%)) over 3.8 years). In contrast, no significant differences in CVD outcomes were seen for another GLP-1 receptor agonist, lixisenatide, which is shorter acting structurally different to liraglutide [394].

In terms of adverse cardiovascular risks, it is well-recognized that the thiazolidinediones are associated with an increased risk of heart failure secondary to renally-mediated fluid retention and hence should be avoided in diabetic patients with symptomatic heart failure [395]. With regard to heart failure risk, there is also potential concern related to the orally active incretin drug class of the dipeptidyl peptidase-4 (DPP-4) inhibitors. As discussed in more detail in the section below, there was a 27% increased risk of hospitalization for heart failure in the cardiovascular safety trial for saxagliptin [396], a trend to more adverse events for alogliptin [397], and no harm nor benefit for sitagliptin [390, 398]; hence whether there is a DPP4 inhibitor class effect is not yet clear.

With time, additional trials, and preferably post-trial follow-up, this clinically important area should become clearer.

A recent meta-analysis of 236 Type 2 diabetes trials (n = 176,310) evaluated CVD and all-cause mortality effects of SGLT2 inhibitors, GLP-1 agonists, and DPP-4 inhibitors [399]. Relative to control groups, SGLT2 inhibitors were associated with lower rates of *heart failure* (absolute risk difference (RD), −1.1%; HR, 0.62 [95% credible interval CrI, 0.54–0.72]) and *MI* (absolute RD, −0.6%; HR, 0.86 [95% CrI, 0.77–0.97]). Relative to control groups, SGLT2 inhibitors reduced *all-cause mortality* (absolute risk differ [RD], −1.0%; [HR], 0.80 [95% CrI, 0.71–0.89]) and GLP-1 agonists (absolute RD, −0.6%; HR, 0.88 [95% CrI, 0.81–0.94]). Relative to DPP-4 inhibitors, which did not significantly reduce all-cause mortality, all-cause mortality was lower with SGLT2 inhibitors (absolute RD, −0.9%; HR, 0.78 [95% CrI, 0.68–0.90]) and GLP-1 agonists (absolute RD, −0.5%; HR, 0.86 [95% CrI, 0.77–0.96]).

Drugs to Control Glucose Levels in Diabetes

There is an increasing array of oral and injectable (insulin and GLP-1 analogues) drug classes to control glucose levels in people with diabetes. Particularly in people with longer Type 2 diabetes duration, more than one drug class is often required, and apart from insulins, one should only use one member from the same drug class at a time. Various strategies for glucose control and the use of combination therapies have been suggested by the major national diabetes organizations, and to help the clinician, various reviews, flow charts, and online decision support tools are available [400, 401]. A summary of the various glucose control strategies and suggested combinations is shown in Fig. 7.5. To reduce tablet burden and promote medication adherence, combination tablets of two glucose control therapies are increasingly available.

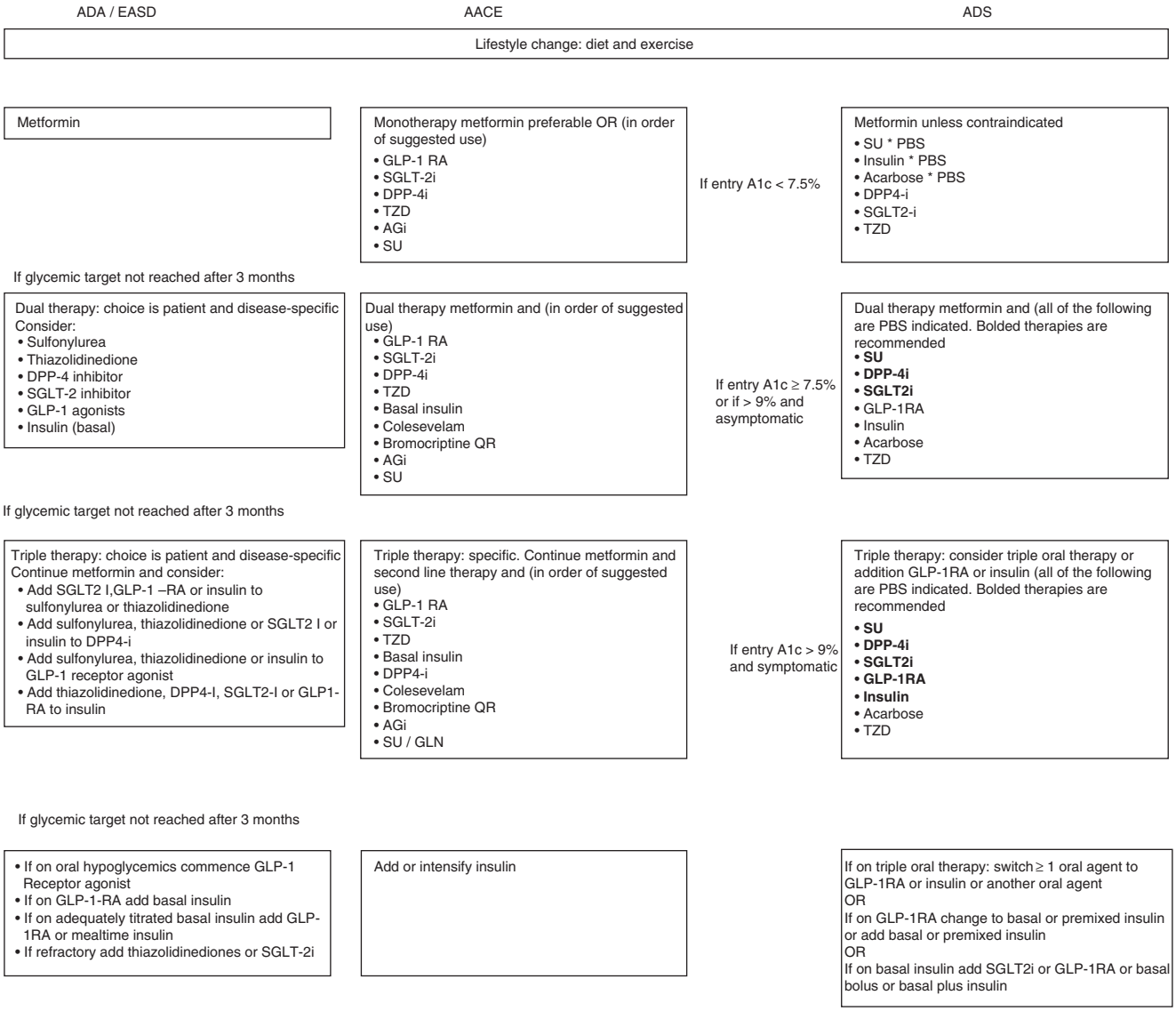

Fig. 7.5 Glucose control strategies and suggested therapy combinations

A brief overview of each of the major drug classes used for glucose control in diabetes is now given. For each drug class, some examples on the mechanism of action, dose range, major side effects, and contraindications, and effects on cardiovascular events are given. Some of the example drugs given may not be available in all countries.

Metformin (Biguanide)

Metformin (oral) therapy is recommended as a first-line pharmacologic agent for the glucose control-related treatment of Type 2 diabetes.

Mechanisms of action: Via reduction in hepatic gluconeogenesis, delayed glucose absorption from gastrointestinal tract, and improved peripheral utilization of glucose.

Dose range: 500 mg–3 g daily.

Expected HbA1c reduction: Approximately 1% [402].

Side effects and contraindications: The most common side effects associated with metformin are gastrointestinal discomfort. It is recommended that the metformin dosage is gradually increased as is tolerated. Slow-release formulations may further reduce the risk of gastrointestinal symptoms.

Metformin is weight-neutral. There is a very low risk of hypoglycemic episodes with these agents, although this can occur with dual therapy. Lactic acidosis risk in patients treated with metformin is very low (0.03 cases per 1000 patient-years) [403]. However, any condition that may affect renal function (dehydration, sepsis) or increase tissue hypoxia and acidosis (cardiac failure, liver failure, ketoacidosis, surgery) may increase the risk of lactic acidosis with

the therapy. As a result, metformin should be ceased if a patient becomes acutely unwell. In at-risk individuals, metformin is recommended to be withheld prior to and for 48 h following iodinated contrast procedures [404]. Metformin should be reduced with renal impairment (eGFR <45 ml/minute) [405]. It is generally not recommended for use when eGFR is below 30 ml/minute. Metformin should not be used in severe hepatic or cardiac failure [3]. Vitamin B12 should be monitored in all patients on metformin therapy as metformin lowers its absorption.

Cardiovascular effects: Protective

Sulfonylureas

Examples: Glibenclamide, gliclazide, glimepiride, glipizide.

Mechanism of action: These oral drugs act via the sulfonylurea receptor on pancreatic beta cells to stimulate insulin secretion [403].

Dose range: Dose reduction should occur in renal impairment due to increased risk of hypoglycemia.

- Glibenclamide: 2.5–20 mg daily.
- Gliclazide immediate release: 40–320 mg daily.
- Gliclazide controlled release: 30–120 mg daily.
- Glimepiride: 1–4 mg daily.
- Glipizide: 2.5–40 mg daily.

Expected HbA1c reduction: Approximately 1.25% [402].

Side effects and contraindications: The major concern of these agents is hypoglycemia. Slow-release compounds are most commonly associated with this side effect. Glibenclamide appears to have the greatest risk of all the sulfonylureas. Another common side effect is weight gain. In this circumstance glipizide or gliclazide is preferable. Sulfonylureas should not be used in severe hepatic impairment.

Cardiovascular and other effects: There may be an increased risk of cardiovascular events with sulfonylurea therapy relative to metformin, although this may be due to a protective effect of metformin [406, 407]. Gliclazide and glimepiride do not appear to be associated with increased cardiovascular mortality relative to metformin [408].

DPP4 Inhibitors

Examples: Alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin.

Mechanism of action: These orally active drugs act by inhibition of dipeptidyl peptidase 4 activity, thereby slowing inactivation of the incretin hormones, such as GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) [403]. As a result, there is an increase in glucose-dependent insulin secretion; reduction in inappropriate glucagon release and gastric emptying is slowed. Thereby, there is minimal risk of hypoglycemia in the absence of other drugs. Combination tablets with metformin are common.

Dose range:

- Alogliptin 25 mg daily (eGFR 30–50 ml/minute 12.5 mg, <30 ml/minute 6.25 mg).
- Linagliptin 5 mg daily.
- Saxagliptin 5 mg daily (eGFR <50 ml/minute 2.5 mg daily).
- Sitagliptin 100 mg daily (eGFR 30–50 ml/minute 50 mg daily, <30 ml/minute 25 mg daily).
- Vildagliptin 50 mg twice daily (eGFR <60 ml/minute 50 mg daily).

Expected HbA1c reduction: Modest, about 0.75% [402].

Side effects and contraindications: Side effects can occur, in particular gastrointestinal symptoms and nasopharyngitis. Due to renal excretion, in the context of renal impairment, dosage reductions are required for all drugs (with the exception of linagliptin, which is excreted in the bile). These drugs should be avoided in the context of pancreatitis. These agents are weight neutral.

Cardiovascular effects: Cardiovascular safety has been reported for these drugs [397, 398], although an increased risk in hospitalization for cardiac failure in at-risk patients has been reported for saxagliptin [396].

GLP-1 Receptor Agonists

Examples: Exenatide, liraglutide, lixisenatide.

Mechanism of action: The glucagon-like peptide-1 (GLP-1) agonist bind to and activates the human GLP-1 receptor, thereby stimulating glucose-dependent beta cell insulin secretion, suppressing inappropriate glucagon secretion and slowing gastric emptying.

Dose range:

- Exenatide 5–10 mg twice daily or 2 mg weekly.
- Liraglutide 0.6–1.8 mg daily.
- Lixisenatide 10–20 mg daily.

Expected HbA1c and glucose reduction: Approximately 1% [409]. Short-acting forms (exenatide) are associated with an improvement in post-prandial glucose, whereas long-acting forms (liraglutide) reduce fasting glucose levels [24].

Side effects and contraindications: There is a low risk of hypoglycemia. Side effects include nausea and vomiting, and the dosage may need to be reduced in those individuals with gastroesophageal reflux disease. There is a small increase in resting heart rate. These agents infrequently increase the risk of cholelithiasis and cholecystitis

and rarely cause pancreatitis. It is recommended that GLP-1 agonists should be avoided in patients with a medical (or family) history of medullary thyroid cancer or multiple endocrine neoplasia type 2 (MEN-2). These agents should not be used in the context of an eGFR <30 ml/minute. It is recommended that GLP-1 agents be avoided in the context of a previous history of pancreatitis [410], and if pancreatitis does occur while on the drug, they should be ceased immediately.

Cardiovascular and other effects: These agents are associated with reductions in both weight (estimated around 2–3 kg if BMI >25) [411] and BP. The LEADER trial reported reduced cardiovascular composite outcome (13% reduction), reduced cardiovascular death (22% reduction), and total mortality (15% reduction) over 3.8 years in at-risk individuals treated with liraglutide therapy [412]. Similar findings were not seen with lixisenatide [394].

SGLT2 Inhibitors

Examples: Dapagliflozin, empagliflozin, canagliflozin.

Mechanism of action: These oral drugs inhibit the sodium-glucose cotransporter 2 within the kidney, reducing renal glucose reabsorption and increasing glycosuria.

Dose range:

- Dapagliflozin 10 mg daily.
- Empagliflozin 10–25 mg daily.

Expected HbA1c reduction: Estimated at 0.7% [413].

Side effects and contraindications: There is an increased risk of urogenital mycotic infection, and hygiene measures and adequate hydration are advised. Due to their mechanism of action, SGLT2 inhibitors are associated with a risk of dehydration and hypotension. In clinical trials, there was a reported increased risk of fracture with canagliflozin [414]. There are also reports of (euglycemic) diabetic ketoacidosis in individuals treated with SGLT2 inhibitors [415]. In the context of acute serious illness and prolonged fasting, it is recommended that an SGLT2 inhibitor be withheld due to increased risk of ketoacidosis [416]. Dapagliflozin is contraindicated if the eGFR is <60 ml/minute, and empagliflozin is contraindicated if the eGFR is <45 ml/minute [3].

Cardiovascular and other effects: Empagliflozin demonstrated a 14% reduction in risk of major cardiovascular events and reduction in cardiovascular and total mortality of 38% and 32% cardiovascular mortality and cardiac failure in an at-risk population [391]. Empagliflozin has also been found to reduce the progression of renal disease in at-risk individuals [417]. It is not clear yet as to whether these benefits are a class effect. SGLT2 inhibitors are associated with weight loss (estimated 3 kg at 2 years) and reductions in BP [418].

Thiazolidinediones

Examples: Pioglitazone, rosiglitazone.

Mechanism of action: Thiazolidinediones are orally active transcription factor PPAR-gamma agonists (although pioglitazone has some alpha agonist activity). Glucose reduction occurs via peripheral insulin sensitization in the muscle and adipose tissue and impairment of hepatic gluconeogenesis.

Dose range:

- Pioglitazone 15–20 mg daily.
- Rosiglitazone 4–8 mg daily.

Expected HbA1c reduction: Approximately 0.8% [409].

Side effects and contraindications: Minimal risk of hypoglycemia. Side effects include weight gain and increased fracture risk. Rosiglitazone is contraindicated in cardiac failure. Pioglitazone is contraindicated in New York Heart Association classes II–IV [403]. There is also a reported association of pioglitazone with bladder cancer [419]. Thiazolidinediones are rarely associated with hepatic injury, and therefore monitoring of liver function tests is recommended [420].

Cardiovascular and other effects: There has been controversy surrounding the cardiovascular effects of these agents. Pioglitazone may have a favorable effect on cardiovascular risk in patients at high risk [419, 421]. In contrast, rosiglitazone had been linked to an increased cardiovascular risk [422], although this has not been consistently supported by clinical trial data [423]. Thiazolidinediones are known to increase risk of edema and exacerbation of cardiac failure.

Alpha Glucosidase Inhibitors

Examples: Acarbose, miglitol, voglibose.

Mechanism of action: Alpha glucosidase inhibitors, which are orally active, act to reduce post-prandial glucose via reduction in gastrointestinal glucose absorption through inhibition of alpha glucosidase enzymes within the small intestine.

Dose range:

- Acarbose 50–600 mg daily.
- Miglitol 75–300 mg daily.

Expected HbA1c reduction: Approximately 0.6% [409].

Side effects and contraindications:

There is a minimal risk of hypoglycemia. Side effects which may limit the use of these agents include diarrhea and flatulence. These agents are contraindicated in individuals with inflammatory bowel disease, intestinal obstruction, or malabsorption [424]. They should also be avoided if the eGFR is <25 ml/minute.

Cardiovascular and other effects: Cardiovascular benefits have been reported in patients with impaired glucose tolerance [425].

Insulin

Insulin, which is usually injected subcutaneously but (usually in the medical setting) can be given intramuscularly or intravenously, is recommended to achieve rapid glycemic control (e.g. preoperatively) or in situations where blood glucose is very high (either at diagnosis or over time) [426].

Insulin is available in a number of formulations with variable time to onset and duration of action.

- Ultrashort-acting analogues: Insulin aspart (NovoRapid), insulin glulisine (Apidra), and insulin lispro (Humalog). Time to onset: 0.25 h. Time to peak: 1 h. Duration: 4–5 h.
- Short-acting: neutral (Actrapid, Humulin R, Hypurin Neutral). Time to onset: 0.5 h. Time to peak: 2–3 h. Duration: 6–8 h.
- Long-acting:
  - Isophane (Humulin NPH, Protaphane, Hypurin, Isophane). Time to onset: 1–2.5 h. Time to peak: 4–12 h. Duration: 16–24 h.
  - U-500 regular insulin (for insulin-resistant patients). Pharmacologic profile similar to NPH.
  - Mixed with short-acting insulin (Humulin 30/70, Mixtard 30/70, Mixtard 50/50). Time to onset: 0.5 to 1 h. Time to peak: 2–12 h. Duration: 16–24 h.
- Long-acting (analogues):
  - Mixed with ultrashort-acting insulin (NovoMix 30, Humalog Mix25, Humalog Mix50). Time to onset: 0.25 h. Time to peak: 1 h. Duration: 16–18 h.
  - Insulin detemir (Levemir). Time to onset: 3–4 h. Time to peak: 9 h. Duration: 12–24 h.
  - Insulin glargine (Lantus 100 units/ml, Toujeo 300 units/ml). Time to onset: 1–2 and 1–6 h. Time to peak: No peak. Duration: 24 and 24–36 h [427].
- Ultra-long-acting insulin (analogue):
  - Insulin degludec (Tresiba 100 units/ml, 200 units /ml). Time to onset: 0.5–1.5 h. Time to peak: No peak. Duration: 42 h [428].

Mechanism of action: Enhances cellular glucose uptake and inhibits lipolysis and endogenous glucose production.

Dose range: Variable according to patient and other therapies.

Expected HbA1c reduction: 0.9–1.1% [409].

Side effects: Hypoglycemia and weight gain, fat hypertrophy at injection sites, fluid retention.

Cardiovascular and other effects: Cardiovascular safety has been proven [429].

7.12.4.5 Heart Failure

As reviewed in our recent review and covered by the mnemonic BANDAID(2) for the treatment of systolic heart failure, there is evidence for diuretics and, under specific circumstances, for aldosterone antagonists (spironolactone or eplerenone), ivabradine, a neprilysin inhibitor, and cardiac devices (e.g., implantable cardiac defibrillators or cardiac resynchronization therapy) [275]. Except for prasugrel and ezetimibe, all of these therapies have been shown to separately confer significant all-cause mortality reductions in appropriately selected populations [275, 276].

7.12.4.6 Referral to a Cardiologist or Other Vascular Specialist

Indications for referral of a diabetic patient to a cardiologist include concerns regarding the diagnosis and management of CAD, resistant hypertension, heart failure, cardiomyopathy, and arrhythmias (which hypoglycemia may exacerbate). Depending on their interests, peripheral vascular disease and cerebral vascular disease opinions may be sought from cardiologists, neurologists (with an interest in stroke), vascular surgeons, or interventional radiologists (who may perform vascular imaging as well as angioplasty or stenting procedures). Lipidologists, some endocrinologists, and vascular medicine specialists also take an interest in vascular risk factor detection and management.

7.13 Microvascular Complication Management

7.13.1 Microvascular Complications

Modifiable risk factors for diabetic retinopathy and nephropathy are similar to those for CVD, and include poor glycemic control, hypertension, dyslipidemia, smoking, and obesity, and the treatment targets and tools are generally as for CVD prevention.

Improved glycemic control has a greater effect on the prevention and retardation of the progression of the microvascular complications of diabetes than for macrovascular disease, and there is metabolic memory for both good and poor glycemic control and likely also for other vascular risk factors [173, 430]. This metabolic memory is relevant to the design and interpretation of clinical trials and to clinical practice.

As discussed previously, the means of achieving glycemic control and control of other risk factors, such as BP, may also be important. For example, for comparable levels of glycemia in Type 2 diabetic patients, metformin is associated with greater reductions in vascular complications and longer-term benefits. In Type 1 diabetes, based on observational data, insulin delivery by CSII vs. MDI is associated with similar

HbA1c levels but significantly lower CVD [431], mortality, and microvascular events [432].

For each of the major microvascular complications (retinopathy, nephropathy, and neuropathy), we will now overview the screening, risk factor control, and treatment strategies, and potential referral points.

7.13.2 Diabetic Retinopathy

7.13.2.1 Screening for Diabetic Retinopathy

At the time of Type 2 diagnosis or within 5 years of Type 1 diabetes diagnosis, people with diabetes should have a comprehensive eye examination through a dilated pupil by an ophthalmologist or optometrist. The ADA guidelines, which are similar to other major national bodies, are that this comprehensive dilated eye exam should be repeated at least annually if any level of diabetic retinopathy is present, but may be more frequent if the retinopathy is progressing or is sight-threatening. If there is good risk factor control and no evidence of diabetic retinopathy for one or more annual examinations, then assessments every 2 years may be reasonable [3]. To optimize resources and reduce patient burden, various algorithms regarding frequency of eye examination have been suggested in both Type 1 [433] and Type 2 diabetes [434, 435].

A comprehensive eye exam should include assessment of intraocular pressure and of lens opacities, as glaucoma and cataracts (and other eye lesions mentioned earlier in this chapter) are more common in people with diabetes. Women with pre-existing (Type 2 or Type 1) diabetes who are contemplating pregnancy or who are pregnant should be counselled and screened by an ophthalmic clinician (optometrist or ophthalmologist) as pregnancy can greatly accelerate the progression of existent diabetic retinopathy. Depending on the retinopathy severity, they should be monitored each trimester and for 1 year postpartum. Due to the longer timeframe needed to develop diabetic retinopathy, women with gestational diabetes do not need ophthalmic screening [3].

Ophthalmic clinicians will often take retinal photos at the ocular examination and share these with other treating clinicians. In addition, a more sensitive method for the detection and monitoring of retinal damage, in particular for diabetic macular edema, is optical coherence tomography (OCT), which ophthalmic clinicians are increasingly using. OCT provides more detailed 3-D retinal images.

Due to the increasingly large number of people with diabetes, including in remote regions, and the usually low rates of ophthalmic clinicians in rural and remote regions, digital retinal photography is increasingly being used as a retinopathy screening tool [436, 437], including in family practice and endocrinology clinics. Photos taken locally, often by a trained health worker or nurse, rather than by an ophthalmic clinician, are often then sent (electronically) to an off-site retinal grading site where grading is done by, or overseen by, ophthalmic clinicians. Such examinations vary in retinal field coverage, based on whether the pupil is dilated or not, the number of photos taken, and the field of view of the retinal camera, but they are usually not as comprehensive as a full clinical eye examination. Good and well-validated retinal photography screening programs do have a place in retinopathy screening, particularly in less well-resourced settings.

7.13.2.2 Systemic Risk Factor Control for Diabetic Retinopathy

Modifiable systemic risk factor control is important for the prevention of diabetic retinopathy, though, as discussed earlier in this chapter, most people with diabetes for long enough will develop some (non-sight-threatening) form of diabetic retinopathy. As yet we lack excellent algorithms for the early prediction of those who will develop clinically significant vascular complications, and there are few microvascular risk equations available.

Glycemic Control

The major trials showing retinopathy benefit of better glucose control are the DCCT/EDIC trial in Type 1 diabetes [155] and the UKPDS trial in Type 2 diabetes [157]. These large trials included people relatively early after their diabetes diagnosis and had long follow-up periods (including post-trial), and the intervention arms were reducing HbA1c levels from relatively high levels compared to those now common in clinical practice in recent decades. These trials clearly demonstrate that better glycemic control reduces the onset and progression of diabetic retinopathy (and other microvascular complications). In the DCCT, 1441 T1D patients were assigned to intensive (insulin pumps or ≥ three insulin injections/day) or conventional diabetes therapy, which resulted in median HbA1c levels of 8.9% 8.95% (74 mmol/mol) vs. 7.2% (55 mmol/mol) for a mean 6.5-year follow-up (until early trial cessation due to favorable effects). Intensive treatment reduced retinopathy onset (primary prevention) by 76% and its progression (secondary prevention) by 54%, respectively. In the first 10 years of the DCCT observational follow-up study, EDIC, despite HbA1c equalization between the former randomization groups, the cumulative incidence of retinopathy continued to diverge, with an overall hazard reduction of 56% in the former intensively treated group [438]. At EDIC year 18, the cumulative annual incidence of retinopathy progression was similar between prior DCCT groups, with less retinopathy in the former DCCT intensive treatment group [162]. Up to 25 years later, this group continues to have lower rates of ocular surgery; the former intervention group has significantly lower rates of

ocular surgery (e.g., 42% fewer vitrectomies) [165] than the control group, reflecting metabolic memory.

In Type 2 diabetes, the UKPDS 4209 newly diagnosed T2D patients aged 53 years (range 25–65 years) were followed for 20 years (1977–1997) [157] after randomization to intensive glucose control (by different drugs: metformin, sulfonylurea, insulin) or conventional treatment, resulting in a HbA1c difference of 0.9%. Intensive therapy significantly reduced CVD and mortality and lowered the cumulative microvascular endpoints by 25% (p <0.01), including retinopathy progression (21% less) (evident at 6 years) which was sustained for 12 years. Thus, these two trials show the benefits of good glucose control early on after a (Type 1 or Type 2) diabetes diagnosis.

In Type 2 diabetes, patients are usually older, with multiple comorbidities and medications and their diabetes onset was gradual, making diabetes duration and thus metabolic stress less certain than in patients with Type 1 diabetes. Perhaps because of these factors, metabolic memory and lower HbA1c targets, more recent (relatively short, about 5 years) clinical trials assessing improved glycemic control in Type 2 diabetic patients have been negative for their primary CVD endpoints and do not show major benefit for retinopathy. ACCORD showed marginal benefit for retinopathy in its intensive glycemic control arm (but was stopped early because of higher mortality in that group) [439]. ADVANCE showed no benefit for retinopathy [160], and the VADT demonstrated retinopathy benefit in younger subjects, but harm in older participants [440]. Thus, in contrast to benefit in younger recently-diagnosed diabetic patients, tighter glucose control does not seem to provide as much retinal protection when commenced later in older patients with longer diabetes duration.

Lipid Control

While generally not as strongly associated with retinopathy as with atherosclerosis, adverse circulating lipid profiles are a risk factor for diabetic retinopathy in both Type1 diabetes (Pittsburgh Epidemiology of Diabetes Complications Study and the DCCT/EDIC study [441]) and in Type 2 diabetes (ETDRS [442], the Hoorn Study [443], ARIC study [444]). While not detectable in clinical practice, a substantial body of clinical and related basic science studies demonstrates retinal damage by lipoprotein extravasation and modification [147, 445–450].

Lipid drugs. While very effective for the primary and secondary prevention of CVD, including in people with diabetes [326], the major LDL-C-lowering lipid drugs, the statins, have not been shown to be effective in clinical trials in preventing the development or slowing the progression of diabetic retinopathy. In contrast, the PPAR-alpha agonist fibrate drug, fenofibrate (classically used as a triglyceride-lowering agent), has been shown to retard retinopathy progression (either alone or on a statin background) in two major prospective randomized controlled trials, FIELD and ACCORD-Eye [251, 337]. Related basic science supports this benefit being PPAR-alpharelated and a result of the pleotropic actions of this drug, such as its anti-inflammatory, antioxidant, anti-apoptotic, and anti-angiogenic effects [451–453].

Blood Pressure and Blood Pressure Drugs

Elevated blood pressure is a risk factor for both the development and progression of diabetic retinopathy [454]. This is evidenced by the Type 2 diabetes UKPDS, in which BP levels, like HbA1c targets, were relatively high compared to today's targets [157]. The more recent META-EYE study in many different countries showed that normal BP is protective against diabetic retinopathy progression compared to those who had hypertension (BP >140/90 mmHg) or were receiving antihypertensive drugs [455]. At least over the few years of most clinical trials, such as in the ACCORD Eye Study, no retinopathy benefits of intensive BP control (BP <120/80 mmHg) has been demonstrated.

There is a RAAS system in the eye, and several clinical trials, including the DIabetic REtinopathy Candesartan Trials (DIRECT-Prevent 1), progression of retinopathy in type 1 diabetes study (DIRECT-Protect 1), and progression of retinopathy in Type 2 diabetes study (DIRECT-Protect 2), have shown that Type 1 and Type 2 diabetic patients may benefit from early use of ACE inhibitors and ARB blockers [101, 456]. While a recent Cochrane review exploring BP control over 4.5 years in Type 2 diabetic patients showed no significant effect on diabetic retinopathy progression [457], even if one doubts retinal retarding effects of RAAS blockade, there is still strong evidence for RAAS blockade for renal and cardioprotection in people with diabetes.

7.13.2.3 Referral and Ocular Treatment for Late-Stage Diabetic Retinopathy

Patients with diabetes should be urgently referred to an ophthalmologist for any sudden-onset symptoms related to vision, such as loss of vision or increased "floaters," which may signal a retinal hemorrhage or retinal detachment. Slowly progressive vision loss should also be referred to an ophthalmologist, which may reflect cataract development, glaucoma, macular edema, or other eye pathology.

People with any level of diabetic macular edema (which can occur at any stage of diabetic retinopathy) and severe non-proliferative or proliferative diabetic retinopathy should be referred to an ophthalmologist skilled in the management of diabetic retinopathy. Such advanced disease can occur in the absence of any symptoms, hence the importance of regular ocular screening. Ocular treatment for late-stage diabetic

retinopathy can substantially reduce the risk of vision loss (from 15.9 to 6.4% as per the DRS study [458]), but usually cannot restore lost vision. The ocular treatments available include pan-retinal laser treatment [459, 460], intraocular anti-VEGF injections (often required monthly for the first year and then less often thereafter) [461–465], intraocular corticosteroid injections, and vitrectomy. Combination therapy may be given. These treatments are not always effective, and there are potential side effects of each treatment. Pan-retinal laser therapy can cause loss of peripheral vision and night vision, intraocular steroids may accelerate cataracts and induce glaucoma, and anti-VEGF injections may be associated with hemorrhage and inflammation [466]. As mentioned previously, two large RCTs (FIELD and ACCORD Eye) demonstrated efficacy in the prevention of progression of diabetic retinopathy in adults with Type 2 diabetes, but the efficacy of such oral treatment in late-stage diabetic retinopathy and in combination with intraocular injection therapy is as yet unknown, and clinical trials are in progress (personal communication, G Liew).

It should be noted that even late-stage diabetic retinopathy is not a contraindication for aspirin therapy (for CVD prevention), as aspirin does not increase the risk of retinal hemorrhages [319].

7.13.3 Diabetic Nephropathy

7.13.3.1 Screening and Diagnosis

As described earlier in this chapter, diabetic nephropathy is a common complication of diabetes (20–45% of patients) and is associated with increased risk of CVD, retinopathy, and mortality. Nephropathy may manifest as increased urinary albumin loss and/or loss of renal function as reflected by declining GFR or creatinine clearance (usually calculated) or (later in the course of the disease) rising serum creatinine levels. Diabetic nephropathy is usually slowly progressive, but the early stages can spontaneously regress or regress in response to treatment of risk factors and the use of RAAS drugs (ACE inhibitor or ARB blockers).

Regular screening, at least annually, should begin at Type 2 diabetes diagnosis, from 5 years after Type 1 diabetes onset, or if concurrent hypertension is present. Some level of diabetic retinopathy is usually present in people with Type 1 diabetes and diabetic nephropathy, but the relationship between retinopathy and nephropathy in Type 2 diabetes is less strong. Suitable screening tests are a spot urine ACR or timed (often 12 or 24 h.) urinary albumin excretion rates and calculated eGFR and serum creatinine levels, though serum creatinine levels do not rise until substantial renal function loss has occurred. eGFR and creatinine clearance calculations incorporate serum creatinine levels. There are various formulae available to calculate eGFR, available at www.nkdep.nih.gov. Multiple abnormal measures, usually at least two of three measures over 3–6 months, are required to make the diagnosis. This is related to high biological variability in AER and ACR, including increases due to exercise in the previous day, infection, fever, heart failure, marked hypertension or hyperglycemia, and in women menstruation, and drugs. Commonly used cut-points for increased ACR are ≥30 mg/g creatinine, and for the various CKD stages are shown in Table 7.5. After diagnosis of nephropathy, most clinicians would usually monitor renal function, including serum potassium levels and urinary ACR episodically (e.g., on a 6–12 monthly basis), as drugs (such as RAAS drugs, diuretics, SGLT2 inhibitors, NSAIDs, nephrotoxic dyes) may alter renal function, and non-progression or even regression of abnormal results may increase the patient's adherence to treatments. Significant reductions in proteinuria (to <300 mg/day), as may occur with RAAS drugs, have also been associated with reduced adverse renal and CVD outcomes.

Other conditions can also cause renal damage, and it is important not to miss an opportunity to treat a potentially preventable cause of CKD, such as glomerulonephritis. Clues that renal damage is not related to diabetes include hematuria, an active urine sediment (white blood cells, red blood cells, or cellular casts) on phase-contrast microscopy, rapid progression of renal dysfunction, the nephrotic syndrome, and renal disease with short Type 1 diabetes duration. If there is any doubt, referral to a nephrologist for investigation, including a potential renal biopsy, should be considered, though renal biopsy at ESRD is usually not informative. A renal ultrasound pre-referral may prove helpful in identifying or excluding some incidental renal conditions, e.g. polycystic kidneys.

7.13.3.2 Risk Factor Control

Lifestyle and Nutrition

Non-smoking, a healthy weight, and healthy diet (including elements for weight, glucose, lipid, and BP control) can retard the onset and progression of diabetic nephropathy. Once nephropathy is established, the recommended daily protein intake (0.8 g/kg body weight/day) is desirable as this slows the rate of GFR loss. Lower than this has no additional benefits, but higher protein intakes (>1.3 g/kg/day) in patients not on dialysis are associated with greater GFR loss, albuminuria, and death due to CVD. Once dialysis has commenced, more liberal dietary protein intake is usually permitted.

Glycemia

Intensive glucose control has been shown to prevent the onset and retard the progression of diabetic nephropathy in

both Type 1 and Type 2 diabetes, as shown predominantly by the DCCT/EDIC and UKPDS studies [103, 157, 158, 467, 468]. Again, there is evidence of a lag effect, likely related to metabolic memory. At least in the setting of pediatric Type 1 diabetes, insulin delivery by CSII therapy has been reported to be associated with lower levels of microvascular damage and better vascular function [469, 470].

Drug dosing may be impacted by renal dysfunction. Monitoring of eGFR is recommended, with increasing frequency once renal impairment is present. The recommendations surrounding metformin and renal damage have been recently (2016) revised. Metformin should not be commenced in people with eGFR levels <45 ml/min/1.73m^2 and withdrawn at eGFR levels <30 ml/min/1.73m^2. With eGFR levels between 30 and 60 ml/min/1.73m^2, metformin should be temporarily ceased before iodine-based contrast procedures or surgery to reduce risks of lactic acidosis.

There is increasing evidence from randomized placebo controlled clinical trials that in people with Type 2 diabetes, more recently available glucose control agents such as the incretin-based drugs and glucosuric SGLT2 inhibitors may also have renal protective effects independent of improved blood glucose levels. Both incretin drugs (injectable GLP-1 receptor agonists, specifically liraglutide; and oral DPP-4 inhibitors, specifically linagliptin) improve renal outcomes in Type 2 diabetes [412, 471]. SGLT2 inhibitors have glucose reabsorption by the renal tubules, reduce intraglomerular pressure and albuminuria, and slow GFR loss independent of glycemia [472]. The evidence regarding renal (and other) benefits for people with Type 1 diabetes using adjunct glucose control drugs will likely increase as trials testing Type 2 diabetes glucose control drugs as insulin adjuncts in people with Type 1 diabetes are completed. In the REMOVAL trial in high CVD risk middle-aged or older adults with Type 1 diabetes, relative to placebo, metformin treatment for 3 years was found to be renoprotective [473]. Renal benefit from tight glucose control in Type 2 diabetes is not uniform nor is it present across the full spectrum of renal dysfunction. In general, the worse the renal function, the less protection there is. Indeed, in the ACCORD study, in patients with renal damage at baseline, tight glucose control during the trial was associated with increased hypoglycemia and cardiovascular and all-cause mortality [474]. In contrast, while glucose control benefit with the SGLT2 inhibitors is usually less with worsening renal function, the renal and cardioprotective effects of empagliflozin were similar in Type 2 diabetic patients with a baseline eGFR 30–59 ml/min/1.73m^2 and in those with an eGFR ≥60 ml/min/1.73m^2 [391, 417].

Blood Pressure Control

While hypertension is a major risk factor for both the development and progression of diabetic nephropathy, recommendations for the use of blood pressure control drugs in diabetes vary depending on whether BP and/or urinary albuminuria is increased. Repeated measures of BP should be used in assessment, preferably 24-h. BP monitoring.

Major drug classes for renal disease are as for CVD, and include RAAS blockade drugs, including ACE inhibitors, ARBs, aldosterone antagonists, diuretics, calcium channel blockers, and beta blockers. Often more than one drug class is required to achieve BP control.

The use of antihypertensive agents, including RAAS (ACE and ARB) drugs for the *primary prevention of diabetic nephropathy in diabetic patients*, is not recommended. In the ROADMAP trial of Type 2 diabetic patients with normal urinary albumin excretion, ARB use (olmesartan 40 mg/day +/− other drugs to reach a BP <130/80 mmHg) reduced the development of microalbuminuria but was associated with increased cardiovascular deaths in patients with CAD [475]. In a 5-year trial in 285 normotensive adults with Type 1 diabetes and normal urinary albumin excretion, ACE or ARB drugs did not prevent the development of diabetic renal lesions on kidney biopsy, though it did retard retinopathy [476]. Further clinical trials in this area to provide a robust evidence base are merited.

For *diabetic patients with hypertension AND with increased albuminuria*, antihypertensive agents retard renal disease progression, and there seems to be particular benefit of RAAS blockade with ACE or ARB drugs. RAAS drugs are recommended first-line drugs for diabetic patients with hypertension *AND* albuminuria (≥300 mg/g Cr) as clinical trials, such as the HOPE and MICRO-HOPE studies, have proven protection against CKD progression and CVD events [477] with comparable benefits of ACE inhibitor and ARB drugs [478]. With hypertension and albuminuria levels 30–299 mg/g Cr, RAAS blockade reduced progression to more severe albuminuria and CVD events, but did not retard progression to ESRD [479]. BP levels below 140/90 mmHg or even below 130/80 mmHg are associated with slower CKD progression and lower rates of CVD, but in older patients lower BP levels (diastolic pressures <60–70 mmHg) are associated with increased risk of harm.

In the setting of *hypertension alone with normal urinary albumin excretion*, a recent meta-analysis demonstrated that other (non-RAAS blockade) classes of BP control drugs may be of comparable efficacy to ACE/ARB drugs [371]. Using 19 randomized controlled trials with 25,414 diabetic participants and 95,910 patient-years of follow-up, RAAS drugs were associated with a similar risk of death (relative risk, 0.99; 95% CI, 0.93 to 1.05), CVD death (1.02, 0.83 to 1.24), MI (0.87, 0.64 to 1.18), angina (0.80, 0.58 to 1.11), stroke (1.04, 0.92 to 1.17), heart failure (0.90, 0.76 to 1.07), and revascularization (0.97, 0.77 to 1.22) and similar differences in ESRD (0.99, 0.78 to 1.28) [371].

There is currently a lack of clinical trial evidence around the use of RAAS blockade for *isolated albuminuria in the setting of normal BP*.

Multiple drugs are often needed for blood pressure control in people with diabetes; hence combination therapy is not uncommon, and patients should be advised of this and of the benefits of reaching the recommended BP targets. The combination of ACE inhibitors and ARB blockers is not recommended due to lack of benefit on diabetic nephropathy and on CVD endpoints and higher rates of adverse events such as renal impairment and hyperkalemia [480, 481]. Commonly used combinations once maximum doses of ACE or ARB drugs are reached and BP targets are not met are (non-thiazide or thiazide) diuretics, calcium channel blockers, and beta blockers [482]. Mineralocorticoid receptor antagonists such as spironolactone, eplerenone, and finerenone added to an ACE or ARB are of interest as the mineralocorticoid receptor blockers have been found to lower BP and reduce albuminuria in short-term studies in diabetic nephropathy and may have anti-fibrotic effects in the heart and kidneys [483–485]. Hyperkalemia is a common side effect.

Lipid Control

While abnormal lipids are a risk factor for the development and progression of renal disease, the renal protective benefits of the commonly used cardioprotective LDL-lowering statin drugs are controversial. A recent meta-analysis evaluated the renal effects of statins from 14 (1–3 years) trials in patients (n = 2866) with diabetic nephropathy. Relative to placebo, statins reduced albuminuria and urinary albumin excretion by SMD 0.46 [95% CI, −0.68 to −0.25, p <0.0001] and 1.68 (95% CI, −3.23 to −0.12, p = 0.03), respectively, but did not significantly reduce eGFR loss and rises in blood urea nitrogen levels [486].

In contrast, two major trials (FIELD and ACCORD Lipid) demonstrated renoprotective effects for both eGFR/creatinine clearance and albuminuria in Type 2 diabetic patients [487–490]. The apparent renal protective effects of fenofibrate are masked by a rise in serum creatinine levels (by 12–20% or more [487]) that, as shown in both FIELD and ACCORD Lipid trials, resolves within several months of drug cessation. This rise in serum creatinine levels is not associated with reductions in GFR [491]. As yet, there is not a regulatory body approved renal indication for either statin or fibrate use in diabetic patients, though based on the FIELD and ACCORD Lipid findings, there is an indication for retinopathy prevention in adults with Type 2 diabetes and diabetic retinopathy and many diabetic patients do meet criteria that would suggest clinical CVD benefit from statin use.

7.13.3.3 Additional Care of Diabetic Patients with Chronic Kidney Disease

Once the eGFR falls below 60 ml/min/1.73m^2, additional monitoring, screening, and treatments are appropriate for patients with diabetic nephropathy. The frequency of monitoring of electrolytes, renal function, calcium, phosphate, and hemoglobin levels should increase to 6 months (if eGFR 45–60 ml/min/1.73m^2) and to 3 months if lower eGFR levels are present. For the early detection and treatment of bone disease, an annual bone density scan and PTH and vitamin D levels are appropriate, with oral vitamin D replacement if low levels.

Drug dosages should be reviewed regularly as the nephropathy progresses as dosage reductions, their frequency of administration, or drug cessation may be required. The advice of a pharmacist or pharmacologist may be helpful.

As people with CKD are immunosuppressed, vaccinations are usually recommended. The US Center for Disease Control (CDC) recommends the following vaccinations for CKD patients: flu (annually), pneumococcal vaccine (5-yearly), hepatitis B pre-dialysis (eGFR 45–60 ml/min/1.73 m^2), whooping cough, tetanus, and, depending on age, herpes zoster if aged ≥60 years, measles/mumps/rubella if born in or after 1957 and not immune, varicella if born in 1980 or later and not immune, and human papillomavirus in woman ≤26 years or men ≤21 years [492].

7.13.3.4 Referral to Other Specialists

Referral to a nephrologist may be appropriate at various stages of diabetic nephropathy. As described above, referral at finding abnormal screening results is appropriate if there is doubt about the cause of the renal damage. Referral should be considered at any stage if there is rapid deterioration of renal function. Late-stage renal disease is also best managed in collaboration with a specialist team who can assist with the management of nutrition, fluid, electrolyte and acid-base imbalance, calcium/PTH disturbances, hypertension, and renal replacement therapy (peritoneal or hemodialysis or kidney transplantation). Referral is usually recommended at a GFR <30 ml/min/1.73m^2 as this gives time to assess and prepare the patient for renal replacement therapy, such as arteriovenous fistula creation. A Cochrane review of 40 cohorts totaling almost 64,000 patients (including people with and without diabetes) confirmed that early referral (more than 1–6 months pre-dialysis) versus late referral to a specialist renal service is associated with lower morbidity, slower progression to ESRD, and lower mortality [493].

People with CKD are at increased risk of diabetic retinopathy and of CVD, and glycemic control options may be more challenging. Drug choices, dosages, and interactions may also be impacted by declining renal function; hence involvement with an ophthalmologist, cardiologist, or

endocrinologist as appropriate should be considered. The mental healthcare team and Allied Healthcare professionals and patient support groups can also be valuable resources in this setting.

7.13.4 Diabetic Neuropathy

7.13.4.1 Screening and Diagnosis

The types of neuropathy that may occur in people with diabetes and their related symptoms were described earlier in this chapter. The common types are peripheral neuropathy and autonomic neuropathy. There are no specific symptoms or signs or tests for diabetic neuropathies; hence other potential causes (e.g., alcohol excess, vitamin B12 deficiency, hypothyroidism, connective tissue disorders, cancers, including multiple myeloma, inherited neuropathies) should be considered.

Screening is advisable at least on an annual basis from Type 2 diabetes diagnosis and from 5 or more years after Type 1 diabetes diagnosis. Peripheral neuropathy signs relate to large nerve fiber dysfunction leading to loss of vibration (128 Hz tuning fork), ankle reflexes, and loss of 10 g monofilament sensation. The latter indicates high risk for foot injury and ulceration and need for increased patient education and vigilance regarding foot care. Small nerve fiber damage is reflected by loss of sensation to pinprick and temperature stimuli.

Blood or imaging tests may be appropriate to exclude other causes of neuropathy. Electrophysiological testing is infrequently needed, but can be helpful if alternate causes are suspected, or multiple conditions are thought to coexist, such as a peripheral neuropathy and an entrapment neuropathy (e.g., carpal tunnel syndrome).

7.13.4.2 Risk Factor Control

Lifestyle risk factors that can contribute to a peripheral neuropathy but are not specific to diabetic neuropathy are alcohol excess and vitamin B12 deficiency (such as related to vegetarianism, long-term metformin use, or pernicious anemia). Increasing age and diabetes duration and greater height are non-modifiable risk factors for neuropathy. The only modifiable risk factor for diabetic peripheral and autonomic neuropathies is glycemic control, with better glycemic control being associated with lower rates of onset and progression for Type 1 diabetes and metabolic memory [494] and slower progression in Type 2 diabetes [439]. A *post hoc* analysis of the 4-year Bypass Angioplasty Revascularization Investigation in Type 2 diabetes (BARI 2D) trial supported that achieving glucose control with insulin sensitizers was associated with lower rates of peripheral neuropathy than with insulin and sulfonylureas [495].

7.13.4.3 Treatment

More detail regarding treatments for diabetic neuropathies can be found in recent position statements, standards of care, and reviews [496–501]. While multiple agents and trials are available, there are concerns regarding their short-term nature and potential bias and confounders. The main goal is symptom control; hence in the case of peripheral neuropathy, the major goal is pain control. The pain can be very severe and debilitating, adversely impact sleep and quality of life, and can induce anxiety, depression, and even suicidal ideation [502].

The most well-studied and often, but not always, effective drugs for the relief of painful diabetic peripheral neuropathy are pregabalin and duloxetine. Prior to these drugs becoming available, tricyclic antidepressants was used, which can still be tried in individual patients. For all neuropathic pain drugs, there is usually pain reduction but usually not total abolition of pain. This is more often so with severe neuropathic pain. Most trials set the point of efficacy as being a 50% reduction in pain levels. Side-effects are more common in the elderly and can often be attenuated by commencing drugs at low doses and slow upward dosage titration. Often multiple oral and topical treatments may be required.

Pregabalin, an orally active calcium channel subunit ligand, has been shown to usually significantly reduce diabetic neuropathic pain [503] and to tend to have benefit in those with refractory neuropathy pain [504]. Side effects of pregabalin include dizziness and drowsiness (in over 10% of patients) and less commonly other CNS effects (blurred vision, nightmares, ataxia), increased appetite and weight gain, irritability, gut upset, loss of libido, sweating, rash, myalgia, arthralgia, and increased CK levels.

Duloxetine, an orally active serotonin and noradrenaline reuptake inhibitor (SNRI), is an antidepressant and in doses of 60–120 mg daily has been shown to be effective in painful diabetic neuropathy [505], including in comparative effect studies with other agents such as pregabalin [506]. Combination therapy with other drugs is also as effective, but not more effective than high-dose monotherapy [507]. Care should be taken with its prescription and use by those with hypertension, renal or liver disease, glaucoma or CVD, or increased risk of bleeding such as related to antiplatelet agent use and common comorbidities in people with diabetic neuropathy. The advice of a pharmacist or neurologist should be sought if required. Side effects include gastrointestinal upset, loss of appetite, tremor, blurred vision, tiredness, and erectile dysfunction.

Tapentadol is a centrally active opioid analgesic and noradrenalin reuptake inhibitor for chronic moderate to severe pain. Available in an oral (once or twice daily) extended-release formulation, it has proven effective in some trials for painful diabetic neuropathy [508, 509], though an International

Pain group has questioned its efficacy [498, 510]. Side effects include gastrointestinal upset and CNS upset, including anxiety, depression, sleep disturbance, drowsiness, headache, tremor, tiredness, itch, and rash. Given its addictive nature and modest level of pain relief, it is usually not recommended as first- or second-line therapy, and perhaps patients with this level of pain and non-responsive to other drugs should be considered for referral to a specialist.

While there is some literature for oral supplements of alpha lipoic acid and topical treatments such as capsaicin creams, lignocaine (lidocaine) sprays and patches, isosorbide dinitrate sprays, and botulinum toxin A, the evidence for their use is less robust, but they can be tried in individual patients.

7.13.4.4 Referral to a Specialist

Electrophysiological testing and/or referral to a neurologist (or other relevant type of specialist such as an endocrinologist, cardiologist, or urologist) may be appropriate if there is (a) doubt about the clinical diagnosis or (b) clinical management problems, such as difficulties with peripheral neuropathy pain control.

7.14 Major Benefits of Multiple Risk Factor Control

As discussed above, there are multiple risk factors for CVD and the microvascular complications of diabetes, and there are proven benefits related to controlling the common risk factors of glucose, BP, and lipids. Supportive of this, even to the extent of mortality risk reduction, are the results of the Steno-2 study [511]. Type 2 diabetic patients with microalbuminuria, hence high CVD risk subjects ($n = 160$), were randomized to intensive therapy or conventional therapy for a mean of 7.8 years and then observed for a mean of 5.5 years. Intensive treatment, including RAAS and statin drugs, reduced systolic BP 130 vs. 145 mmHg and total cholesterol 3.5 vs. 5.0 mmol/L (135 vs. 193 mg/dL) and HbA1c by 0.5% (6 mmol/mol). The primary endpoint of the study was death from any cause. Of the intensively treated group, 24 died vs. 40 in the conventional group (HR, 0.54; 95% CI, 0.32–0.89; $p = 0.02$). Intensive therapy was associated with a lower risk of CVD death (HR, 0.43; 95% CI, 0.19–0.94; $p = 0.04$) and of CVD (HR, 0.41; 95% CI, 0.25–0.67; $p < 0.001$). Fewer patients in the intensive therapy group required retinal laser treatment (RR, 0.45; 95% CI, 0.23–0.86; $p = 0.02$), and intensive treatment was also associated with only one patient progressing to ESRD versus six in the conventional treatment group ($p = 0.04$) [511]. In our experience, when this (or similar) examples are explained to them, many patients can appreciate the benefits of such a pill burden.

7.15 Barriers to Optimal Diabetes Care

Since the turn of the century, there has been an exponential increase in new anti-diabetes and CVD medications and devices. Some of these new medications have overcome some of the major barriers (weight gain and hypoglycemia) to achieving good glycemic control. Despite increasing evidence supporting the utilization of these new agents either on their own or in combination with both new classes of medication and older agents, we have not witnessed the hoped for higher proportion of patients achieving glycemic targets. In most countries and clinics, a little over half of patients achieve HbA1c levels below the commonly recommended target of 7% (53 mmol/L) [512], and fewer than 10% [513–516] meet all the metabolic and anthropometric goals. Underutilization of proven existent tools is common. There is more work to be done.

The reasons for our failure to achieve optimal therapeutic targets and clinical outcomes in our diabetic patients are complex and multifactorial. These relate to patient factors, doctor factors, and broader systemic factors. The WHO has identified five interacting and overlapping domains or dimensions affecting adherence and long-term persistence, summarized in Fig. 7.6 [517]. As healthcare practitioners, we can influence some of these dimensions more than others. Those that the clinician might have the most immediate and lasting impact on are those relating to healthcare practitioner factors and patient factors. Some condition-related factors may be mitigated or addressed most effectively by individualizing

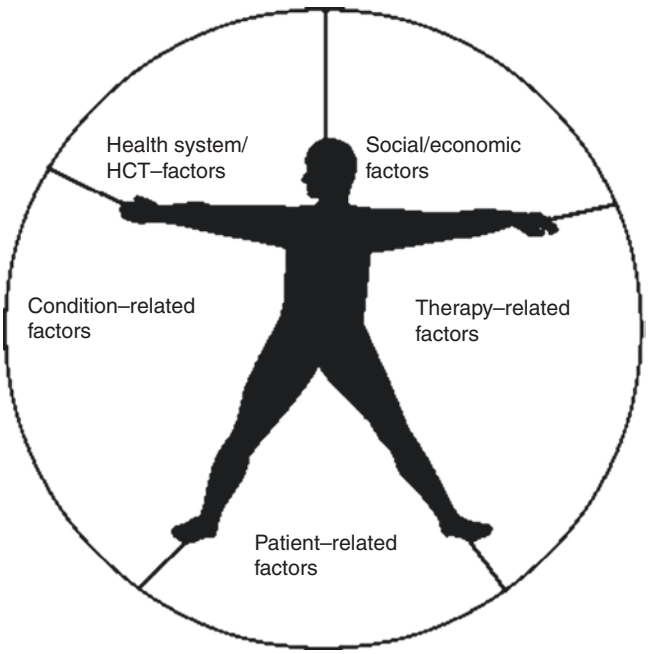

Fig. 7.6 Factors associated with health outcomes [517]. (HCT – Health Care Team)

our choice of therapeutic agents, individualizing targets, and increasing the health literacy and self-efficacy of our patients. Sociocultural influences and factors relating to healthcare systems and government policies are generally further out of the clinician's reach and often beyond our spheres of influence. Each of the five domains shown in Fig. 7.6 are now discussed.

1. Social and Economic Factors

Policy makers and funders must be cognizant of factors impacting patient adherence and health outcomes and in turn need to design and support systems to better serve the specific requirements of diverse population groups. As diabetes is a chronic condition and crosses all ethnic, geographical, and socioeconomic boundaries, these aspects are important. Factors well recognized as impacting on adherence and health outcomes include poverty, medication (and monitoring tools) costs, health literacy, social and cultural traditions, mores and beliefs, and levels of social and cultural support.

2. Healthcare Team and Health System Factors

The funding of multidisciplinary teams to educate, empower, and increase patient self-efficacy is essential for optimal outcomes in diabetes, including its complications, as it is for all other chronic disease states.

The healthcare team must be cognizant of the unique and specific needs of its constituents. The team must have the requisite skills and knowledge base and be empowered and have the necessary tools to deliver optimal diabetes care. Team members must be aware of the factors impacting on adherence and ensure clear and ongoing communication within the multidisciplinary team and between the team and the patient and (as relevant) their family/carers.

3. Disease-Specific Factors

Adherence to therapeutic regimens is impacted by disease-specific factors such as severity of symptoms and the perception of the seriousness of the complaint. While early in the disease trajectory symptoms might be minimal or absent, patient education of the potential impact of untreated or suboptimally managed diabetes must be timely and effective. As mentioned previously, Type 2 diabetes should not be described as "mild", as this may encourage patient perception of diabetes as a trivial condition. Patient education must be ongoing and updated as required, such as with need for additional pharmacologic agents or the emergence of complications or comorbidities. Comorbidities and multimorbidity impacting the primary disease, such as depression or diabetes distress, must be managed.

4. Therapy (Medication)-Related Factors

Effectiveness of therapeutic interventions depends on not only the efficacy of the treatment, but just as critically, adherence to the therapeutic regimen. This in turn is impacted by factors such as dosing frequency, pill burden, cost, regimen complexity, mode of drug delivery and adverse effects, tolerability, and safety.

5. Patient-Related Factors

A robust therapeutic alliance between healthcare providers and the patient can result in improved outcomes. The healthcare team is charged with the responsibility of educating the patient about the disease, its health impact, and the most effective interventions to address both near-term and future risk. The education must be ongoing and updated as required. The team must also address patient motivation, and behavioral issues that negatively impact the disease must be addressed.

Factors impacting patient self-care, adherence, and persistence include (a) literacy, including health literacy and numeracy (e.g., insulin dosing, carbohydrate counting); (b) the locus of control (internal versus external); (c) the stage of change (DiClemente and Prochaska's transtheoretical model of behavioral change); (d) and their premorbid personality.

7.15.1 Clinical Inertia in Diabetes Care

The vast majority of people with diabetes will be cared for in primary practice. The diabetic patient may also have multiple other acute and chronic conditions that also require care. The primary care practitioner will also have to care for many other patients with a wide range of health conditions, hence may be time poor for keeping up with the increasingly large evidence base related to diabetes care alone, and also have limited time available per appointment. The clinician must guard against clinical inertia.

Clinical inertia [518], defined as a lack of treatment intensification in a patient not at evidence-based goals for care, is a major factor that contributes to inadequate chronic disease care in patients with diabetes and other commonly associated conditions such as CVD, hypertension, dyslipidemias, and mental health issues. The personal and economic costs are enormous. Meta-analyses suggest that for approximately every 20 adults with Type 2 diabetes with a HbA1c level 1% above target (of 7%), one patient will develop a microvascular complication over 5 years.

With regard to macrovascular complications, for every 20 diabetic patients with an LDL-C level 30 mg/dL above goal, over 5 years there will be one excess MI or stroke.

Similarly, for every 20 diabetic patients with a systolic BP 10 mmHg above 150 mmHg, over 5 years there will be an additional heart attack or stroke and a new onset or progression of a microvascular complication.

Clinician factors contributing to clinical inertia include clinicians overestimating the quality of care they provide, underestimating the number of patients who are not at treatment targets, and justifying their not intensifying care, such as due to lack of time or presumed patient resistance or nonadherence. These issues may be compounded by lack of clinician knowledge and healthcare systems (e.g., allied healthcare clinician support, adequate funding). Patient factors contributing to clinical inertia are denial of diabetes or its complications or their potential severity and nonadherence to lifestyle or pharmacologic therapies, mental health problems, or cognitive impairment.

As there are multiple factors contributing to clinical inertia, multiple interventions are required. Three major avenues to reduce clinical inertia have been suggested [519]: (i) cognitive behavioral interventions for clinicians; (ii) information system-based interventions, such as prompts via electronic medical records and electronic decision support [520]; and (iii) patient empowerment, which may be enhanced by support groups or referral to excellent websites, pamphlets, books, or magazines. Clinical practice audits, increased frequency and/or duration of patient visits, and the involvement of other allied healthcare professionals and clinicians may assist.

7.15.2 Cognitive Impairment

Unfortunately, both Type 1 and Type 2 diabetes are associated with increased risk of cognitive impairment and dementia [521, 522]. This may be related to macrovascular and/or microvascular damage related to diabetes or to other non-diabetes-specific causes such as Alzheimer's disease, other forms of dementia, space-occupying lesions, or (treatable) hypothyroidism or vitamin B12 deficiency, or be a "pseudodementia" due to depression.

The primary care clinician should remain alert to clues of cognitive impairment from patient behavior, information from the family, caregivers, and other healthcare professionals involved in the patient care. Cognitive health screens should be conducted and if deficits are found appropriate investigations and monitoring undertaken. Referral to a neurologist should be considered for diagnostic or therapeutic and management issues.

With cognitive impairment, adjusting treatment targets, such as accepting a less tight HbA1c level, may be appropriate. Adjustments to meal plans, food provision, and glucose control medications may reduce the risk of hypoglycemia. Assistance from family members of carers may overcome some challenges such as remembering to take medications or with injectable drug delivery. A pillbox ("dosette") or pharmacist prepared ("Webster") pack of oral medications for each dosage time of the day of the month may help with adherence and monitoring thereof. Combination medications to reduce pill burden or simplified insulin regimens may also be helpful. One-on-one education and repeated education for both the patient and their carer, with an emphasis on factors of major importance, such as hypoglycemia treatment, are important. Recognition and attention to the well-being of the carer are also important. A helpful overview of diabetes care in cognitively impaired people for the clinician was provided recently [523], and there are textbooks on diabetes care in the elderly and in institutionalized patients that may be of assistance to the primary care physician [524, 525].

7.16 A Patient Example

Mrs. TP, a Caucasian 55-year-old accountant, has had Type 2 diabetes for 10 years, which was diagnosed on the background of prior gestational diabetes (at ages 32 and 35 years), a strong family history of Type 2 diabetes, and progressive weight gain since age 30, which she attributes to the sedentary nature of her accounting job and menopause at age 51 years. Mrs. TP recently moved to your area as her husband relocated for his work. She was an erratic attender of her previous primary care physician, approximately twice a year, mainly for scripts. Apart from feeling tired for the past 9 months, shortness of breath on doing housework, and being unhappy with her excess weight, she says she feels reasonably well, but when she saw her previous GP for a checkup (6 months ago), she was advised her BP and lipid levels were suboptimal. She has been advised to take a statin in the past but preferred not to for fear of side-effects she heard discussed on a current affairs program on TV. She has never smoked and drinks 10–20 g of alcohol per week, usually over a weekend dinner.

Family history Her parents both had Type 2 diabetes, and her father died of an AMI age 55, and her mother died of renal failure in her mid-60s. She has no siblings, and her two daughters are well but overweight, and her older daughter is pregnant with gestational diabetes.

Current medications Metformin 1 g oral daily and usually a daily (self-prescribed) multivitamin tablet. No known allergies. She does not have any regular vaccinations.

Physical examination Mrs. TP is obese, but not cushingoid. HR 86 regular and BP 150/90 mmHg supine and erect. RR 18. Afebrile. BMI 32 kg/m^2. On cardiovascular exam, her apex beat was impalpable, and S2 was loud. There was

mild peripheral edema to her ankles. Fundoscopy via undilated pupils revealed copper wiring, some microaneurysms, and soft and hard exudates. Dental screening exam revealed periodontal disease. Examination was otherwise unremarkable, including no vascular bruits, signs of heart failure, peripheral vascular disease, or peripheral neuropathy. Urinalysis in the clinic with a dipstick revealed glucose +++ as the only abnormality.

Laboratory tests HbA1c 9% (74.9 mmol/mol). Lipids: total cholesterol 6.7 mmol/L (259 mg/dL), calculated LDL-C 4.5 mmol/L (174 mg/dL), triglycerides 3.0 mmol/L (266 mg/dL), HDL-C 0.8 mmoL/ (31 mg/dL). Renal function: eGFR 75 ml/min/1.73 m^2. Normal >90 ml/min/1.73 m^2). Urine ACR 12.0 (normal ACR <3.5).

Thyroid tests normal. FBE normal. LFTs normal. EKG – Left ventricular hypertrophy. No evidence of prior AMI.

The ASCVD CVD Risk calculator (ASCVD) estimates her risk for a first CVD event to be 10.3% over 10 years and 50% over her lifetime.

Suggested changes Mrs. TP is counselled regarding her risk factors and the benefits of improving various aspects of her diabetes control, including her glucose and lipids by attention to lifestyle and changes to her medications.

The need for additional tests (24-h BP monitoring) and timed urine collections and input by other clinicians related to her vision and heart is discussed. A 24-h BP monitor test confirms elevated day and nocturnal BP levels, with a mean BP of 150/90 mmHg. She is advised regarding a low-salt (DASH) diet and the benefits of weight loss. Because of elevated albuminuria on two 12-h urine collections (and an inactive urine sediment), she is recommended to start an ACE inhibitor (enalapril 2.5 mg daily to be taken at bedtime) with checking of her renal function and electrolytes within 2 weeks and increased dose (to 5 mg daily) if not to BP target after at least 4 weeks on treatment.

To improve her glycemic control, a change to metformin XR and increase dose to 2 g/day to improve HbA1c. If not to target (<7%, <53 mmol/mol) combination therapy with a DPP4 inhibitor or a SGLT2 inhibitor or could be considered. Triple oral therapy (metformin, DPP4 inhibitor, and a SGLT2 inhibitor) in the future may be suitable. Mrs. TP should be reminded of the progressive nature of Type 2 diabetes and that at some stage in the future, injectable glucose control agents, such as insulin, may be needed to help her maintain optimal glucose control and health status.

At least annual monitoring of her renal function is required as metformin is contraindicated at GFR <30 ml/min/1.73 m^2. It is wise to check her vitamin B12 level annually due to its reduced absorption with metformin use.

Referrals are made to a diabetes educator and to a dietitian for nutrition advice, including a Mediterranean diet and oily fish and weight reduction. She is advised of a local walking group (but not to increase exercise until after cardiology opinion).

A comprehensive eye examination by an optometrist identified moderate background diabetic retinopathy and bilateral elevated intraocular pressure (glaucoma), and she is referred to an ophthalmologist for follow-up, who prescribes eye drops and recommends review in 3 months for the glaucoma and in 12 months for the diabetic retinopathy. He counsels the patient on the importance of glucose, BP, and lipid control via her primary care physician to reduce retinopathy progression.

Regarding her lipid levels, a statin (at moderate dose, atorvastatin 10 mg) is recommended due to her high CVD risk (related to diabetes, age over 40 years, albuminuria, hypertension, obesity, and family history of premature CVD) and is supported by the ASCVD risk calculator. The dose may be increased to high dose (atorvastatin 40 mg) depending on her acceptance and tolerability of the statin treatment. Fenofibrate is added (145 mg daily) due to her combined hyperlipidemia and to retard retinopathy progression (as per FIELD and ACCORD Eye Studies) [102, 251]. It is noted that an artifact of increased serum creatinine and eGFR decline is expected, but should a greater decline in her renal function occur over time, her fenofibrate dose will be reviewed and reduced accordingly.

Low-dose enteric-coated aspirin (100 mg daily with food) is recommended for CVD primary prevention as Mrs. TP is at relatively high CVD risk.

An echocardiogram identifies left ventricular hypertrophy and impaired ejection fraction, and a cardiologist arranges an exercise stress test for ischemia (which is negative) and follow-up related to her myocardial dysfunction, which the cardiologist thinks may relate to hypertension and diabetic cardiomyopathy. BP control to a target of 130/80 mmHg, such as with an ACE inhibitor initially due to her albuminuria, preferably documented by repeat 24-h BP monitoring and home BP checks, is recommended.

The primary care practitioner recommends an annual flu vaccination for general health. For people with high CVD risk, flu vaccination may reduce MI risk by a third [526]. A regular dental check-up is also recommended including assessment of her periodontal health as periodontal disease is a risk factor for diabetic nephropathy, CVD (via increased inflammation), and mortality [527]. Management of periodontitis can reduce HbA1c levels by as much as 0.5% (5.5 mmol/mol) [528, 529].

7.17 The Future

Unfortunately, in the foreseeable future, it is likely that the incidence of all common forms of diabetes (Type 1, Type 2, and gestational diabetes) will increase; hence the primary care practitioner will likely care for increasing numbers of people with diabetes. They will need to continue their key roles in diabetes prevention, diabetes screening, diagnosis, and management. Alongside ongoing clinical research to devise and translate into clinical practice even more effective ways to prevent diabetes and its complications, there must be attention to practical tools that will support both the clinician and the person with diabetes and their carers to optimize diabetes outcomes.

Electronic medical records with high-quality evidence-based decision support will assist the clinicians in their decisions and in their communications with other members of the diabetes care team. Mobile devices, "apps", and the Internet will likely continue to support people living with diabetes in their healthy lifestyle choices and diabetes and cardiovascular healthcare [530–532]. Quality research and means to assess and validate these modern resources and facilitate/fund the availability and use of those of proven benefit should be undertaken [533–535].

Currently 75% of people with diabetes live in low- and middle-income countries, and half are not aware they even have diabetes. By 2030 over 80% of the world's population with diabetes will be in disadvantaged regions [2], and healthcare clinicians and systems must be prepared to diagnose and to support diabetes care in these people as well [536, 537]. Many of the gains in diabetes prognosis and life expectancy relate to medications to control vascular risk factors, and many of these drugs are often not available or affordable to people in disadvantaged regions [538]. For those of us in affluent countries, precision medicine for diabetes will emerge.

7.17.1 Precision Medicine

Precision medicine, also often called personalized medicine, is the custom delivery of healthcare, with medical practices, testing, decisions, and treatments tailored to the individual patient level [539, 540]. The field of oncology is perhaps the most advanced branch of medicine in precision medicine, tailoring cancer treatments to tumor molecular characteristics [541]. Emerging new fields such as genomics are starting to better inform us to what type of diabetes (e.g., monogenic diabetes) a person has [542] and what their risk of diabetes complications may be [543–545]. Other biomarkers include those related to the early detection of diabetes complications (e.g., retinal vessel caliber for diabetic retinopathy, or "omics" signatures for diabetic nephropathy [546]) and genetic markers for clinical outcomes [547], including response to therapies (pharmacogenomics) such as risk for cardiovascular mortality during intensive glucose control in Type 2 diabetes [376]. Risk algorithms will help cost-effectively optimize complication screening programs, such as for diabetic retinopathy [433]. Electronic medical records and electronic decision support will help the "connected clinician" to integrate this expanded knowledge base into their clinical practice.

7.18 Useful Sources of Information

The knowledge base regarding diabetes and the management of CVD risk factors and of the macro- and microvascular complications of diabetes is also increasing rapidly. There are new treatments emerging and many ongoing trials and likely new trials. Regular review of the often annual recommendations by national diabetes and cardiovascular bodies, who sometimes release a combined position statement, is desirable. In January each year, the ADA publishes an issue of evidence-based issue related to the Standards of Medical Care in Diabetes (in the journal Diabetes Care), which is usually available on the internet at no cost. Major diabetes and cardiovascular and general medical journals should also feature important updates of this common problem. Discussions with colleagues and relevant specialists and attendance of medical conferences and workshops can be helpful.

7.19 Conclusions

People with diabetes are common in clinical practice, and CVD is still a leading cause of morbidity and mortality for people with diabetes. People with diabetes are also at risk of microvascular damage, which also signals particularly high CVD risk. Relative to their non-diabetic peers, people with diabetes typically have a higher frequency of cardiovascular risk factors, and an incrementally higher absolute cardiovascular risk, than from diabetes alone. For primary prevention, estimation of this CVD risk using a CVD risk calculator can help guide treatment decisions and also demonstrate the potential impacts of risk factor modification to patients. While attention to the most poorly controlled modifiable risk factor is obvious, improving multiple risk factors can reduce absolute risk significantly. Even if vascular disease is not clinically evident, we should comprehensively assess and treat their vascular disease risk factors due to the slow evolution of vascular damage prior to it becoming clinically evident (primary prevention) and also for the proven benefits of

secondary prevention. Individual and multiple risk factor control is now known to be associated with long-term metabolic memory [20].

We hope that this chapter will help clinicians help their patients with diabetes to achieve better risk factor control and better vascular health. Drug and device developers, clinicians, researchers, and clinical trial participants shall likely continue to demonstrate means to further reduce the vascular complications of diabetes. These findings must be appropriately translated into clinical practice, and this will depend greatly on the primary care physician. Precision (personalized) medicine should become a reality in diabetes care. Clinicians, researchers, health policy makers, health funding agencies, industry, and community members must do all that they can to ensure accessibility and affordability of the required healthcare services and proven therapeutics for all people with diabetes.

Acknowledgments AJJ was supported by a NHMRC Practitioner Fellowship and grants from the University of Sydney, the Sydney Medical School Foundation, and the NHMRC Clinical Trials Centre. ES was supported by grants from the Australian Research Council, the University of Sydney, the Juvenile Diabetes Research Foundation Australia, and the Royal Australasian College of Physicians.

This book chapter is dedicated to the memory of our friend and colleague, Dr. Kevin Rowley, PhD (1964–2016), a multitalented, community-minded biomedical scientist, biostatistician, epidemiologist, and health advocate who helped us understand and contribute to improving equitable health access and health outcomes for people at high CVD risk, including people with diabetes and Indigenous Australians.

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Chronic Kidney Disease in the Primary Care Setting: Cardiovascular Disease Risk and Management

8

Jay I. Lakkis and Matthew Weir

8.1 Introduction

Several epidemiological studies have identified chronic kidney disease (CKD) as a risk factor for cardiovascular disease (CVD) and vice versa. However, whether such a complex relationship is a causal relationship or a mere epiphenomenon remains to be established. On the one hand, kidney disease and cardiovascular disease share a cluster of traditional modifiable and non-modifiable risk factors, such as tobacco use, obesity, diabetes mellitus (DM), systemic arterial hypertension (HTN) and dyslipidemia. On the other hand, the onset of CKD is often associated with findings which have been identified as non-traditional cardiovascular risk factors, unique to this patient population, such as reduction in estimated glomerular filtration rate (eGFR), micro- or macroalbuminuria, anemia in CKD, CKD-Mineral and Bone Disorder (CKD-MBD) with vascular calcifications, chronic inflammation and protein-energy wasting (PEW), acid-base and electrolyte disturbances, and volume overload. Thus, eGFR and albuminuria, both of which are independent risk factors of CVD, ought to be incorporated into any reliable clinical prediction model aimed at quantifying CVD risk. Although CVD is the leading cause of death in all CKD groups (dialysis, non-dialysis, transplant recipients), most major clinical trials aimed at managing CVD or its risk factors exclude patients with advanced CKD, making an evidence-based approach to CVD risk reduction and management quite challenging. Finally, formulating a roadmap that combines non-pharmacological as well as pharmacological therapeutic strategies to slow down the progression of CKD and minimize CVD risk is essential to promote survival.

J. I. Lakkis · M. Weir (✉)
Division of Nephrology, University of Maryland Medical System, Baltimore, MD, USA
e-mail: mweir@medicine.umaryland.edu

8.2 Epidemiology: The Burden of CKD and CVD Traditional Risk Factors

8.2.1 Systemic Arterial Hypertension

In 2013, the World Health Organization (WHO) published "A Global Brief on Hypertension", in which it identifies CVD as the most common cause of death among humans, claiming about one third of the total mortality burden in our species, and resulting in around 17 million deaths annually, of which 9.4 million deaths are due to complications of HTN. Among patients who died of heart disease, HTN was the leading cause of death in at least 45%, and in 51% amongst those who died of stroke. Hypertension affects 40% of all adults aged 25 years or higher worldwide with the highest prevalence being among Africans and in low-income countries [1].

In the United States (US), the National Health and Nutrition Examination Survey (NHANES) 2011–2012 reports that 29.1% of adults older than 18 years have HTN, 17.2% of whom have not been diagnosed and 75.7% were on blood-pressure (BP) lowering medications, and a mere 51.9% had controlled HTN [2].

In patients with stage 1–5 CKD, the prevalence of systemic arterial hypertension exceeds 70% [3–5] and varies proportionately with the degree of kidney disease [6]; the 2015 USRDS-ADR estimates that 74% of NHANES 2007–2012 participants with stage 1–4 CKD have HTN and as many as 84.1% of patients with stages 4–5 CKD having systemic arterial hypertension [7].

8.2.2 Diabetes Mellitus

Similarly, in 2016, the WHO published a "Global Report on Diabetes", in which it reports that DM affects 8.5% of adults as of 2014, almost double the 1980 rate and totaling 422 millions adults worldwide. This rise mirrors the epidemic of

P. P. Toth, C. P. Cannon (eds.), *Comprehensive Cardiovascular Medicine in the Primary Care Setting*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-319-97622-8_8

overweight and obesity, and it is not confined by geographical location or income. In 2012, dys-glycemia directly resulted in 3.7 million deaths: DM was directly responsible for 1.5 million deaths and pre-DM was responsible for the remaining 2.2 million deaths, with 43% of all these deaths occurring at an age less than 70 years [8].

In the US, the 2014 National Diabetes Statistics Report estimates that DM affects 12.3% of the adult population (28.9 million) of whom around 27.8% have not been diagnosed, and a further 36.6% (86 millions) have pre-DM of whom around 90% are not aware of their diagnosis and without lifestyle modifications 15–30% will progress to DM within 5 years [7, 9].

The 2015 USRDS-ADR estimates that 39.2% of NHANES 2007–2012 adult participants with stage 1–4 CKD have DM [7]. Inversely, DM is the major cause of CKD and ESKD worldwide. Kidney disease complicates diabetes in 25–40% after a course of 20–25 years and around one third of those patients develop ESKD requiring renal replacement therapy but the majority will die of cardiovascular causes before progression to ESKD [10]. The 2015 USRDS-ADR lists DM as the primary cause in 43.9% of incident ESKD patients. In a cohort of 2097 diabetic participants in the NHANES 2009–2014, aged 20 years and over, diabetic nephropathy was present in 26.2% with 15.9% having Stage A2 or A3 albuminuria and 14.1% having an abnormal eGFR; this data projects that as of 2014, 8.2 million Americans have diabetic CKD [11].

8.2.3 Dyslipidemia

In its 2015 "Heart Disease and Stroke Statistics" report, the American Heart Association (AHA) estimated that 31.7% of American adults have a high cholesterol or a high low-density lipoprotein, of whom 48.1% are receiving pharmacological therapy and only 29.5% have achieved optimal control [12, 13].

In patients with CKD, dyslipidemia is common and is dependent on severity of CKD stage, degree of urine protein excretion, and DM status [14].

8.2.4 Tobacco Use

Data from the 2014 NHANES survey reveals that 16.8% of adults age 18 years and over are active tobacco users [15] and tobacco use ranks second amongst all causes of deaths and disability and third for death from coronary heart disease [13]. Great progress has been made in the fight against tobacco use and rates have steadily declined over the past decades; however, such advances may be threatened by e-tobacco use and e-cigarettes, potential risks and benefits of which are being actively researched.

8.2.5 Obesity

In the aforementioned 2016 WHO "Global Report on Diabetes", the report also highlighted that more than 1 in 3 adults worldwide were overweight and more than one in ten were obese in 2014 [8]; with a calculated rise in the age-standardized global mean body mass index (BMI) by 0.4 kg/m^2 in men and by 0.5 kg/m^2 in women per decade between 1980 and 2008 [16].

In the US, DM affects 9.3% of the population (29.1million as of 2012) of whom 27.8% have not been diagnosed [9]; 70.7% of adults age 20 years and higher are overweight or obese: 32.8% overweight and 37.9% obese (2013–2014 data) [17].

8.2.6 Exercise

The 2014 NHANES survey show that 49.2% of Americans adults (≥18 years) met the 2008 Federal Physical Activity Guidelines for leisure-time aerobic physical activity (but only 20.8% met the guidelines for both aerobic physical and muscle-strengthening activity. For aerobic physical activity, the weekly recommendation is for 150 min of moderate-intensity exercise, or 75 min of high-intensity, or some combination, and most favorably spread over many weekdays. For muscle-strengthening, the weekly recommendation is to exercise all muscle groups in a moderate- to high-intensity workout at least twice a week [18].

8.2.7 CKD

CKD affects about 10% of adults worldwide. In the US, 10% of adults have CKD (more than 20 million people), with the rising incidence and prevalence being almost all concentrated in individuals aged 60 years or more; approximately one third of diabetic patients have CKD and about one fifth of hypertensive patients have CKD [19]. Worldwide, there are huge disparities in the access to CKD care, in fact, care is limited in its majority to the developed world; 80% of patients with end stage kidney disease (ESKD, Stage 5D CKD) who are receiving renal replacement therapy (RRT) live in the developed world where the cost of RRT is most likely to be subsidized [20].

8.3 CKD: Definition, Stages and Causes

CKD refers to an abnormality in kidney function or structure that persists beyond a period of 3 months. Such abnormalities manifest in one or more of the following clinical biomarkers: (1) a relative rise in serum creatinine with a resultant reduction in the eGFR (2) micro- or macro-albuminuria (3)

microscopic or macroscopic/gross hematuria (4) abnormal urine sediment (e.g. cellular elements, casts or crystals) (5) urinary system structural abnormalities detected by imaging studies (e.g. congenital anomalies, cysts, stones) (6) acid-base or electrolyte imbalances reflecting renal tubular disease (7) abnormal results confirmed by a kidney biopsy [21].

8.3.1 KDIGO eGFR and Albuminuria Categories

In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group recommended a CKD prognostic classification that adds the level of urine albumin excretion rate to the 2002 National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (K/DOQI) definition and staging of CKD based on the eGFR. Six categories of eGFR (mL/min/1.73 m^2 BSA) (G1 ≥ 90, G2 60–89, G3a 45–59, G3b 30–44, G4 15–29, G5 < 15) and three categories of albuminuria based on the urinary albumin-to-creatinine ratio (ACR, mg Albumin/g Creatinine) (A1 < 30, A2 30–300 also known elsewhere in the literature as micro-albuminuria, A3 > 300 also known as macro-albuminuria) are described. This system incorporates mounting evidence of the deleterious effects of a higher urine albumin excretion rate and helps predict and classify the patient's risk of CKD progression into the following categories: low risk, moderately increased risk, high risk and very high risk (Fig. 8.1) [21]; an example of such evidence comes from the Multiple Risk Factor Intervention Trial (MRFIT) team, who identified a 41-fold increased risk of progression to ESKD amongst individuals with an eGFR <60 mL/min per 1.73 m^2 and ≥2+ dipstick proteinuria, amongst 12,886 men with high CVD risk and followed for a period of 25 years [22]. For example, a patient with an estimated GFR of 58 mL/min/1.73 m^2 BSA and a urine albumin excretion rate of 358 mg albumin/ g creatinine would be classified as having stage 3 (G3a A3) CKD and has a "very high risk" of CKD progression.

8.3.2 Prevalence of CKD by eGFR and Albuminuria Category

The 2015 USRDS-ADR estimates the prevalence of CKD in the 2007–2012 NHANES samples at 13.65% amongst adults aged 20 years and over with the 4.18% having category G1 CKD, 2.95% having category G2 CKD, the biggest cluster of 5.90% having category G3 CKD, 0.48% having category G4 CKD and only 0.14% having category G5 CKD [7]. Among all 1988–2012 NHANES participants, 90.8% had category A1 albuminuria (70.7% < 10 mg albumin/g creatinine and 20.1% 10–29 mg/g), 7.8% had category A2 albuminuria, and 1.4% had category A3 albuminuria. Adopting the 2012 KDIGO prognostic classification, 86.2% of the 2007–2012 NHANES participants were classified as low risk CKD, 9.8% as moderately increased risk CKD, 2.3% as high risk CKD, and 1.7% as very high risk CKD. As mentioned earlier, CKD affects the elderly much more than it does the young; for example, in an Italian cohort of 4574 patients, <1% of individuals aged 18–24 had Stage 3–5 CKD compared to an excess of 30% for individuals aged 75 years or older [23].

8.3.3 Most Common Causes of CKD

Amongst incident ESKD patients, DM was the primary cause in 43.9%, HTN in 28.7%, glomerulonephritis in 7.5%,

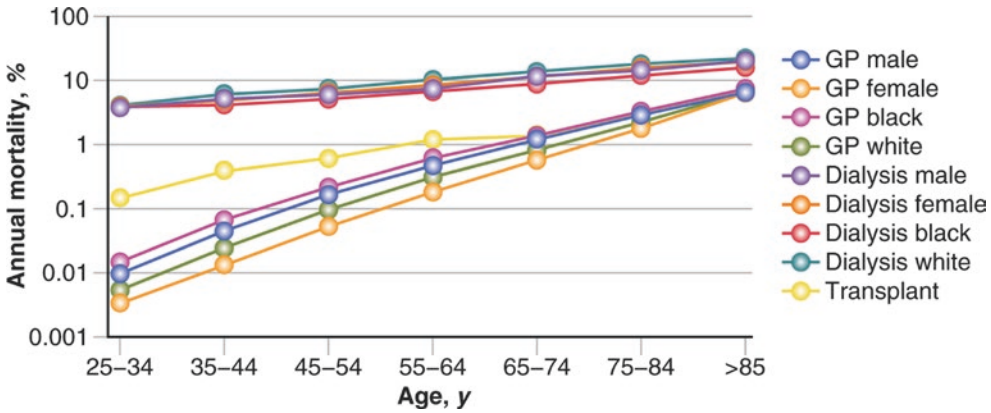

Fig. 8.1 (**a**) Cardiovascular disease mortality by age, race, and gender in the general population and in dialysis patients. Cardiovascular mortality is defined as death due to arrhythmias, cardiomyopathy, cardiac arrest, myocardial infarction, atherosclerotic heart disease, and pulmonary edema. Data from the general population are from the National Center for Health Statistics multiple cause of mortality files 1993. Data from dialysis patients include hemodialysis and peritoneal dialysis combined from USRDS 1994–1996. (Reprinted with permission from National Kidney Foundation Task Force on Cardiovascular Disease [252])

cystic kidney diseases in 2.1%, and other or unknown in 17.8% [7]. Among 2007–2012 NHANES participants with ND-CKD, DM was present in 39.2% of patients and HTN in 31% [7].

8.3.4 CKD Awareness and CKD Lifetime Risk

CKD awareness remains a problem just as is seen with HTN and type 2 diabetes (DMT2). Only 44.2% of 2001–2012 NHANES participants were aware of their stage 4 CKD, 8.4% of their stage 3 CKD, 5.0% of their stage 2 CKD and 3% of their stage 1 CKD. It is also important to note that epidemiological studies have shown that African Americans have three times the risk of progression to ESKD when compared to whites, and Hispanics 1.5 times the risk when compared to non-Hispanics; both male and female African-Americans have a significantly higher lifetime risk of stage 4 CKD and stage 5 CKD than Caucasians, and they develop ESKD around 15 years earlier than Caucasians [24]. It is no surprise then that the highest adjusted incidence and prevalence of ESKD is present amongst Black/African Americans; Hispanics had a higher incidence at 1.4 when compared to non-Hispanics. African Americans, Asians, Pacific Islanders, and Native Americans all had a higher incidence and prevalence of EKSD than Caucasians [7].

8.3.5 Therapeutic Options for ESKD

As CKD progresses, patients with stage 5 CKD are started on renal replacement therapy (RRT) when a clinical indication arises; usually this occurs when the eGFR is below 10 mL/min/1.73 m^2 BSA and occasionally when below 15 mL/min/1.73 m^2 BSA, and it is at this point that a patient is said to have ESKD. The most superior form of RRT is kidney transplantation, which offers the best survival rates and quality of life especially with pre-emptive kidney transplantation; however, with the shortage of organ supply in the face of increasing demand, dialysis (in-center or home hemodialysis HD, peritoneal dialysis PD) remains a valuable life-saving form of therapy albeit an inferior one. Short of a clinical indication, there is no known benefit for early versus late start of RRT with dialysis in patients with stage 5 CKD [25]. The 2015 USRDS-ADR reports that as of 2013, there were 116,990 incident patients with ESKD who received RRT (88.4% initiated HD, 9.0% initiated PD, 2.6% received pre-emptive kidney transplantation) and a total of 659,869 prevalent Americans with ESKD (63.9% on HD, 6.9% on PD, 29.3% with a functioning kidney transplant) [7].

8.3.6 Referral to Nephrology

Unfortunately, up to 38% of incident ESKD patients in 2013 received minimal or no nephrology care at all prior to initiation of RRT [7].

8.4 CKD Biomarkers: Estimating GFR and Quantifying Urinary Protein Excretion

Screening for CKD must be aimed at patients with a high pre-test probability, namely individuals with DM, HTN, aged over 55 years or a relevant positive family history [26]. A timely nephrology referral is strongly recommended for any patient with stage 3–5 CKD or stage 2–3 albuminuria, in other words any patient who has a risk of progression other than low as per the 2012 KDIGO risk classification (Fig. 8.2). For such a timely referral, it is essential to use the eGFR rather than the serum creatinine, since the latter seems to lead to an underestimation of the severity of CKD [27].

The 2002 National Kidney Foundation Kidney Disease Outcomes Quality (NKF K/DOQI) definition and the 2012 KDIGO prognostic classification of CKD created a shift in clinical practice in the new millennium, which made eGFR mathematical models the point of focus for quantifying CKD. Many major laboratories in the US currently report an eGFR, marking a decline in the use of reciprocal serum creatinine and the timed (classically 24-h) urine Creatinine clearance (UV/P).

8.4.1 Estimated Glomerular Filtration Rate eGFR

Creatinine (Cr) remains the major measured serum biomarker used by many such models (eGFRcr models) but it has its limitations; for example, Cr is dependent on muscle mass and dietary protein intake, and while Cr is freely filtered at the glomerular level, it is also secreted by the proximal tubular cells and estimating the secretion rate is not uniformly reliable. Cystatin C (Cys-C) provides an alternative measured serum biomarker, which is not affected by muscle mass or dietary protein intake, giving it an advantageous edge over Cr in certain populations, such as the elderly or those afflicted with neuromuscular disease. Cys-C has also been used by mathematical models to estimate GFR (eGFRcys models), while a third set of mathematical models combines both serum biomarkers (eGFRcr-cys).

The best mathematical model to calculate the eGFR, currently based on measured serum biomarkers Cr or

Fig. 8.2 2012 KDIGO risk classification

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Cys-C or both, must minimize bias (difference between the population mean of a set of calculated eGFRs and the true GFR) while maximizing precision (measures random error or degree of variability amongst calculated eGFRs) and accuracy (measures systematic errors and the overall difference between calculated eGFRs and the true GFR); usually, the true GFR is measured by urinary clearance of ^{125}I-iothalamate which remains the gold standard. At this time, there does not seem to be one model where "one size fits all". The most commonly used mathematical models which have been validated in clinical practice and research are: (1) the Modification of Diet in Renal Disease (MDRD) Study equation, (2) the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and (3) maybe to a lesser extent the Cockcroft-Gault equation.

The CKD-EPI equation performs better than the MDRD equation, and provides an eGFR which is more accurate and reflective of the true GFR, in patients with normal kidney function or Stage 1–2 CKD [28]. Thus, it should be adopted as the equation of choice in the general population; using the MDRD equation in the general population would result in a falsely high prevalence of CKD and misclassification of patients by CKD stage [29]. Both formulae are comparable in stages 4–5 CKD. Both these eGFRcr models are limited in subjects with altered body habitus (such as the obese, muscular bodybuilders, amputees and the pregnant), in individuals on a special diet such as vegetarian or vegan diets or those who consume large amounts of meat, in patients with a chronic illness such as malnutrition or neuromuscular diseases and in patients who are on prescription medications that compete with tubular creatinine secretion such as trimethoprim [30]. In such individuals, it is recommended to estimate the creatinine clearance by two separate 24-h urine collections or to use eGFRcys models.

8.4.2 Spot or Random Albumin to Creatinine Ratio (ACR)

An ACR, or a random protein to creatinine ratio (PCR), have become the most commonly used methods to quantitate urinary protein excretion and both have been validated against the gold-standard timed or 24-h urine collection for protein. The ACR or PCR urine sample is much more conveniently and quickly collected and cheaper than a timed sample; however, the latter has the advantage of more reproducible results with less variability in time, less concern for the timing of sample collection, providing additional clinical pearls such as quantitation of daily fluid and sodium and urea/protein and intake. A 24 h urine collection remains

the most reliable clinical tool in pregnant women, morbidly or extremely obese, or when making major clinical decisions [31, 32].

8.4.3 Other Biomarkers

Numerous other biomarkers have been evaluated over the years such as urinary kidney injury molecule 1 (KIM-1), urinary liver–type fatty acid–binding protein (L-FABP), and neutrophil gelatin-associated lipocalin (NGAL), but they have a very limited current evidence-based established role in the wider clinical practice arena.

8.5 Relationship Between CKD and CVD: The CKD-CVD Connection

Cardiovascular disease (CVD) is the leading cause of death in patients with non-dialysis CKD, dialysis CKD as well as in kidney transplant recipients. CKD and CVD are intricately related; the overlap in risk factors makes the task of separating these two disease clusters rather difficult, if not impossible. Furthermore, the number of CVD risk factors increases proportionately with the severity of CKD; in fact, all patients with Stage 4–5 CKD have at least two or more CVD risk factors [33]. Not all facets of the CKD-CVD connection are well-understood.

8.5.1 CKD as a Sentinel for CVD Risk

Both biomarkers of CKD, reduced eGFR and abnormal urinary albumin excretion, are risk factors for ESKD as well as CVD morbidity and mortality [26, 34].

Albuminuria has been validated as a surrogate end point for the progression of CKD and it is estimated that a 30% reduction in the urinary albumin excretion results in a 23.7% reduction in the risk of progression to ESKD [35]. Similarly, Albuminuria has also been validated as an independent risk factor for cardiovascular and all-cause mortality [36–38]; it is a predictor of CVD and all-cause mortality in patients with DM or HTN, and even in non-diabetic normotensive individuals [39, 40]. For example, in a cohort of patients who had elective percutaneous coronary angiogram and revascularization, 11% of patients with macro-albuminuria (stage A3) met the primary endpoint of cardiac death or myocardial infarction after a median follow-up period of 1564 days, compared to 8% in the micro-albuminuria group (stage A2) and 3% in the normal-albuminuria group (stage A1) (p-value 0.004) [41]. Furthermore, a reduction in the rate of urine albumin excretion decreases the risk of CVD [42].

Reduced eGFR, especially at levels less than 60 mL/min/1.73 m^2, has also been validated as an independent cardiovascular and all-cause mortality risk factor [36, 37, 43–45] and a patient with CKD is 16–40 times more likely to die than to reach ESKD, with the risk of CVD and death increasing proportionately with worsening stage of CKD [19, 46, 47]. For example, CKD is associated with a higher risk of mortality, estimated at 51%, 1 year after a myocardial infarction (MI), when compared to a 36% mortality risk in non-CKD patients [48]; the two-year mortality rate is 43% for non-CKD patients, 54% for CKD Stage 1–2 patients and 70% for Stage 4–5 patients [7]. Amongst patients who have their first acute myocardial infarction (AMI), there was a graded and proportionate association between eGFR decline/CKD stage, even when the CKD was mild/Stage 2, and risk of all-cause mortality, cardiovascular mortality, myocardial re-infarction, HF, cardiac arrest, or stroke [49]. Thus, CKD with a reduced eGFR, is a coronary heart disease risk equivalent, which means that a stage 3–5 CKD patient has a 10-year risk of coronary death or MI equivalent to that of patient who has already had an MI (>20%) [50]. Many guidelines currently incorporate risk stratification and risk calculators to guide initiation of a certain pharmacological therapy; thus, eGFR and albuminuria ought to be incorporated into any novel clinical prediction model aimed at quantitating and treating CVD risk in any patient with CKD [51]. Hardly any risk calculators have incorporated eGFR or urine albumin excretion rate at this time in their prediction models; for example, the only calculator that does so is the Joint British Societies (JBS3) risk calculator, which uses the presence or absence of CKD as a prediction variable in their model, but does not account for the stage/severity of CKD or albuminuria [52].

8.5.2 CVD Phenotypes in CKD

CVD in the CKD population can manifest as one of several phenotypes such as left ventricular hypertrophy (LVH), acute MI or atherosclerotic heart disease (AHD), heart failure (HF), valvular disease, atrial fibrillation, pulmonary hypertension, sudden cardiac death due to a cardiac arrest or an arrhythmia, or cerebrovascular accident (CVA). There are several pathophysiologic pathways that may explain the CKD-CVD connection, and fortunately, kidney transplantation not only stops but also reverses many of these processes.

1. There is accelerated obstructive AHD with a staggering 5–20 fold increased risk compared to non-CKD individuals, 38–62.5% of incident ESKD patients starting dialysis have established coronary artery disease (CAD) and 36% have HF [53–55]. In a prospective cohort of 24

incident HD patients, a surveillance coronary angiogram after 1 month of initiating HD showed that 62.50% (15/24) had AHD/CAD and 45.8% had multi-vessel disease (4/24 or 16.7% had single vessel disease, 5/24 or 20.8% had two-vessel disease, and 6/24 or 25.0% had three-vessel disease) with 46.9% of the lesions detected being complex and 29.0% being diffuse [56].

Furthermore, coronary yellow plaques in patients with CKD seem to occur more frequently [57] and to be different in composition from non-CKD patients and have thin-cap fibroatheromas with more calcium and cholesterol crystals with a higher risk of thrombogenicity, plaque rupture [58] and intra-plaque hemorrhage and neo-angiogenesis [59].

When DM and CKD coexist, the cumulative risk for CVD mortality is additive, with CKD being the major contributor for the risk accrued. In NHANES III participants, CKD with eGFR category G3-G5 or stage 2–3 albuminuria was present in 9.4% of those with no DM and in 42.3% of those with DMT2; the 10-year cumulative all-cause mortality was 7.7% in participants without either condition, 11.5% in participants with DMT2 but no CKD, and a staggering 31.1% in patients with both DMT2 and CKD, with similar trends whether the mortality is cardiovascular or not [60].

2. CKD patients are at risk of development of systolic and diastolic dysfunction and secondary complications such as HF. CKD is associated with structural and functional myocardial changes such as LVH and cardiac fibrosis with a secondary decline in left ventricular (LV) function and in myocardial tolerance to ischemia.

Many risk factors, such as anemia, elevated BP and volume overload, conglomerate to result in LVH in patients with CKD. Importantly, LVH (or an increased left ventricular mass index, LVMI) is an independent predictor of all-cause mortality, cardiovascular-mortality and cardiovascular events such as HF, ischemic heart disease, cardiac arrhythmias and sudden cardiac death [61, 62] and it is the most common phenotypical abnormality in ESKD [63].

The CRIC study investigators evaluated serial echocardiograms in a total of 190 patients with stage 4–5 non-dialysis CKD initially upon enrollment, and later after progression to ESKD requiring RRT (HD or PD) (mean time between 2 echocardiograms 2 years), and detected an increase in systolic dysfunction reflected by a significant decline in LVEF but no significant change in LVH or LVMI [64]. In a cohort of 254 asymptomatic patients with ESKD on dialysis therapy, 26–48% had evidence of systolic dysfunction assessed by abnormal myocardial contractility on echocardiography (e.g. LVEF) [65].

Finally, the increased risk of diastolic dysfunction measured by an E/A ratio on echocardiography in CKD patients predicts HF risk in the is population; HF risk increases by two-fold when E/A ratio is less or equal to 0.75 compared to a ratio of 0.75–1.5 [62].

3. CKD patients have enhanced vascular calcification and stiffness due to arterial medial smooth muscle cell calcifications; they also develop atherosclerotic, plaque, neo-intimal calcification, a finding also proportional to the severity of CKD [55]. These abnormalities may manifest with a wide pulse pressure, treatment-resistant HTN or isolated systolic HTN. The finding of calcified atherosclerotic lesions in large-conduit arteries and the increased stiffness of large capacitive arteries gain significant clinical relevance as contributors to CVD and predictors of mortality in CKD patients [63].

For example, in a cohort of patients aged 30–65 years with non-dialysis CKD, increased coronary-artery calcification (CAC) risk was detected in patients with stage 3–5 CKD but not stage 1–2 CKD; the CAC risk was most pronounced, a substantial nine-fold higher, among diabetics with stage 3–5 CKD when compared to diabetics with no CKD [66]. Total CAC score predicted the number of affected coronaries, and single-vessel CAC score predicted the degree of stenosis [67]. As to ESKD requiring dialysis (HD or PD), a cohort of young patients (age 7–30 years) detected a high CAC score by electron-beam computed tomography (EBCT) in patients who were older than 20 years or who had a higher dialysis vintage ($p < 0.001$) when compared to healthy controls; for example, 87.5% (14 out of 16) of patients aged 20–30 years had CAC which was progressive, but none of those younger than 20 years had CAC [68]. CAC score is an independent predictor of mortality amongst patient with ESKD on dialysis [69, 70], but not in patients with mild to moderate CKD [71].

Based on the current evidence, using an EBCT CAC score as a sole diagnostic tool to predict or diagnose AHD may have a role in the general population or non-dialysis patients, but has no current role in patients with ESKD on dialysis due to a low accuracy, a significant variability in sensitivity/specificity depending on the CAC score cutoff chosen, and failure to correlate with the severity of coronary stenosis [72–74].

4. Acute or chronic inflammation, increased oxidative stress, and protein energy wasting are prevalent in patients with CKD and are associated with a sequence of undesirable events such as endothelial dysfunction and protein-calorie malnutrition; biomarkers of inflammation and malnutrition have been shown to correlate with CVD risk or mortality risk [75–77].

For example, in a cohort of 840 patients with stage 3–5 CKD (eGFR 12–55, 96% non-diabetic) followed over a median duration of 125 months, a C-reactive protein (CRP) level at 3 mg/L or more was an independent risk factor for cardiovascular mortality and independently predicted a 56% increase in all-cause mortality; while serum albumin was not an independent risk factor for cardiovascular mortality, each 0.1 g/dL increment independently predicted a 6% decline in for all-cause mortality [76]. Similarly, patients with ESKD on hemodialysis have CRP levels that are 5–10 times higher than non-CKD controls [78], and a CRP level exceeding 10 mg/L at three or 6 months or on both occasions after initiation of hemodialysis was associated with a higher cardiovascular as well as non-cardiovascular mortality when compared to patients with a normal CRP over a five-year followup, the risk was highest in patients who had an elevated CRP on both occasions [79].

Many inflammatory biomarkers have been evaluated in CKD patients over the years, such as homocysteine, fibrinogen, ceruloplasmin, pro- and counter-inflammatory cytokines, CRP, and ESR, but their role in clinical practice remains very limited.

5. In patients with stage 3–5 CKD, there is an increased risk of sudden cardiac death that is proportional to the severity of CKD [80].

8.5.3 CVD in ESKD + RRT

The most striking association between CKD and CVD can be illustrated in patients with EKSD on RRT with dialysis, where CVD accounts for 53.1% of mortality and is attributed to sudden cardiac death (cardiac arrest, arrhythmia) in 37%, acute MI and AHD in 6.7%, HF in 5.8%, CVA in 3.1% and other cardiac causes in 0.5% [7]. Furthermore, the risk of pulmonary hypertension increases proportionately with dialysis vintage [53, 54].

ESKD and dialysis seem to be associated with an additional flurry of increased CVD risks such as the aforementioned AHD, LV changes, repeated cardiac stress and ischemia in patients receiving HD, autonomic dysfunction, steep electrolyte and volume shifts, uremic ambience, all of which may contribute to this significantly increased risk of sudden cardiac death and cardiovascular mortality [81, 82]. For instance, ESKD patients with no evidence of any significant coronary occlusive disease, experience repetitive myocardial ischemia during hemodialysis, evidenced by sharp global as well as segmental reductions in myocardial blood flow, and some of these reductions are associated with regional wall motion abnormalities [83]. Finally, a patient with ESKD on dialysis who develops a first AMI, has an all-cause mortality risk of 59.3% at 1 year, 73.0% at 2 years, and 89.9% at 5 years, and a cardiac mortality risk of 40.8% at 1 year, 51.8% at 2 years and 70.2% at 5 years [84].

Based on this evidence, it is worth noting that a unique and atypical cardiovascular risk profile (e.g. intermittent and/or chronic volume overload, aberrant mineral metabolism, cardiovascular including valvular and coronary calcifications, chronic inflammation and malnutrition) in patients with ESKD on RRT with dialysis outcompetes the traditional cardiovascular risk factors responsible for CVD in non-dialysis CKD and non-CKD patients, and likely accounts for the excessive mortality in this patient group. This may also offer an explanation as to why standard pharmacological agents used for CVD secondary prevention, such as HMG-CoA reductase inhibitors, have a very limited benefit, if any, in patients with ESKD.

8.6 Diagnostic Challenges of CVD in CKD Patients

8.6.1 Atypical Clinical Manifestation of CVD

A major challenge in the CKD population is that the clinical manifestations of CVD are different and atypical, they may be subtle or not apparent at all, and this often leads to missed or delayed diagnosis.

For example, patients with Stage 3b-5 CKD are 3.82 times more likely to manifest their AHD suddenly with an AMI rather than with any typical warning symptoms of angina (e.g chest or arm or shoulder or neck pain) when compared to patients with a normal eGFR [85], and were more likely to experience shortness of breath than non-CKD patients [86].

Similarly, in a retrospective analysis comparing 3049 patients with ESKD on HD to 534,395 matching non-dialysis patients, all of whom were hospitalized and diagnosed with an AMI during their hospital stay, an admission diagnosis of AMI was missed in 44.8% of dialysis patients compared to 21.2% of the non-dialysis group, the typical symptom of chest pain was a presenting symptom in 44.4% of dialysis patients and 68.3% of the non-dialysis group, and finally the typical electrocardiographic abnormality of ST segment elevation was present in 19.1% of dialysis patients and 35.9% of the non-dialysis group [87]. In one cohort of 24 patients with incident EKSD starting HD, the presence of significant occlusive AHD was confirmed by coronary angiogram in 53.8% of patients without any symptoms (and in 72.7% of those with symptoms) [56].

8.6.2 Cardiac Biomarkers and Diagnostic Tools

Another challenge is that some standard non-invasive cardiac diagnostic tools have been validated in the general population to detect a CVD rooted in traditional risk factors, but may not offer any adjustments for the non-traditional risk factors and thus may be of limited utility in this population.

Cardiac biomarkers, routinely used to assist in the diagnosis of AMI or HF may be elevated in asymptomatic patients with CKD due to reduced eGFR and clearance or structural heart disease rather than true myocardial damage or fluid overload, thus reducing their diagnostic specificity. Despite such observations, numerous studies have validated high-sensitivity cardiac troponin T and natriuretic peptides as biomarkers that enhance CVD prediction in CKD patients [88].

- In a cohort of 18 asymptomatic hemodialysis patients, 72% had at least one high creatinine kinase (CK) and 88–100% had at least one elevated MB isoenzyme (CK-MB) levels when serial testing was done over a 36-month period [89].
- A rising level of cardiac troponin followed by a later decline, along with a suggestive clinical picture is highly suggestive of an acute coronary syndrome in patients with CKD; in contradistinction, a persistent and stable high level of cardiac troponin is more consistent with a "troponin leak" due to volume overload, or structural heart disease due to poorly controlled HTN or systolic/diastolic dysfunction or LVH [90]. It must be noted, however, that a steady troponin T elevation is associated with an increased risk of cardiovascular as well as all-cause mortality in asymptomatic dialysis-CKD patients; said mortality risk is incremental and starts at levels equal to or exceeding 0.01 ng/mL and patients with a level exceeding 0.10 ng/mL have double the mortality rate of patients with a lower level. Troponin I is less reliable in the CKD patient population due to variable cut-off values in clinical trials and lack of unified assay standardization [74].

In a systematic review of the role of troponin in patients with non-dialysis CKD (ND-CKD) and suspected ACS, the sensitivity and specificity were 71–100% and 31–86% respectively for troponin T, and 43–94% and 48–100% for troponin I. Elevated levels of either isozyme predicted higher risk for cardiac events and short-term mortality; only elevated troponin I predicted long term mortality, it also carried a worse prognosis in patients with advanced CKD [91].

A similar review in patients with CKD but without suspected ACS reported that an elevated troponin level in dialysis patients carried an increased risk for cardiovascular as well as all-cause mortality. An elevated troponin T was associated with an adjusted hazards ratio of 3.0 for all-cause mortality and 3.3 for cardiovascular mortality, an elevated troponin I was associated with an adjusted hazards ratio of 2.7 for all-cause mortality and and 4.2 for cardiovascular mortality. Similar findings were reported in ND-CKD patients [92].

- As far as stress testing, stressing the myocardium with exercise may not be possible in some patients, and use of electrocardiogram (ECG) may be hindered by baseline abnormalities in others. For example, in a cohort of 30 patients with Stage 5 CKD about to start RRT, who were asymptomatic and had no cardiac or anginal symptoms or prior MI, subclinical and occult significant AHD (more than 50% narrowing in 1 or more coronary arteries) was detected by coronary angiography in 53.3% (16/30, 10/16 had single-vessel disease, 4/16 had two-vessel disease, 2/16 had three-vessel disease) of the patients; five patients had >90% luminal narrowing and underwent dipyridamole stress cardiac scintigraphy with a sensitivity of 40% (two patients had a positive test and three had a negative test) [93].

Similarly, amongst 45 kidney-transplant candidates with ESKD who had screening for AHD with dipyridamole single photon emission computed tomography (SPECT) thallium imaging and with a coronary angiogram, the latter diagnosed significant AHD (more than 50% narrowing in 1 or more coronary arteries) in 42% of the patients; thallium imaging had a lower sensitivity (37%) than in the control non-ESKD population, falsely diagnosed seven patients with AHD (negative coronary angiogram for any stenosis >50%), and most significantly missed diagnosing AHD (detected by coronary angiogram) that resulted in five out of the six cardiac deaths during the study followup duration of 25 months [94].

In 66 asymptomatic hemodialysis patients who had simultaneous high-dose dipyridamole and symptom-limited exercise stress echocardiography and stress myoview, combined pharmacological and exercise echocardiography had a 92% accuracy (sensitivity 86%, specificity 94%) at detecting myoview cardiac ischemia, and both tests were accurate (echocardiography 84%, myoview 91%) at detecting CAD confirmed by an angiogram [95].

A meta-analysis confirmed that among kidney transplant candidates, with diabetic or non-diabetic ESKD, a positive myocardial perfusion study, either dobutamine stress echocardiography (DSE) or a nuclear myoview with thallium scintigraphy, predicted an increased risk of AMI (RR 2.73) and of cardiovascular mortality (RR 2.92) [96].

Finally, a 2012 "American College of Cardiology Foundation (ACCF)/American Heart Association (AHA)" scientific statement for "Cardiac Disease Evaluation and Management Among Kidney and Liver Transplantation Candidates" pooled data from clinical trials which compared results of cardiac stress testing (DSE or MPS) to coronary angiography findings in patients with stage 5 CKD (GFR < 15 mL/min/1.73 m^2 or dialysis) and calculated that DSE had a sensitivity of 44–89% and a specificity of 71–94%, MPS had a sensitivity of 29–92% and a specificity of 67–89% for identifying at least one coronary occlusion of 70% or more. The statement concludes that DSE may be "somewhat superior" [74].

As mentioned earlier, the use of EBCT CAC score has no established role at this time as a stand-alone diagnostic tool in assessing cardiovascular risk in patients with CKD [74].

8.6.3 Underutilization of Evidence-Based Therapeutic Interventions

A further challenge is that CKD patients with CVD tend to be historically under-treated; for example, patients with Stage 3b-5 CKD who had an AMI were less likely to receive pharmacological therapy with anti-platelet agents, beta-blockers or HMG CoA-reductase inhibitors or coronary revascularization than others [49]. Although a more recent analysis of trends in providing evidence-based care for CVD shows an improvement in all CKD stages, underuse of evidence-based pharmacological therapy remains a significant problem [97].

Similarly, patients with ESKD on dialysis who are diagnosed with an AMI are less likely have coronary reperfusion interventions due to eligibility exclusions based on parameters such as contraindications to thrombolytic therapy, kidney failure or a poor quality of life. They were also less likely to have coronary bypass graft surgery or to receive standard pharmacological therapy than non-dialysis patients [87].

8.6.4 Therapeutic Interventions Have a Lower Success Rate

Yet another challenge is that patients with CKD have less successful outcomes and higher mortality than non-CKD patients, and this may discourage healthcare providers from pursuing invasive cardiac diagnostic and therapeutic interventions.

For example, in a cohort of 5244 patients with ST-elevation acute MI (STEMI) who underwent primary percutaneous coronary intervention (PCI) found that patients with lower eGFR had a higher mortality rate and were less likely to achieve desired angiographic outcomes such as post-intervention TIMI flow grade or ST-segment elevation resolution [98].

Similarly, studying temporal trends shows that among 12,087 patients diagnosed with acute MI between 1985 and 2008, although patients with stage 4–5 CKD had a decline in 30-day mortality over the two decades studied reflecting improved MI care, the outcomes for these patients remained quite poor: median survival was only 1.8 years for patients with stage 4–5 CKD, compared with 8 years for stage 3 CKD, 15 years for stage 2 CKD, and 20 years for normal kidney function [97].

8.6.5 Delaying Diagnostic and Therapeutic Interventions Over Concerns of Contrast Nephropathy

A final challenge is the timing of a coronary angiogram, when indicated for diagnostic or therapeutic purposes in patients with CKD; many a time, the angiogram is put off over concerns of AKI and worsening CKD.

The European Renal Best Practice (ERBP) guidelines for managing patients with diabetic stage 1-3a CKD recommend that a clinically indicated coronary angiogram should not be delayed for concerns over contrast induced nephropathy (CIN) .

CIN is the end result of contrast induced tubular toxicity, intense vasoconstriction and tubular as well as medullary ischemia, and oxidative stress [99]. Risk factors for CIN include pre-existing CKD, DM, effective arterial volume depletion especially in patients on diuretics, HF and reduced LVEF, hypotension and age. Prevention of contrast nephropathy after a coronary angiogram is a constant cause for nephrology consultations. Thus, several prediction models have been devised and validated but none reported their impact on clinical decision-making or patient outcomes [100]. Strategies to prevent contrast induced nephropathy include isotonic fluid resuscitation with sodium bicarbonate or normal saline to maintain optimal effective arterial volume and avoid volume depletion, using iso-osmolal contrast agents, minimizing the volume of contrast used and avoiding repetitive administration over a short time-frame, oral N-acetylcysteine, and an oral statin [101]. Furthermore, it may be advisable to stop RAAS inhibition 1–3 days before the administration of the contrast; a pilot study Cerebrolysin Asian Pacific trial in acute brain injury and neuro recovery (CAPTAIN trial) in patients with moderate CKD (serum creatinine ≥1.7 mg/dL within 3 months or creatinine ≥1.5 mg/dL within 1 week prior to angiogram) demonstrated a non-significant reduction in CIN and a significantly lower rise in serum creatinine after the angiogram [102].

8.6.6 Guidelines

The 2012 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) scientific statement for "Cardiac Disease Evaluation and Management Among Kidney and Liver Transplantation Candidates" recommends that asymptomatic advanced-CKD patients who are enlisting for a kidney transplant be risk stratified and considered for non-invasive cardiac stress testing accordingly, even if they have a functional status equal to or exceeding 4 metabolic equivalent tasks (METS); with a recommendation to proceed with such testing if the patient has three or more of the following risk factors: age over 60 years, dialysis vintage exceeding 1 year, prior history of CVD, LVH, DM, HTN, dyslipidemia, and active tobacco use.

This guideline echoes prior recommendations from the 2007 report of the Lisbon conference, the 2005 NKF/KDOQI Guidelines, 2001 American Society of Transplantation (AST) Guidelines, and the 2000 ERBP, with one difference that the NKF/KDOQI and the AST recommend periodic stress testing in all diabetic patients irrespective of lack of any symptoms.

The scientific statement did not find adequate evidence to make a recommendation for repeated and periodic testing for myocardial ischemia while on the kidney transplant waiting list.

The statement found it reasonable to perform an echocardiogram to evaluate for pulmonary hypertension, and if present, to investigate for secondary causes; if right ventricular systolic pressure exceeds 45 mmHg then a right heart catheterization is warranted and if pulmonary HTN is confirmed than referral for advanced vasodilator therapy ought to be initiated [74].

8.7 Management of Traditional CVD Risk Factors in CKD

8.7.1 Blockade of the Renin Angiotensin Aldosterone System

Aberrations in the systemic or local renin-angiotensin-aldosterone system (RAAS) accelerate AHD, HTN, inflammation, promote the development of metabolic syndrome at the center of which are insulin resistance and obesity [103] while at the same time accelerating eGFR decline and urinary albumin excretion rates. Angiotensin II (Ang II) and aldosterone play an important role in the genesis and progression of both CKD and CVD.

Pharmacological therapy with RAAS blockade in the CKD patient population reduces the rate of albumin excretion, decelerates the progression of CKD, and thus the development of ESKD; while observational studies also report a resultant reduction in all-cause and cardiovascular mortality rate, a systematic review detected such a trend but the benefits did not meet statistical significance [104].

Most best practice guidelines recommend an angiotensin converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) as first line antihypertensive therapy for systemic arterial hypertension, including patients with non-dialysis CKD, micro- or macro-albuminuria, and secondary prevention of cardiovascular disease such as HF and CAD.

8.7.1.1 RAAS Inhibition in ESKD

In patients with dialysis-CKD receiving RRT, therapy with an ACEi or an ARB, results in a progressive regression in LVH, as assessed by left ventricular mass index (LVMI) [105, 106]; long term use of ARB (>365 days) significantly reduces the incidence of major cardiovascular events (including AMI, CAD requiring coronary stenting or percutaneous transluminal coronary angioplasty (PTCA), peripheral artery disease (PAD) requiring PTCA, and acute CVA among dialysis-CKD patients with no prior history of a major cardiovascular event and protective effect was directly proportional to the cumulative prescription days of ARB.

ACEi or ARB therapy in patients receiving RRT with continuous ambulatory peritoneal dialysis (CAPD) provides a significant and similar benefit on preserving residual kidney function with long-term therapy (≥12 months) with wither class; however, one randomized controlled trial (RCT) pooled in this meta-analysis evaluated the effect of ACEi therapy on cardiovascular events and mortality when compared with other anti-hypertensive agents and reported no significant differences [107]. The results of this meta-analysis are concordant with prior published literature [108].

In conclusion, we recommend the initiation of RAAS inhibition with an ACEi or an ARB in patients with ESKD receiving HD or PD for antihypertensive therapy, prevention of major cardiovascular events, and preservation of residual kidney function. Aldosterone receptor antagonism (ARA) may be added for patients with treatment resistant hypertension (TRH) or with reduced LVEF (<35%).

8.7.1.2 RAAS Inhibition in Kidney Transplant Recipients

In kidney transplant recipients, the use of RAAS inhibition is usually preserved for the intermediate (1–4 months) and late (≥4 months) post-transplant period and avoided in the early post-transplant period (first month) due to the increased risk of hyperkalemia and worsening kidney allograft function [109, 110].

Therapy with an ACEi (captopril) or an ARB over a period of 27 months was associated with significant reductions in GFR, hematocrit and urinary protein excretion [110], but there was a paucity of evidence evaluating the long-term

effect of RAAS inhibition on allograft survival, cardiovascular events or all-cause mortality.

Finally, therapy with ARB in patients with Interstitial fibrosis/tubular atrophy (IF/TA), a major cause of kidney transplant allograft loss, resulted in a significant decrease in the volume of the cortical interstitium when compared to placebo, but this pathological benefit failed to translate into any clinical endpoints on secondary analysis, namely time to a composite endpoint of doubling of serum creatinine, ESKD or death. However, there was a trend towards decreased incidence of all-cause ESKD with AIIT1RA therapy [111].

In conclusion, we suggest the use of RAAS inhibition with an ACEi or an ARB in kidney transplant recipients in the late post-transplant period, and in the intermediate post-transplant period if a compelling indication arises, for antihypertensive therapy, prevention of major cardiovascular events, slowing down progression of CKD, and proteinuria. ARA may be added for patients with treatment resistant hypertension (TRH) of with reduced LVEF (<35%).

8.7.1.3 CKD and Acute MI or HF

The use of an ACEi (Captopril) within 3–16 days after an acute myocardial infarction MI in patients whose LVEF was ≤40% and whose serum creatinine was <2.5 mg/dL reduced risk of future cardiovascular events [112].

In patients with HF due to decreased LVEF or valvular disease, there is a state of chronic renal hypoperfusion in the setting of an increased overall extracellular fluid volume; counter-regulatory adaptive mechanisms to restore perfusion result in neurohormonal activation of the RAAS, sympathetic nervous system and anti-diuretic hormone, the end result being more sodium and water retention and further volume expansion.

In patients with HF, kidney dysfunction portends a worse long-term prognosis with higher hospitalization rate [113] and a higher cardiovascular as well as all-cause mortality and the risk rises with the severity of the kidney disease [114, 115] with a 7% increase in mortality for every eGFR decrement of 10 mL/min per 1.73 m^2 of body-surface area [116]. The renal impairment is a more powerful predictor of mortality in patients with advanced HF than the LVEF or New York Heart Association (NYHA) class [117] and its validity as a prognosticator does not change whether the HF is due to systolic or diastolic dysfunction [118]. Similarly, renal impairment predicts a higher all-cause mortality and cardiovascular mortality as well as recurrent myocardial infarction in patients who had an acute myocardial infarction especially with an eGFR <45 per 1.73 m^2 of body-surface area [112, 119].

In patients with clinically diagnosed HF and angiographic evidence of coronary artery disease (CAD), ACEi reduces mortality at 12-months in patients with stage 1–2 CKD but not in those with more advanced CKD stage [120]. However, other trials have shown a survival benefit with ACEi in patients with HF across all strata of creatinine clearance and CKD stage [118].

In summary, ACEi are essential for secondary cardiovascular prevention in patients with HF and/or reduced LVEF; they help optimize cardiac function, decrease mortality as well as hospitalization rate. Furthermore, evidence from the Randomized Aldactone Evaluation Study (RALES) trials supports adjunctive aldosterone receptor antagonist therapy with spironolactone to decrease mortality and morbidity in patients with severe HF and a LVEF <35% [121]; similarly, the EMPHASIS-HF Study Group reported that adjunctive eplrenone therapy decreased mortality and morbidity in patients with NYHA class II HF and LVEF<35% [122].

8.7.1.4 Dual RAAS Blockade

While dual or multi-level RAAS blockade offers further lowering of BP as well as further reductions in urine albumin excretion rate, it may be associated with symptomatic hypotension and a higher risk of hyperkalemia and/or AKI [123].

1. The Cardiorenal end points in a trial of aliskiren for type 2 diabetes (ALTITUDE) investigators evaluated the impact of adjunctive aliskiren therapy added to ACEi or ARB on cardiovascular and renal outcomes in patients with systemic arterial hypertension, DMT2 and with diabetic nephropathy (micro- or macro-albuminuria) or cardiovascular disease or both, stage 3 CKD, aged 35 years or older, and reported that addition of aliskiren resulted in a (statistically non-significant) trend with an increase in adverse primary composite outcome of cardiorenal events, secondary composite outcome of cardiovascular and renal events, and all-cause mortality; more patients in the treatment group experienced an adverse event and subsequently discontinued the direct renin inhibition (DRI) ($p < 0.001$) with he most encountered complications being hyperkalemia, acute kidney injury and hypotension. Dual therapy was associated with lower BP and urinary protein excretion rate [124].
2. The Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (ONTARGET) investigators showed a significant increase in the primary renal outcome (dialysis, doubling of serum creatinine, death) and secondary renal outcomes (dialysis, doubling of serum creatinine) and a significant decline in GFR (−6.11 mL/min, $p < 0.0001$) amongst patients with CAD, PAD, cerebrovascular disease or DM with target-organ damage who received dual therapy [125, 126].
3. A meta-analysis of thirty-three RCTs evaluated the impact of long-term (> 1 year) dual RAAS blockade with an ACE-i and an ARB versus monotherapy on all-cause as well as cardiovascular mortality, and concluded that

there was no benefit of dual blockade over monotherapy for either endpoint. Dual therapy resulted in a significant decrease in HF hospitalization rate (18% reduction), but there was a significantly higher risk of hyperkalemia (55% increase), hypotension (66% increase), AKI (41%) and adverse events leading to withdrawal of therapy (27% increase). Subgroup analysis showed a significantly higher risk of AKI with dual therapy in patients with HF as compared to those without HF, and a higher all-cause mortality in patients without HF when compared to those with HF [127].

4. The risk-benefit of dual versus single RAAS blockade in patients with albuminuria or stage 3–5 CKD was evaluated in a meta-analysis of fifty-nine RCTs, and reported a statistically significant reduction in urinary albumin excretion rate with dual blockade, as well as a higher success rate at achievement of blood pressure goal; however, dual blockade was associated with a statistically significant reduction in GFR and a higher rate of hypotension and hyperkalemia and had no effect on mortality rates [128].
5. The addition of spironolactone to an ACEi or an ARB, in patients with proteinuric stage 1–3 CKD, over a period of 2–20 months, reduced the degree of proteinuria and SBP but had no effect on cardiovascular outcomes or on the rate of progression to ESKD; it had a less well defined effect on eGFR but it increased the risk of hyperkalemia and gynecomastia. Individual trials report similar results with eplerenone; addition of eplerenone, too, increased risk of hyperkalemia but there was no risk of gynecomastia [129].
6. The addition of a DRI or an ARB or and ARA to ACEi-based conventional therapy in patients with HF and its impact on mortality and cardiovascular event rate was evaluated in a meta-analyses of 16 RCTs (31,429 patients) over a period of 3 months. Only additional aldosterone receptor antagonists, and not DRI or an ARB, significantly reduced the risk of all-cause mortality, cardiovascular mortality, HF hospitalization but there was an increase in the rate of hyperkalemia. The addition of an ARB increased the rate of hyperkalemia, AKI and hypotension; additional DRI increased risk of hypotension [130].

In summary, while most trials report reduction in BP and urinary excretion rates, and in view of the increased risks of AKI, hyperkalemia, and symptomatic hypotension associated with dual or multilevel RAAS blockade, dual RAAS blockade should be preserved for clinical use where evidence rather than theory exists. Its major use is in patents with HF and reduced LVEF where aldosterone receptor antagonists offer a survival benefit [131].

8.7.2 Blood Pressure Control, Goals and Choice of Pharmacological Agents

HTN is a major CVD risk factor and is the second most common cause of ESKD; on the other hand, it is also a complication of CKD. Achieving BP goals is one of the cornerstones of any therapeutic plan aimed at primary and secondary prevention of CVD risk as well as slowing down the progression of CKD. One cannot over-emphasize that achieving goal BP, in itself, is a more important and reno-protective end-point than the choice of the BP lowering class or agent. However, the main challenge lies in the nuances of determining the ideal BP goal for different patient groups, such as patients with CKD of different stages, stage A2-A3 albuminuria, DM status, patients with AHD, elderly patients, ethnicity, etc…

8.7.2.1 Exclude Secondary Causes

As mentioned earlier, CKD is a cause as well as a complication of HTN. An evaluation for secondary causes of HTN, when warranted, must be pursued. For example, obstructive sleep apnea (OSA) is an under-diagnosed contributor to hypertension which may need to be evaluated when a clinical index of suspicion arises or if the patient has treatment-resistant hypertension.

8.7.2.2 What Is the Optimal BP Goal?

Non-pharmacological lifestyle modifications and pharmacological interventions should target a BP less than 140/90 mm Hg in all patients (regardless of age) with stage 1–5 CKD or DM according to Joint National Committee 2014 evidence-based guideline for the management of high blood pressure (JNC8) [132], and to levels less than 130/80 mm Hg in the presence of micro- or macro-albuminuria as per the 2012 KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease [133]. A 2014 ERBP position statement endorsed the KDIGO guidelines for the management of BP in CKD patients [134].

While, the optimal level of blood pressure control in different patient populations continues to evolve, it is widely acceptable that controlling blood pressure (BP) to levels <140/90 mmHg has kidney as well as cardiovascular protective effects; as mentioned earlier, lower target BP levels have been recommended for patients with CKD, proteinuria >1 g per day, and cardiovascular disease. For example, the SPRINT research group evaluated the impact of two different systolic BP (SBP) goals on 9361 high cardiovascular-risk non-diabetic patients over a period of 3.26 years and reported that the group with more intensive SBP control (121.4 mm Hg versus 136.2 mm Hg) had a significantly lower all-cause mortality and a lower rate of the primary composite end point of AMI, other acute coronary syndromes, CVA, HF and death from cardiovascular disease. However, there was a significantly higher rate of hypotension, syncope, AKI, electrolyte abnormalities in the intensive treatment group [135].

8.7.2.3 Home BP Logs

All patients with HTN must be empowered and encouraged to keep a daily home BP log, which will assist the health care provider in evaluating the patient for white-coat hypertension as well as masked hypertension, and thus avoid a lot of potential complications of missing either diagnosis. This useful tool may also keep the patient engaged and involved in their care plan and may assist in achieving desired BP goals.

Home BP logs will also assist in the diagnosis of white coat hypertension as well as masked hypertension. A persistent discordance between home BP logs and office BP measurements should trigger a referral for 24 h ambulatory BP monitoring (ABPM).

8.7.2.4 Non-pharmacological Therapeutic Strategies

Non-pharmacological therapy consists of lifestyle modifications aimed at [132]:

1. Adopting the Dietary Approaches to Stop Hypertension (DASH) diet which combines low-sodium, fruits and vegetables and low fat dairy products,
2. Weekly aerobic physical activity for 150 min of moderate-intensity exercise every week or 75 min of high-intensity, or some combination, and most favorably spread over many week-days,
3. Muscle-strengthening aiming to exercise all muscle groups in a moderate- to high-intensity workout at least twice a week,
4. Moderate alcohol use (not to exceed one standard drink for women and two for men per day),
5. Weight regulation (goal BMI 20–25 kg/m^2) and
6. Tobacco cessation.

8.7.2.5 Pharmacological Therapy

The ideal pharmacological agent to be used ought to help achieve BP goal, offer cardiovascular protection, reduce urine albumin/protein excretion rate, and slow down the progression of CKD all at the same time while being maximally tolerated by patients and having minimal adverse reactions.

Both ACEis and ARBs are recommended by many best-practice guidelines, as first line antihypertensive therapy for systemic arterial hypertension in patients with CKD (with the strongest evidence for benefit being in those with micro- or macro-albuminuria) and secondary prevention of cardiovascular disease such as HF and CAD, regardless of race, age, or diabetes status. Recommendations for use as first line therapy were made by the JNC 8 [132], KDIGO [133], National Kidney Foundation K/DOQI [136], American College of Physicians (ACP) [137], and ERBP [134] guidelines for treatment of systemic arterial hypertension in CKD. Such inhibition reduces albuminuria and slows down progression of CKD, with a BP-independent effect which offers more protection than can be accounted for by BP lowering alone. However, the bulk of clinical evidence at the core of these guidelines applies to patients with stages 1–3 CKD or with micro- or macro-albuminuria; evidence is scarce regarding its role in stages 4–5 CKD or patients with normal urinary albumin excretion rate [138].

In the kidney, AngII is a potent vasoconstrictor with preferential vasoconstrictive effects on the glomerular efferent arteriole; this effect plays a physiologic role in maintaining normal hydrostatic and glomerular filtration pressures. RAAS inhibition with an ACEi or an ARB, results in a more marked glomerular efferent arteriolar dilatation, which in turn, reversibly reduces the hydrostatic and glomerular filtration pressures. Thus, it is quite expected, as well as desirable, that such RAAS inhibition may result in a reversible rise in the serum creatinine and subsequently a decline in the eGFR; it is widely acceptable that such a change is not to exceed 30% from baseline within the first 2–4 weeks after initiation of therapy, especially when optimal BP goals are achieved. The magnitude of such a change in GFR and serum creatinine becomes more prominent clinically in patients with (1) decreased effective arterial blood volume due to conditions such as excessive diuresis, or low forward cardiac output due reduced left ventricular ejection fraction (LVEF), valvular disease, or heart failure (HF), and (2) adaptive glomerular hyper-filtration due to CKD or diabetic nephropathy where this compensatory effect is blunted by glomerular afferent arteriolar vasodilatation [139].

Diuretics should be prescribed for the majority of patients with CKD and HTN; they are second line therapy to ACE-i or ARBs in patients with stage A2-A3 albuminuria. In patients with stage 1–3 CKD, especially in the presence of increased extracellular fluid volume (ECF volume), (e.g. peripheral edema), a thiazide diuretic is indicated along with dietary sodium restriction to 1.5–2.0 grams daily and is thought to promote the effect of RAAS blockers on reducing urinary protein excretion; in more advanced stage 4–5 CKD, thiazides become less effective and thus a loop diuretic is preferred. When a diuretic is used, it is strongly recommended to evaluate patients for continued volume overload, volume depletion or hypotension or AKI, electrolyte disturbances especially hypomagnesemia and hypokalemia [140].

If goal BP is not achieved with the ACE-i or ARB and the diuretic, the addition of a non-dihydropyridine calcium

channel blockers (non DHP-CCB), namely diltiazem or verapamil, offers further blood pressure lowering and an additional inherent anti-proteinuric effect [141]; either agent may be used in addition to ACE-i or ARBs or as first-line when a patient with albuminuria is intolerant to both RAAS blockers. Dihydropyridine calcium channel blocker (DHP-CCB) also offer further BP lowering effects but do not have any inherent anti-proteinuric effects, and thus, DHP-CCB should not be used as sole agents or first-line agents in patients with CKD and stage A2-A3 albuminuria [142, 143].

In patients with ESKD on HD, HTN and LVH, atenolol-based antihypertensive therapy was associated with a lower rate of serious cardiovascular events (AMI, stroke, hospitalization for HF, cardiovascular death) and all-cause hospitalization when compared to lisinopril-based antihypertensive therapy [144]; this may promote the use of beta-blocker therapy in this patient population but further studies reproducing similar results are needed.

Finally, in 2013, the KDIGO Blood Pressure Work Group published a "Clinical Practice Guideline for the Management of Blood Pressure in Non-Dialysis CKD" [133], the major recommendations are hereby listed:

1. Customize goal BP and pharmacological therapy based on patient's age, CKD risk, CVD risk, presence of retinopathy in patients with DM and monitor for any adverse reactions such as orthostatic dizziness and evaluate for orthostatic hypotension each clinical visit. Adopt lifestyle modifications as detailed earlier.
2. Hypertensive patients (regardless of DM status) with no micro- or macroalbuminuria (stage A1) should target a goal BP is ≤140/90 mmHg.
3. Hypertensive patients (regardless of DM status) with micro- (stage A2) or macro-albuminuria (stage A3) should target a goal BP is ≤130/80 mmHg with a regimen to include an ACE-i or an ARB.
4. Hypertensive kidney transplant recipients should target a goal BP is ≤130/80 mmHg.
5. In elderly patients, start pharmacological therapy, when needed, at the lowest dose possible, and increase dose slowly while always evaluating for safety and adverse reactions such as orthostatic hypotension, AKI, electrolyte imbalances.

Needless to say, many CKD patients have a higher than average daily pill burden; thus, to maximize compliance, it its essential to simplify the regimen as much as possible by minimizing the frequency of administration as well as number of pills (e.g. by using dose combinations) and ensuring that the medication is affordable.

8.7.3 Diabetes Mellitus and Optimal Glycemic Control

DM is the major cause of CKD worldwide. Kidney disease complicates diabetes in 25–40% after a course of 20–25 years and around one third of those patients develop ESKD requiring renal replacement therapy but the majority will die of cardiovascular causes before progression to ESKD [10]. Microalbuminuria in diabetic patients is a predictor of early cardiovascular mortality [145] with a two to four-fold increase in such risk with microalbuminuria, and an even higher risk in patients who have systemic arterial hypertension and macro-albuminuria [146]. In a cohort of 2097 diabetic participants in the NHANES 2009–2014, aged 20 years and over, diabetic nephropathy was present in 26.2% with 15.9% having stage A2 or A3 albuminuria and 14.1% having an abnormal eGFR; this data projects that as of 2014, 8.2 million Americans have diabetic CKD [11].

8.7.3.1 Blood Pressure Control and Drugs of Choice

Achieving BP goal in patients with DM and CKD is essential to reduce risks of CVD and progression to ESKD. Goal BP is determined by presence of micro- or macro-albuminuria where the goal BP is <130/80 mmHg; otherwise, goal BP is <140/90 mmHg.

In patients with DMT2 and diabetic nephropathy with stage A3 albuminuria, the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study (RENAAL) team, among many others, demonstrated that the ARB losartan significantly decreases the urine albumin excretion rate and slows down the progression of diabetic nephropathy after a mean follow-up of 3.4 years, albeit without a survival benefit and without a reduction cardiovascular morbidity and mortality, and with a beneficial effect independent and more than can be accounted for by the BP lowering effect alone [147]. Similar results were demonstrated by the Irbesartan Diabetic Nephropathy Trial (IDNT) team with he ARB irbesartan [143].

A Cochrane Database Systemic review of fifty RCTs highlighted the important concept that neither ACEi nor ARB had a significant effect on all-cause mortality in patients with diabetic CKD unless full-dose or maximum-tolerable dose was used with ACEi; both classes seem to be equally effective, three RCTs compared ACEi to ARB and found no difference in all-cause mortality between the two forms of therapy in diabetic kidney disease. Both forms of therapy resulted in a statistically significant reduction in the risk of ESKD and of progression from micro- to macroalbuminuria with a significant increase in regression from micro- to normaalbuminuria [146].

8.7.3.2 Glycemic Control

Glycemic control plays an essential role in preventing diabetic microvascular (retinopathy, neuropathy and nephropathy), and has a less clear role in preventing macrovascular (CAD, PAD, CVA) complications.

In DMT1, The Diabetes Control and Complications Trial (DCCT) group randomized 1441 patients to intensive therapy versus conventional therapy and reported, after a mean duration of 6.5 years, a significant reduction in the incidence (by 76%) or progression (by 54%) of retinopathy, as well as a significant reduction in the onset of microalbuminuria (by 39%) and macro-albuminuria (by 54%), and a decrease in the incidence of clinical neuropathy (by 60%) [148]. The DCCT/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group followed 93% of the original DCCT cohort for an additional mean 17 years, and reported a 42% reduction of any CVD events (macrovascular), as well as reductions in fatal and non-fatal MI and mortality in the intensive therapy group [149, 150].

In DMT2, several major trials have confirmed that tight glycemic controls reduces microvascular complications; for example, the UK Prospective Diabetes Study (UKPDS) Group evaluated 3867 incident DMT2 patients over a 10 year period and found that a more intensive glycemic control (HbA1c 7.0%) reduced the risk of microvascular complications, mainly retinopathy, by 25% when compared to conventional glycemic control (HbA1c 7.9%), but there was no statistically significant reduction in macrovascular complications [151].

Similarly, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) Collaborative Group evaluated 11,140 patients with DMT2 over a median follow-up period of 5 years and reported that intensive glycemic control (mean HbA1c 6.5%) reduced the rate of microvascular complications, namely incidence of nephropathy (HR 0.79) when compared to standard glycemic control (mean HbA1c 7.3%), but had no effect on the rate of retinopathy and offered no benefit as far as macrovascular complications [152]; among 8494 patients who had continued post-trial followup for an additional median of 5.4 years and for whom HbA1c differences between the two groups have dissipated by the first post-trial visit after a median of 2.9 years, there remained a benefit of reduced ESKD in the intensive control group albeit relatively few events were reported [153].

Finally, the ACCORD trial group randomized 10,251 patients with DMT2 to intensive glycemic control (median HbA1c 6.4%) versus standard control (median HbA1c 7.5%) and had to transition all patients in the intensive-control arm of the trial to standard control after a median followup of 3.4 years due to increased cardiovascular as well as all-cause mortality rates in the intensive-control group, followup was continued for 5 years and there was a significant delay in the onset of albuminuria in the intensive-control group at the time of the transition as well as at the time of the trial completion [154].

It's worth noting that all the above trials showed a higher risk of hypoglycemia with more intensive protocols.

8.7.3.3 American Diabetes Association (ADA) Standard of Medical Care in Diabetes

The American Diabetes Association (ADA) issued a periodic revision of the "Standard of Medical Care in Diabetes" and its most recent recommendations are summarized in Table 8.1 [155].

8.7.3.4 European Renal Best Practice (ERBP) Guidelines for Managing Patients with DM and Stage 1-3a CKD

The European Renal Best Practice (ERBP) guidelines for managing patients with DM and stage 1-3a CKD (GFR > 45 mL/min per 1.73 m^2 BSA) provide the following recommendations for primary and secondary prevention and treatment of cardiovascular disease [156]:

1. A clinically indicated coronary angiogram should not be delayed for concerns over contrast induced nephroapthy.
2. Medical therapy for stable CAD should be optimized and is the preferred choice of therapy unless there is significant myocardial ischemia, proximal left anterior descending (LAD) or left main coronary disease is present.
3. In patients with multi-vessel CAD or complex lesions, coronary artery bypass graft is preferred over percutaneous coronary interventions for revasularization.
4. Neither the presence of DM nor that of CKD should impact the therapy of acute coronary syndrome.
5. Maximal dose ACEi, and not an ARB, is the treatment of choice for secondary prevention of cardiovascular disease in patients with HF or CAD; combination RAAS inhibition should be avoided.
6. Goal BP is <140/90 mmHg and in the absence of micro-albuminuria all anti-hypertensive agents are equal to lower BP.

8.7.3.5 European Renal Best Practice (ERBP) Guidelines for Managing Patients with DM and Stage 3b-5 CKD

Similarly, the ERBP issued guidelines for managing patients with DM and stage 3b-5 CKD (GFR < 45 mL/min per 1.73 m^2 BSA) provide the following recommendations [156]:

1. HbA1c remains the recommended diagnostic tool to monitor long-term glycemic control in patients with stage 3b-5 CKD, although its accuracy may be

Table 8.1 American Diabetes Association (ADA) – "Standard of Medical Care in Diabetes-2016" [155]

1. Diagnosis:
1a. Screen for DMT2 in any individual whose BMI equals or exceeds 25 kg/m^2 and repeat at least once every 3 years; in Asians screen at at a BMI equals or exceeding 23 kg/m^2.
1b. Screen for DMT2 in all patients age 45 years or older and repeat at least once every 3 years.
1c. Test for DMT2 or pre-DM with fasting plasma glucose, plasma glucose 2 h after 75-gram glucose tolerance test or HbA1C. When DMT2 or pre-DM is diagnosed treat other CVD risk factors.
1d. Acute onset DMT1 is best diagnosed with blood glucose rather than HbA1C.
2. Foundations of care and medical evaluation:
2a. All patients with DM should be empowered by participating in a customized patient-centered diabetes self-management education (DSME) and support (DSMS) to achieve effective self-management, improved clinical outcomes and quality of live.
2b. All patients with DM must consult with dietitian to construct a customized medical nutrition therapy (MNT) program.
2c. All patients with DM are encouraged to follow the Federal Physical Activity Guidelines for leisure-time aerobic physical activity and to avoid extended periods of sedentary time exceeding 90 min, patients are also advised to perform resistance training at least twice a week unless contraindciated.
2d. All patient must be advised, counseled and offered assistance to quit tobacco use and e-cigarettes.
2e. Adults with DMT2 should receive routine immunizations and receive hepatitis B vaccine.
2f. Adults with DM should have regular screening for pyschocoial problems, and older adults should have regular evaluations for cognitive function and depression.
3. Prevention or delaying onset of DMT2: Patients with pre-DM should be advised behavioral modifications and undergo an intensive diet and exercise program, as part of a diabetes prevention program (DPP) aimed at a 7% weight loss. Metformin therapy should be considered in adults with pre-DM, BMI exceeding 35 kg/ m^2 BSA, age less than 60 years and those with prior history of gestational DM.
4. Glycemic targets:
4a. Self-monitoring of blood glucose (SMBG) may help guide treatment decisions and empower patient to adjust therapy and its frequency must be higher in patients with intensive insulin regimens. In select patients with DMT1 over 25 years of age, continuous glucose monitoring (CGM) in conjunction with intensive insulin regimen may assist in achieving target glycemic and HbA1c goals.
4b. Check HbA1c every 3 months when targets are not met or when assessing recent interventions, otherwise stable patients meeting glycemic goals may have their HbA1c checked at least every 6 months.
4c. An HbA1c goal of <7% is reasonable for many patients. More intensive glycemic control and a HbA1c < 6.5 may be suitable in motivated adults with low risk for hypoglycemia, long life expectancy and no microvascular CVD. A less intensive glycemic control with a HbA1c < 8 may be more suited to elderly patients, those with a limited life expectancy, patients with poor cognitive function, patients at moderate to high risk for hypoglycemia, established microvascular or macro-vascular complications, or patients with extensive comorbid conditions.
4d. Hypoglycemia should be treated with 15–20 g of glucose in conscious adults. Patients with severe hypoglycemia (i.e. hypoglycemia requiring assistance) should be prescribed glucagon. Hypoglycemia unawareness or severe hypoglycemia should trigger a thorough re-evaluation with cognitive function assessment, and revising therapeutic strategies as well HbA1C and glycemic goals.
5. Management of obesity in DMT2:
5a. Obese patients with DMT2 are advised to adopt behavioral modifications with therapy including diet modification and regular exercise aimed at achieving a daily caloric deficit of 500–750 kcal (regardless of content in protein, fat, or carbohydrate) and a 5% weight loss over a six-month period. Continued and regular assistance and comprehensive programs to sustain successful weight loss in the long term (≥1 year) are essential with continued caloric restriction and high-intensity physical activity.
5b. Obese patients with DMT2 may benefit more from pharmacological therapy associated with weight loss with the goal being 5% and results re-evaluated in 3 months; DM medications associated with weight-gain ought to be avoided in the overweight and the obese.
5c. Bariatric surgery should be considered in patients with DMT2 and a BMI > 35 kg/m^2 especially if glycemic control is challenging.
6. Glycemic therapy: Metformin is the preferred first-line medication to treat DMT2 unless contraindicated or not tolerated. If maximal tolerated monotherapy does not meet or maintain desired HbA1C goal after 3 months, then add a glucagon-like peptide-1 (GLP-1) receptor agonist or basal insulin whichever suits the patient best. Insulin therapy must not be delayed if glycemic control are not being met.
7. CVD risk management – HTN:
7a. All patients with DM must have BP checked every visit and high readings must be repeated on a separate occasion to diagnose HTN.
7b. Patients with pre-HTN should be counseled to adopt non-pharmacological lifestyle modifications.
7c. For patients with HTN, goal BP is <140/90 mm hg; a lower BP goal of <130/80 mmHg may be adopted in younger patients, patients with stage A2-A3 albuminuria, patients with HTN and one or more CVD risk factors.
7d. Patients with an office BP exceeding 140/90 mmHg should be treated promptly with non-pharmacological life style modifications (weight loss for the overweight or obese, DASH-diet, exercise) as well as pharmacological therapy titrated till goal BP is achieved. An ACEi or an ARB at maximal tolerated dosage is considered first-line antihypertensive therapy (monitor serum creatinine and potassium), but often combination therapy is required usually with a thiazide diuretic.

(continued)

Table 8.1 (continued)

7e. In older adults, BP should be kept above 130/70 mm hg as lower SBP values do not offer any cardiovascular benefit and lower DBP values are associated with a higher mortality.
7f. In pregnant patients with DM and HTN, BP goal is 110–129/65–79 mm hg.
8. CVD risk management – lipid management:
8a. In patients not on lipid-lowering therapy, check a lipid panel at time of DM diagnosis, or initial encounter and then at least every 5 years.
8b. Check lipid profile when initiation of a statin is planned and periodically thereafter to monitor for response.
8c. In patients with dyslipidemia, advise non-pharmacological therapy with lifestyle modifications including weight loss, regular exercise, and dietary modifications to reduce cholesterol and saturated and trans-fat intake while increasing intake of omega-3 fatty acids viscous fiber and plant stanols/sterols.
8d. For patients with hyper-triglyceridemia exceeding 150 mg/dL or a low HDL (< 40 mg/dL in men, < 50 mg/dL in women), optimize glycemic control and advise lifestyle modifications. If triglyceride (TG) level exceeds 500 mg/dL, exclude secondary causes and initiate pharmacological therapy to reduce risk of pancreatitis.
8e. For all patients with DM and CVD, initiate high-intensity statin on top of lifestyle modifications.
8f. For patients with DM and additional risk factors for CVD, aged less than 40 years, consider initiation of moderate-intensity or high-intensity statin on top of lifestyle modifications.
8g. For patients with DM aged 40–75 years, consider initiation of moderate-intensity statin on top of lifestyle modifications if they have and no additional risk factors for CVD, and high-intensity statin on top of lifestyle modifications if they have additional risk factors for CVD.
8h. For patients with DM aged >75 years, consider initiation of moderate-intensity statin on top of lifestyle modifications if they have and no additional risk factors for CVD, and moderate- or high-intensity statin on top of lifestyle modifications if they have additional risk factors for CVD.
8i. Statin dose may be adjusted based on response and patient tolerance.
8j. In patients with acute coronary syndrome (ACS) and LDL cholesterol at or more than 50 mg/dL, adding ezetimibe to moderate intensity statin therapy on top of lifestyle modifications offers cardiovascular benefit when compared to statin alone, or add ezitmibe for patients who cannot tolerate high-intensity statin therapy.
8k. Statin/vibrate combination therapy offers no additional cardiovascular benefit and should not be routinely used. Such a combination may be used in men with a TG level ≥ 204 mg/dL and an HDL ≤ 34 mg/dL.
8l. statin/ niacin therapy offers no additional cardiovascular benefit and may may increase risk of stroke and is not recommended.
9. CVD risk management – antiplatelet agents:
9a. Initiate aspirin therapy at a dose of 75–162 mg daily for primary prevention in any patient with DM and a 10-year cardiovascular risk exceeding 10% unless contraindiacted. This includes most patients aged 50 years or older with DM and who have at least one more risk factor for CVD.
9b. Aspirin is not recommended if the 10-year cardiovascular risk is below 5% due to bleeding risk. This includes most patients aged less than 50 years with DM and who have no additional risk factors for CVD.
9c. Use aspirin for secondary prevention in all patients with DM and a prior history of CVD. If aspirin intolerance or allergy is documented, clopidogrel 75 mg daily may be used as alternative therapy.
9d. Dual anti-platelet therapy may be prescribed for 1 year following an ACS.
10. CVD risk management – coronary heart disease:
10a. In asymptomatic patients, treat CVD risk factors but do no screen for CAD.
10b. Investigate for CAD if patient has atypical symptoms such as dyspnea or chest discomfort, ECG abnormalities, vascular disease such as PAD or claudication or carotid bruits or history of TIA or CVA.
10c. In patients with established CVD, treat with aspirin, statin and ACEi. In patients with history of MI, continue beta blockers for at least 2 years after the MI.
10d. Avoid thiazolidinedione (TZD) in patients with HF.
10e. In patients with stable HF and normal kidney function, metformin may be used but ought to be avoided in patients with unstable or hospitalized patients with HF.
11. Microvascular complications – diabetic CKD:
11a. Check urine ACR at least once a year. Check eGFR at least once a year in patients with DMT2, DMT1 of five or more year duration, and in all patients with DM and HTN.
11b. Optimize glycemic and BP (<140/90) control to slow down CKD progression.
11c. For patients with ND-CKD, restrict daily protein intake to 0.8 g/kg healthy body weight.
11d. Initiate ACEi or ARB therapy for patients with stage A2-A3 albuminuria or stage 3–5 CKD and monitor urine ACR, serum creatinine and potassium while on RAAS blockers.
11e. Do not use an ACEi or an ARB in a patient with DM for primary prevention, that is a patient who is normotensive, has a normal eGFR and normal urine ACR.
11f. Refer patients to nephrologist in case or rapid progression, challenging management, or uncertain diagnosis; refer patients for education and preparation for RRT once eGFR declines below 30.

Table 8.1 (continued)

12. Microvascular complications – diabetic retinopathy:
12a. Optimize glycemic, BP and lipemic control to slow down progression of diabetic retinopathy.
12b. Patients with DMT1 must have a comprehensive and dilated eye exam within the first 5 years of diagnosis. Patients with DMT2 must have a comprehensive and dilated eye exam at the time of diagnosis.
12c. If any retinopathy is present, then followup must be schedule d at least once a year. If no retinopathy is diagnosed, then frequency of eye examination may be reduced to every 2 years.
12d. Initiate an immediate referral to an experienced ophthalmologist if any macular edema, severe non-proliferative or any proliferative diabetic retinopathy is detected.
12e. Laser photocoagulation is the treatment of choice for high-risk proliferative retinopathy and occasionally severe non-proliferative retinopathy.
12f. Intra-vitreal or anti-vascular endothelial growth factor is the treatment of choice for central (beneath foveal center) macular edema which is a threat to vision.
12g. Aspirin does not increase risk of retinal hemorrhage and thus retinopathy should not deprive patients of its cardioprotective effects.
13. Microvascular complications – neuropathy:
13a. Patients with DMT1 must be evaluated for neuropathy within the first 5 years of diagnosis and patients with DMT2 at the time of diagnosis.
13b. Obtain a careful history and perform 10-g monofilament testing and an additional test for pinprick or temperature or vibration sensation.
13c. Evaluate for autonomic dysfunction in any patient with microvascular complications an neuropathy.
13d. Optimize glycemic control to prevent or slow down progression of neuropathy.
13e. Treat patients to alleviate symptoms of peripheral and autonomic neuropathy.
14. Foot care:
14a. Perform a comprehensive foot check at least once a year and assess relevant risk factors.
14b. Patients with claudication or abnormal pedal pulses should be referred for a vascular evaluation.
14c. Patients with foot ulcers or high-risk feet (dialysis, charcot foot, history of ulcers or amputation) require a team approach.
14d. Refer patients at risk to a podiatrist for preventive care.
14e. Counsel active tobacco users to quit.

diminished by the effect or uremic toxins (higher than expected HbA1c), decreased RBC survival in more advanced CKD or increased erythropoiesis when an erythropoiesis stimulating agent (ESA) or iron is used (lower than expected HbA1c).

2. Setting a goal HbA1c must be customized to each individual patient and weighed against their risk of hypoglycemia, a risk which increases with severity of CKD.
   - 2a. The risk of severe hypoglycemia (i.e. patient requires assistance for management) is high in patients with stage 5 CKD or hepatic failure or gastroparesis, or in patients receiving insulin or long-acting sulfonylurea with active metabolites.
   - 2b. Moderate risk for hypoglycemia is seen in patients prescribed short acting sulfonylureas or sulfonylureas with inactive metabolites or meglitinides.
   - 2c. Low risk for hypoglycemia is seen in patients taking the biguanide metformin, alpha glucosidase inhibitors, dipeptidyl peptidase IV (DPP-4) inhibitors, incretin mimetics such as glucagon-like peptide-1 (GLP-1) receptor agonists, thiazolidinediones, and Sodium-glucose co-transporter-2 (SGLT2) inhibitors.
   - 2d. Hypoglycemia risk must be avoided, and if risk is high, this may necessitate adopting more liberal goals for glycemic control with a HbA1c $\leq$ 8.5%; such a liberal goal may also be suitable for patients with a reduced life expectancy, established cardiovascular (macrovascular) disease or micro-vascular complications, poor motivation; yet, continued vigilant efforts must be made to achieve such a goal if the HbA1c is higher. If a patient is high risk for hypoglycemia, then more frequent self-monitoring is required.
   - 2e. In patients who are on non-pharmacological lifestyle modifications or on pharmacological therapy with low risk for hypoglycemia, a goal HbA1c of $\leq$7.0% is recommended.
   - 2f. In patients with a DM vintage exceeding 10 years and who are on pharmacological therapy with moderate risk for hypoglycemia, a goal HbA1c of $\leq$8.0% is recommended.
   - 2g. For patients who do not fit into any of the previous categories, a goal HbA1c of $\leq$7.5% is recommended.
3. Metformin continues to be first line therapy in DM, after life style modifications, and dose must be reduced as CKD progresses and should be used with extreme caution in stage 4 CKD and must be stopped in stage 5 CKD; empower patient and provide printed educational

reminders to hold metformin if any AKI risk develops such as with volume depletion (e.g. recurrent vomiting or diarrhea) or administration of IV contrast, and continue to hold until a time when the risk disappears. If additional pharmacological therapy is needed, then additional medications which are low-risk for hypoglycemia may be added.

4. When a coronary angiogram is indicated, it should not be omitted for the sole concern of contrast-induced nephropathy.
   - 4a. In patients with stable AHD/CAD, maximal medical therapy is preferred, unless there is significant left main coronary or significant proximal LAD disease for which an elective CABG is the treatment of choice.
   - 4b. In patients with mutlivessel or complex disease, CABG is favored over PCI.
   - 4c. In patients with an acute MI, treatment strategies should not be any different from those offered to patients with DM/no-CKD or stage 1-3a CKD/no-DM. In patients with STEMI, primary PCI, whenever available in a timely fashion, is preferred over thrombolytic therapy. In patients with non-STEMI and left main disease or multi-vessel disease, CABG is associated with better outcomes and lower mortality rate when compared with PCI.
   - 4d. Dose of thrombolytic therapy must be adjusted by severity of CKD and eGFR level.
5. Treat patients with HF or ischemic heart disease with ACE-i at maximal dose tolerated; evidence to use ARB in these patients is lacking and combining ACE-i, ARB or DRI must be avoided.
6. Treat patients with lipophilic (rather than hydrophilic) selective-beta blockers as these agents may decrease the risk of sudden cardiac death.
7. Avoid lower BP goals than in the general population (<140/90 mmHg) as some patients may have autonomic dysfunction and orthostasis. In the absence of albuminuria, all BP lowering meds may be used equally.
8. Recommend start a statin in patients with stage 3b-4 CKD and consider doing so in stage 5 CKD; use a fibrate if patient is intolerant to statin.
9. Advise patients to adopt an individualized and regular exercise program to achieve goal body mass index (BMI), build muscle mass and reduce body fat and improve quality of life.
10. Start an aspirin for primary as well as secondary prevention in the absence of major bleeding risk or contraindication; if intolerant, consider clopidogrel as alternative therapy.
11. In patients with ACS or high-risk coronary intervention, do not add glycoprotein IIb/IIIa inhibitors to standard care due to potential increase in bleeding risk.
12. In patients with ACS or high-risk coronary intervention, avoid adding thienopyridine or ticagrelor to standard care unless it is certain bleeding risk is not increased.
13. When providing education for RRT (usually GFR < 30 mL/min/m^2 BSA), kidney transplantation is by far the most superior therapeutic option available, but there is no evidence that any dialysis modality of RRT (CAPD, continuous cycling peritoneal dialysis (CCPD), home HD, in-center HD, nocturnal HD) is superior to the others, and thus dialysis modality-education should be unbiased and help the patient choose the modality which suits them best.
14. There is no benefit for early versus late initiation of RRT with dialysis and thus dialysis should be initiated when a clinical indication arises while simultaneously accounting for dialysis access best-choice and readiness of use.
15. When HD is chosen, vein-preservation strategies would be adopted and a native arteriovenous (AV) fistula would be the best choice for access, followed by an AV graft; catheters must be avoided if at all possible due to increased risk of mortality, infections and secondary vascular complications.
16. For patients with DMT1, live-kidney transplantation or simultaneous pancreas-kidney (SPK) transplantation or pancreas after kidney (PAK) transplantation be sought with a complete understanding of risks involved with each procedure, but islet transplantation is not recommended. For patients with DMT2, kidney transplantation is recommended for suitable candidates after evaluation, but not SPK or PAK or pancreas transplantation.

8.7.3.6 Safety of Oral Hypoglycemics in DMT2 and CKD

In patients with CKD and DMT2, metformin must be used with extreme caution when eGFR declines below 30 mL/min/1.73 m^2 BSA, due to concerns over severe life-threatening type B lactic acidosis. It may be used in patients with stage 1–3 CKD with dosage adjustments to eGFR and close monitoring of kidney function [157, 158].

Sodium-glucose cotransporter type 2 (SGLT2) inhibitors prevent renal proximal tubular glucose reabsorption and have been associated with urinary tract infections, increased risk of ketoacidosis [159], and some reports to the FDA cite concerns of acute kidney injury. Thus, these agents must be used with caution in patients with stage 3–5 CKD until their safety is clarified. Health care providers and patients must aggressively mitigate any risk factors for AKI such as hypovolemia (e.g. diuretics, HF) and avoid concurrent use of agents resulting in hemodynamic renal hypoperfusion (e.g. non-steroidal anti-inflammatory drugs (NSAIDs) or ACE-i or ARBs) [160].

In patients in whom sulfonylurea therapy is planned, short-acting agents with no active metabolites, such as glipizide are preferred to longer-acting agents or those with active metabolites in order to avoid increased risk of hypoglycemia.

8.7.4 Lipid Management

Dyslipidemia is an established modifiable major risk factor for CVD in patients with ND-CKD.

The Study of Heart and Renal Protection (SHARP) Investigators followed 6247 ND-CKD patients and 3023 ESKD patients on dialysis, with no prior history of MI or coronary revascularization, for a median duration of 4.9 years after they were randomized to either receive simvastatin plus ezetimibe or placebo and found that the LDL reduction in the active treatment group was associated with a significant 17% risk reduction of a first major atherosclerotic event (coronary death or non-fatal MI, any arterial revascularization procedure or any non-hemorrhagic CVA), and significant protection against non-hemorrhagic CVA and arterial revascularization [161].

However, the power of high LDL-cholesterol to predict AHD risk seems to grow weaker with the severity of CKD and may dissipate entirely in dialysis patients where a more accelerated CVD pathway and a higher mortality rate are driven by other non-traditional risk factors. Clinical trials in hemodialysis patients, such as the Die Deutsche Diabetes Dialyse Studie trial [162] and the A Study to Evaluate the Use of Rosuvastatin in Subjects on Regimen Hemodialysis: An assessment of survival and cardiovascular events (AURORA) trial [163], failed to show any significant beneficial effects of LDL reductions with statin therapy on cardiovascular mortality or all-cause mortality.

8.7.4.1 KDIGO Guidelines for Lipid Management in CKD

In 2013, the KDIGO Lipid Work Group published a "Clinical Practice Guideline for Lipid Management in CKD" [164]:

1. Check a lipid panel only in patients with newly diagnosed non-dialysis CKD, ESKD, or kidney transplant recipient (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides). Followup lipid panels are not required in the majority of patients with non-dialysis CKD, ESKD on dialysis, or kidney transplant recipients.
2. In patients aged 50 years or over and with non-dialysis non-transplant Stage 1–5 CKD, initiate pharmacological therapy with a statin or statin/ezetimibe combination.
3. In patients aged 18–49 years with non-dialysis non-transplant Stage 1–5 CKD, pharmacological therapy with a statin is suggested if any of the following co-morbidities exist: (3a). known coronary disease (myocardial infarction or coronary revascularization) (3b). diabetes mellitus (3c). prior ischemic stroke (3d). estimated 10-year incidence of coronary death or non-fatal myocardial infarction >10%.
4. In patients with dialysis-dependent CKD, initiation of pharmacological therapy was not recommended; continuation of any previously prescribed said therapy is suggested.
5. In kidney transplant recipients, initiate pharmacological therapy with a statin.
6. In patients with non-dialysis CKD, ESKD on dialysis, or kidney transplant recipients who are diagnosed with hypertriglyceridemia, therapeutic lifestyle changes are advised.

In summary, it seems that the recommendations for established non-dialysis stage 1–5 CKD patients age 50 years and over, adopt a strategy of "test no one and treat everyone". This establishes a major shift in clinical practice, where the focus on LDL-cholesterol levels and targets is abandoned in this patient population.

8.7.5 Obesity and the Metabolic Syndrome

The epidemic of obesity seems to have no geographic, ethnic /racial, gender or age boundaries; obesity carries an increased risk of morbidity and mortality and is the second leading cause of preventable disease in the US.

Epidemiological studies have identified obesity or a higher body mass index (BMI) as an independent risk factor for the development and progression of CKD [165–167] and for CVD [168]. Obesity at a younger age (18–34 years) carries an increased risk for future ESKD; compared to a normal BMI, the adjusted RR for future ESKD was 1.87 for a BMI of 25.0–29.9, 3.57 for a BMI of 30.0–34.9, 6.12 for a BMI of 35.0–39.9 and 7.07 for a BMI at or exceeding 40 kg/m^2 [169].

Obesity may also cause obesity-related glomerulomegaly and glomerulopathy, with glomerular hyperfiltration and pathological features of secondary adaptive focal segmental glomerulosclerosis with sub-nephrotic proteinuria [170]. Furthermore, obesity has been associated with increased risk of metabolic syndrome, sleep apnea, obesity-associated HTN, insulin resistance and DMT2, dyslipidemia, and various cancers.

The obese population is not a homogenous one; up to one third of obese patients have a "metabolically benign" profile with no apparent increase in CVD risk [171]. The mechanisms by which obesity alters CVD and CKD risk are not fully elucidated, the obesity-CKD association is especially complex. For example, when compared with individuals who have a normal weight and no metabolic syndrome,

overweight and obese patients with the metabolic syndrome had a higher risk of ESKD (hazards ratio 2.03), but overweight and obese patients without the metabolic syndrome had a lower risk of ESKD (hazards ratio 0.47) [167]. In patients with established prevalent ND-CKD, some have suggested a U-shaped association between obesity and clinical outcomes of CKD progression and all-cause mortality with the best clinical outcomes at a BMI of 25–35 kg/m^2; a BMI < 25 predicted worse outcomes in all patients regardless of CKD stage while a BMI > 35 predicted worse outcomes in patients with stage 1–3 CKD with said risk growing weaker in advanced CKD [172].

In dialysis patients, use of BMI to diagnose obesity and overweight should be done with extreme caution; this is due to protein-energy wasting and loss of muscle mass seen in patients with ESKD on dialysis. Thus in such patients, excessive central or total body adiposity may be masked by a balancing loss of muscle mass, keeping the BMI apparently "normal" [173]. In fact, a higher BMI, when it reflects weight gain resulting from increased muscle mass, was associated with a better and incremental survival rate in a cohort of 121,762 patients on maintenance hemodialysis followed over 5 years [174]. A measure of abdominal and visceral adiposity, such as weight circumference, in a cohort of 537 patients with ESKD, was found to be a reliable and direct predictor of cardiovascular as well as all-cause mortality whereas BMI was not, cardiovascular mortality was highest amongst participants with a waist circumference at or exceeding the median and a BMI below the median, and it was lowest in patients with a waist circumference below the median and a BMI at or above the median; similarly waist/hip ratio also predicted cardiovascular as well as all-cause mortality [175].

Lifestyle modifications focused on caloric restriction, weight loss, regular daily exercise, and when needed surgical interventions, to achieve a BMI of 20–25 kg/m^2 are recommended for patients with ND-CKD to reduce risk of CVD and prevent incident or new-onset CKD; however, the ideal target BMI in patients with established-prevalent CKD may be more complex and more clinical studies are needed, some studies have suggested a U-shaped association with best clinical outcomes achieved at a BMI of 25–35. In morbidly obese patients, who fail to achieve or sustain weight loss, surgical interventions such as bariatric surgery ought to be pursued. In ESKD patients on maintenance dialysis, health care providers need to focus on strategies to increase muscle weight.

8.7.6 Tobacco Cessation

Tobacco use is the leading cause of preventable disease in the US, and ranks only second to HTN as the health risk factor responsible for the highest number of deaths worldwide [176].

Tobacco use is a known risk factor for CVD as well as cardiovascular and all-cause mortality, and it has been associated with nephrosclerosis [177], idiopathic nodular glomerulosclerosis [178–180] and worsening progression of CKD and albuminuria in many primary and secondary kidney diseases such as DM, IgA nephropathy, lupus nephritis and polycystic kidney disease [181–185].

However, the evidence for the tobacco-CKD association has not been always reproducible or uniform. For example, in a cohort of 23,534 participants followed over a period of 20 years, tobacco use carried a significant increase in risk of CKD (identified by ESKD or CKD on death certificate verified by a chart review) with a hazard ratio of 2.9 in women and 2.4 in men, with a 31% proportion of the increased risk of CKD attributed to smoking [186]. On the other hand, the SHARP Collaborative Group evaluated the effects of tobacco use in a cohort 9270 CKD patients (13% current smokers, 35% former smokers and 51% never smokers) over a mean duration of 4.9 years and found increased risk in current-smokers for atherosclerotic and non-atherosclerotic vascular events (RR 1.36), lung cancer (RR 9.31) and upper aerodigestive tract cancers (RR 4.87), as well as all-cause mortality (RR 1.48) when compared to never-smokers, but there was no association with rate of change in eGFR or incidence of ESKD [187].

Tobacco use remains a strong risk factor for CVD in patients with CKD of any stage [188]; it is also hypothesized that toxic metabolites of tobacco may accumulate in patients with more advanced CKD, thus enhancing CVD risk. Tobacco cessation reduces CVD risk in patients with CKD [189] and may also be beneficial in slowing down CKD progression in some kidney diseases. Finally, most transplant centers in the US do not accept active tobacco users with advanced CKD or ESKD as candidates for kidney transplant waitlisting.

The most recent update of the US Preventive Services Task Force (USPSTF) guidelines for interventions for tobacco smoking cessation in adults that all healthcare providers inquire about tobacco use, advise active users to stop, evaluate willingness to quit, offer interventions to help the patient quit and arrange for followups; the guidelines advise interventions with evidence-based effectiveness be pursued and to steer away from electronic smoking due to lack of adequate evidence to risks and benefits [190]. Offering behavioral and pharmacological interventions with nictoine-replacement therapy or partial nicotine agonists enhances successful quit rate and must be tailored to patient's safety and eGFR.

8.7.7 Exercise

"Exercise is medicine". A sedentary lifestyle, with a lack of regular exercise, is a risk factor for CVD and has been associated with progression of CKD in some observational studies.

CKD itself and its complications may limit exercise tolerance via factors such as anemia and vascular disease [191]; walking seems to be the most popular form of exercise in patients with stage 3–5 CKD and has been associated with improved survival and decreased risk of RRT [192].

All able CKD patients must be encouraged regularly to follow the 2008 Federal Physical Activity Guidelines for:

1. Leisure-time aerobic physical activity, a weekly recommendation for 150 min of moderate-intensity exercise, or 75 min of high-intensity, or some combination, and most favorably spread over many week-days, and
2. Muscle-strengthening, a weekly recommendation to exercise all muscle groups in a moderate- to high-intensity workout at least twice a week [18, 193].

In a cohort of 256 individuals with stage 3–4 CKD from the Seattle Kidney Study, those who had more than 150 min of weekly physical activity had a slower CKD progression over a median 3.7 years of follow-up [194].

Additionally, exercise is encouraged in patients with ESKD on HD. Use of intra-dialytic exercise during HD time has been shown to be beneficial and safe in many small studies and is implemented in some dialysis centers in Europe and Australia [195] but has not made it to North America.

In summary, many studies have shown the benefits of aerobic physical activity and muscle strengthening in patients with stages 2–5 CKD, including those on RRT, and thus exercise is medicine in this patient population and should be prescribed to all who are able and who have no restricting clinically-active CAD, either in a home-based program, or in-center during dialysis, or in another setting [196].

8.8 Management of Non-traditional CVD Risk Factors in CKD

8.8.1 Preventing or Slowing Down Progression of CKD

Strategies to slowing down the progression of CKD must focus on achieving optimal blood pressure control, optimal glycemic control, optimal lipemic control, tobacco cessation, achieving ideal BMI and waist/hip ratio for CKD stage, anemia management, correction of acid-base and electrolyte abnormalities, management of mineral and bone disorder, dietary protein restriction, treatment with an ACEi or an ARB especially in patients with stage A2-A3 albuminuria.

8.8.1.1 Depression and Cognitive Dysfunction in CKD

Furthermore, CKD, whether lower eGFR or albuminuria, is associated with cognitive dysfunction, and around 26.5% of CKD patients are clinically depressed [197]; both conditions result in a decreased quality of life. Thus, it is important to evaluate every CKD patient thoroughly for either problem as either may interfere with compliance, motivation, and the success of preventive and therapeutic strategies.

8.8.1.2 Genetic Predisposition

The role of genetic predisposition in CKD and CVD is not yet well established, but clinical research continues to make slow and steady strides in this futuristic field. For example, black individuals with variants of apolipoprotein L1 (APOL1) are more susceptible to develop certain forms of CKD and progress to ESKD; two APOL1 alleles incur a 1.49 higher risk for CKD and a 1.88 higher risk for ESKD when compared to zero or one allele [198].

8.8.2 Reduction of Urine Albumin Excretion Rate

Urine Albumin excretion rate (UAER) is an independent CVD risk factor; it is also an excellent prognosticator of CKD progression as well as a strong biomarker of response to therapy. Pharmacological therapies that have been shown to decrease (UAER) include RAAS inhibitors (ACEis, ARBs, DRIs and ARAs), and when not tolerated non-dihydropyridine CCBs (Diltiazem).

8.8.3 Treatment of Anemia in CKD

Anemia in CKD may represent different pathophysiological pathways such as erythropoietin deficiency, erythropoietin resistance due to a multitude of causes such as chronic inflammation or secondary hyperparathyroidism (SHPT), chronic blood loss (may be more significant in dialysis patients), iron deficiency, vitamin B12 or folate deficiency, or a shortened erythrocyte life span [199, 200]. Furthermore, angiotensin II may play a minor physiological role in stimulating erythropoietin production in humans [201–203]; ACEi may theoretically reduce the response to ESAs and contribute to ESA hypo-responsiveness or resistance [204, 205].

Anemia usually occurs once eGFR declines below 60 and hemoglobin (Hb) levels usually correlate with severity of CKD. The best marker in CKD patients is the Hb, rather than the hematocrit, which may vary with ECF volume, measuring methods, and sample storage time. Workup for anemia in patients with CKD should reinforce:

1. age-appropriate screening for occult blood loss,
2. evaluate a peripheral smear and a reticulocyte count,
3. check an iron panel with ferritin keeping in mind that ferritin is an acute phase reactant that is often increased in patients with chronic inflammation [206]. CKD patients also have increased plasma hepcidin levels, thus inhibiting duodenal iron absorption and further contributing to iron deficiency [207].
4. check a vitamin B12 and RBC-folate levels, but
5. should not include erythropoietin levels, which rarely add anything to the evaluation and management plan.

Anemia has been associated with increased mortality, more frequent hospitalizations, impaired cognitive function, reduced functional status and exercise tolerance, a higher left ventricular mass index (LVMI) and left ventricular hypertrophy (LVH, an independent predictor of increased mortality risk) [61], and increased cardiovascular disease.

Treatment of anemia decreases the need for RBC transfusions [208], may cause partial regression of LVH [209], reverses most clinical manifestations, may improve functional status, and some even report improved survival. The benefits of treatment of anemia remains a topic of debate; for example, a systematic review of the effect of ESA therapy on affects health-related quality of life (HRQOL) in CKD patients did not reveal any significant improvement [210].

Currently approved ESAs by the FDA in the USA include recombinant human erythropoietin, darbepoetin alpha, and methoxy polyethylene glycol-epoetin beta. One of the adverse effects of erythropoietic stimulating agents (ESAs) is a higher BP. Oral iron must be taken between meals and should not be combined with calcium-based binders as they bind each other.

In summary, for the majority of patients, ESA therapy is initiated when Hb levels decline below 9 g/dL and therapy should target a goal Hb of 10–11 g/dL and levels higher than 12 g/dL must be avoided. Higher goals have been associated with poorer BP control and increased risk of stroke and mortality [208, 211].

8.8.3.1 KDIGO Clinical Practice Guideline for Anemia in CKD

In 2012, the KDIGO Anemia Work Group published a "Clinical Practice Guideline for Anemia in CKD" [212].

1. Diagnosis and Evaluation:
   - 1a. Diagnose anemia in CKD when the hemoglobin (Hb) concentration is <13 g/dL in men and < 12 g/dL in women.
   - 1b. In patients with CKD but *no* anemia, measure Hb when a clinical indications arises and at least once every 12 months in patients with stage 3 CKD, at least once every 6 months in patients with stage 4–5 non-dialysis CKD, and at least every 3 months in patients on hemodialysis or peritoneal dialysis.
   - 1c. In patients with CKD and anemia receiving pharmacological therapy with ESA, measure Hb when a clinical indications arises and at least once every 3 months in patients with stage 3–5 non-dialysis CKD or who are on peritoneal dialysis, and at least every 1 month in patients on hemodialysis.
   - 1d. In any patient with CKD diagnosed with anemia, initial workup must include a complete blood count (CBC), absolute reticulocyte count, serum ferritin level and a serum transferrin saturation (TSAT), serum vitamin B12 and folate levels.
2. Iron Therapy. When prescribing intravenous (IV) iron therapy for patients with CKD, anemia and iron deficiency:
   - 2a. Weigh the advantages (alleviation of clinical symptoms, minimization of blood transfusions, optimal utilization of ESA therapy) against the short-term and long-term potential risks (anaphylactoid and other acute reactions, unknown long-term risks).
   - 2b. Exclude any active infection, especially systemic.
   - 2c. Confirm pre-requisite laboratory data: transferrin saturation (TSAT) ≤ 30% and a ferritin ≤ 500 ng/ml.
   - 2d. For patients not receiving any ESA therapy, a trial of IV iron may be initiated when a higher Hb concentration is desired without ignition any ESA.
   - 2e. For patients receiving ESA therapy who are not receiving iron supplementation, a trial of IV iron may be initiated after exclusion other causes of ESA hypo-responsiveness, and when a higher Hb concentration or a lower ESA dose is desired.
   - 2f. For patients with non-dialysis CKD, a trial of oral iron therapy for 1–3 months may be initiated as an alternative to IV iron depending on "the severity of iron deficiency, availability of venous access, response to prior oral iron therapy, side effects with prior oral or IV iron therapy, patient compliance, and cost".
   - 2g. Evaluate clinical picture, past and present responses to iron therapy, iron parameters, blood loss, Hb

trends, ESA dose and responsiveness to judge the utility of future iron use.

2h. Measure TSH and Ferritin at least every 3 months when starting or maintaining iron therapy, or more often when monitoring response to IV iron or when starting, maintaining or changing ESA therapy, or when a clinical indication arises.

2i. Study the safety of the IV iron formulation used and ensure a safe environment for administration, adequate monitoring and resuscitation if an adverse event occurs.

3. ESA Therapy: When prescribing ESA therapy for patients with CKD and anemia:

3a. Exclude, and treat, reversible causes such as iron deficiency of inflammatory diseases.

3b. Weigh the advantages (alleviation of clinical symptoms, minimization of blood transfusions, optimal utilization of ESA therapy) against the potential risks (higher BP, increased thrombotic complications such as clotting of arteriovenous access or stroke).

3c. In patients with active malignancy with a favorable prognosis, history of malignancy or history of CVA, uses ESA with extreme caution.

3d. For patients with ND-CKD and a Hb ≥ 10 g/dL, ESA therapy should not be initiated; if Hgb < 10 g/dL then clinical risk-benefit analysis should be done to reach an individualized decision whether to initiate ESA therapy.

3e. In patients with stage 5D-CKD, avoid Hb decline to a level below 9.0 g/dL and initiate ESA when Hb is 9.0–10.0 g/dL.

3f. ESA may be started at higher Hb in select patients who may have a better quality of life.

3g. Maintenance ESA therapy should be used to maintain a Hgb level at 10–11.5 g/dL in most patients and never to intentionally target a Hgb above 13 g/dL.

3h. Initial ESA dose is weight based, and considers severity of anemia and clinical manifestations. Dose adjustments are tailored to ESA responsiveness, rate of Hb increments, clinical picture, patient safety and freedom from adverse events. When a Hb drop is desired, decreasing ESA dose is preferred to withholding dose whenever possible.

3i. For patients with ND-CKD or stage 5D-CKD on PD, subcutaneous administration of ESA is suggested; for patients on hemodialysis either intravenous or subcutaneous is suggested.

3j. Frequency of ESA administration must be customized based on CKD stage, ESA type and half-life, administration setting, responsiveness, and patient preference.

4. Difficulty Achieving Goal Hb:

4a. When initiating ESA therapy, check Hb at least once a month. For patient on maintenance therapy, measure Hb at least monthly in stage 5D-CKD patients and at least every 3 months in ND-CKD patients.

4b. Identify initial ESA hypo-responsiveness in new patients receiving the proper weight-based ESA dose and whose Hb fails to respond; titrating ESA dose should not exceed double the initiation dose.

4c. Identify subsequent acquired ESA hypo-responsiveness in patients who had a stable Hb on a maintenance ESA therapy, and who then require two dose increases of 50% or more of the original maintenance ESA dose for a declining Hb; titrating ESA dose should not exceed double the original maintenance ESA dose.

4d. Evaluate hypo-responsive patients for specific causes such as inadequate iron stores, infection or inflammation, SHPT, etc… and if correcting any secondary causes fails to achieve goal Hb, then individualize therapy with ESA and or blood transfusions to achieve minimum safe Hb.

5. Red Blood Count (RBC) Transfusion:

5a. Avoid RBC transfusions, whenever possible, for treatment of anemia due to inherent transfusion risks; especially in kidney transplant candidates to minimize risk of allosensitization.

5b. Consider RBC transfusion in select patients, where benefits outweigh risk, such as patients with ESA hyporesonsiveness or bone marrow failure or hemoglobinopathies where ESA therapy is ineffective, or in patients with an active or past malignancy or a history of a CVA.

5c. RBC transfusion should be guided by occurrence of symptoms and not be any Hb threshold.

8.8.4 Managing CKD-MBD

Patients with CKD develop a series of abnormalities relating to mineral (calcium and phosphorus) and bone metabolism. The earliest biomarker abnormality to herald this complex disorder is a rise in parathyroid hormone (PTH) reflective of parathyroid tissue hyperplasia, usually seen when the eGFR declines below 60, and other biomarkers include an elevated fibroblast growth factor 23 (FGF-23), elevated bone alkaline phosphatase, a low 1,25-dihydroxy-vitamin D3 (calcitriol) level, hyperphosphatemia, and hypocalcemia [213]. Such biochemical abnormalities usually indicate defective bone metabolism (with increased fracture risk) with one or other of two major phenotypes: high bone turnover as is seen in osteitis fibrosa cystica, or low bone turnover as is seen in adynamic bone disease or osteomala-

cia. Furthermore, this chain of events is believed to trigger the transformation of vascular medial smooth muscle stem cells into osteoblast progenitor cells, which promote vascular calcification.

8.8.4.1 Hyperphospahtemia

In patients with ND-CKD, hyperphosphatemia or a serum phosphorus in the upper normal range is a risk factor for CVD, arterial and valvular calcification and all-cause mortality, and for every rise in serum phosphorus by 1 mg/dL, there was a statistically significant rise in prevalence of CAC by 21%, thoracic aortic calcification by 33% and mitral valve calcification by 25% [214]. Similarly, high FGF-23 levels independently predicted increased LVMI and risk of LVH [215].

With reduced renal phosphorus clearance, hyperphosphatemia is usually treated with dietary modifications to restrict daily phosphorus intake to one gram and with phosphate binders. Phosphorus is an intracellular ion, and while most dialysis patients develop hypo-phosphatemia during a dialysis session, rebound hyperphosphatemia may still ensue post-dialysis.

Currently, FDA approved phosphate binders available in the US include:

1. Calcium-based phosphate binders such as calcium acetate and calcium carbonate,
2. Non-calcium-based binders:
   - 2a. sevelamer hydrochloride and sevelamer bicarbonate. Sevelamer has the added benefit of producing reductions in LDL-cholesterol.
   - 2b. lanthanum carbonate,
   - 2c. iron-based phosphate binders such as sucroferric oxyhydroxide, and ferric citrate,
   - 2d. aluminum hydroxide. Regular use of aluminum hydroxide has been abandoned due to bone toxicity (osteomalacia and cysts) and neurotoxicity (encephalopathy or dementia).

There is conflicting evidence whether calcium-based binders are inferior to non-calcium based binders in patients with non-dialysis CKD or ESKD on dialysis, as far as all-cause mortality or cardiovascular mortality, due to concerns that calcium-based binders may enhance CAC and other arterial calcifications [216].

A recent meta-analysis, including 77 clinical trials and 12,562 patients, mostly dialysis patients, compared the effects of calcium-based phosphate binders or non-calcium-based phosphate binders on cardiovascular events and all-cause mortality and found no difference when compared to placebo; in subgroup analysis, sevelamer had a lower overall mortality rate (OR 0.39) when compared to calcium-based phosphate binders [217]. Similar major systematic reviews failed to show a similar survival benefit with Sevelamer [218, 219].

8.8.4.2 Vitamin D Insufficiency or Deficiency

Traditionally, the role of Vitamin D replacement in CKD patients has been to treat secondary hyperparathyroidism (SHPT) with the activated hormonal vitamin D form, calcitriol (1,25-dihydroxycholecalciferol), or with a synthetic vitamin D analog (e.g. calcifediol, doxercalciferol, paricalcitol). However, 25-hydroxy vitamin D insufficiency or deficiency has been increasingly diagnosed in CKD patients and it is believed it accelerates SHPT, and thus when diagnosed in this setting, it is recommended to replace this deficiency with vitamin D2 (ergocalciferol) or vitamin D3 (cholecalciferol).

One of the reasons that pharmacological therapy, rather, than augmented dietary intake is favored, is that vitamin D, a fat-soluble vitamin, would dictate a high-fat food items, a diet not generally encouraged in this patient population.

With vitamin D receptors being discovered in many tissues (e.g. heart, prostate), the scope of vitamin D therapy may be expanded beyond SHPT, for example, some observational data have linked activated vitamin D intake in patients with EKSD on dialysis to improved cardiovascular outcomes and survival [220, 221].

8.8.4.3 SHPT

Current therapies for SHPT include pharmacological therapy with a vitamin D analog or a calcimimetic, or surgical parathyroidectomy.

There is no current evidence that either form of pharmacological therapy is superior to the other in SHPT, and many patients may receive a combination of both forms of therapy. When monotherapy is suitable, the choice is usually guided by the patient's biochemical profile, i.e. serum calcium and phosphorus levels: vitamin D analogs tend to promote hyperclacemia and hyperphosphatemia whereas calcimimetics may cause hypocalcemia [222]. There is no clinical evidence at this time that vitamin D analogs enhance vascular calcifications via promoting a higher serum calcium level.

Cinacalcet, an oral calcimimetic, used to treat SHPT in patients with ESKD on dialysis, failed to show any survival benefit in patients with moderate to severe SHPT and receiving standard therapy when compared to placebo; furthermore, the EVOLVE trial investigators did not detect and decrease in cardiovascular events with cinacalcet [223].

While SHPT and hyperphosphatemia are risk factors for increased mortality, no pharmacological intervention to this date have been shown to offer any survival benefit. For example, a recent metanalysis of 28 clinical trials with 6999 participants reported "weak and imprecise" associations between different pharmacological agents, surrogate biomarkers and mortality and added that many trials were plagued with risk of bias [224].

8.8.4.4 KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of CKD–Mineral and Bone Disorder

The "2009 KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of CKD–Mineral and Bone Disorder (CKD-MBD)" recommends the following for patients with stage 3–5D CKD [225]:

1. Biochemical:
   - 1a. Start checking calcium, phosphorus, iPTH, and alkaline phosphatase regularly in any patient with stage 3–5D CKD and monitor calcium and phosphorus every 6–12 months in stage 3 CKD, every 3–6 months in patients with stage 4 CKD and every 1–3 months in stage 5 CKD; monitor alkaline phosphatase and iPTH less frequently depending on baseline levels and rate of CKD progression. Monitoring frequency may be increased when abnormalities are identified or when therapeutic interventions are initiated.
   - 1b. Check 25-hydroxy-vitamin D (calcidiol) and correct any insufficiency or deficiency and order follow-up levels based on baseline levels and whether therapeutic interventions have been initiated.
   - 1c. It is best to base therapeutic decision making on trends of biomarkers rather than single laboratory values.
   - 1d. Its is suggested that calcium and phosphorus levels be used to guide clinical decisions rather than the CaxP product.
   - 1e. All labs must be interpreted in lieu of the sample source and handling, and assay methods used at the laboratory.
2. Bone:
   - 2a. A bone biopsy may be performed if a clinical indication arises, such as persistent bone pain, unexplained fractures or hyperclacemia or hypophosphatemia, suspected aluminum toxicity, prior use of bisphosphonates.
   - 2b. In patients with clinical evidence of CKD-MBD, routine bone mineral density testing is not recommended because it fails to predict fracture risk or type of renal osteodystrophy.
   - 2c. Bone disease can be evaluated with iPTH or bone-specific alkaline phosphatase, both of which may provide clues to state of bone turnover.
3. Vascular calcifications:
   - 3a. When indicated, a lateral abdominal radiograph to detect vascular calcifications and an echocardiogram to detect valvular calcifications be used rather than an EBCT.
   - 3b. Patients with vascular or valvular calcifications should be classified as highest cardiovascular risk.
4. Treatment of Mineral Disorders:
   - 4a. Keep serum phosphorus in normal range for ND-CKD patients and lower phosphorus toward normal range in dialysis patients.
   - 4b. Keep serum calcium in normal range.
   - 4c. (4c) In stage 5D-CKD a dialysate calcium between 2.5 and 3.0 mEq/L is suggested.
   - 4d. Restrict dietary phosphorus intake in patients with hyperphosphatemia.
   - 4e. Use phosphate binders to treat hyperphosphatemia, and restrict calcium-based binders and vitamin D analogs in patients with persistent or recurrent hypercalcemia or arterial calcifications or dynamic bone disease or a persistently low iPTH.
   - 4f. Avoid long-term use of aluminum-based phosphate binders.
5. Treatment of SHPT:
   - 5a. In patients with stage 3–5 ND-CKD, optimal ipTH level is not clear and patients with SHPT should be checked and treated if reversible causes are detected such as hyperphsophatemia, hypoclacemia, and low 25-hydroxy vitamin D insufficiency or deficiency.
   - 5b. In patients with stage 3–5 ND-CKD with persistent SHPT despite treating all potential causes, initiate calcitriol or vitamin D analog therapy.
   - 5c. Look for trends in iPTH levels to guide therapy, rather than single values, and maintain levels between 2–9 upper normal limit of the assay.
   - 5d. In patients with stage 5D-CKD and SHPT, therapy with calcitriol or vitamin D analog therapy or a calcimimetic or a combination should be started and choice should be guided by serum calcium and phosphorus levels. Vitamin D therapy should be reduced or stopped when hypercalcemia or hyperphosphatemia ensue; similarly calcimimetic therapy should be adjusted or stopped if hypocalcemia develops and based on clinical manifestations. Stop any therapy if iPTH goes below two times the upper normal level of the iPTH assay.
   - 5e. In patients with stage 5D-CKD and SHPT, who fail to respond to therapy, surgical parathyroidectomy is suggested.
6. Other pharmacological therapies:
   - 6a. In patients with stage 1–2 CKD with osteoporosis or high fracture risk, manage as non-CKD patients.
   - 6b. In patients with stage 3 CKD and normal PTH with osteoporosis or high fracture risk, manage as non-CKD patients.

6c. In patients with stage 3 CKD and CKD-MBD with low bone mineral density or fragility fractures, consider a bone biopsy and customize therapy based on magnitude and reversibility of CKD-MBD.
6d. In patients with stage 4–5D CKD and CKD-MBD with low bone mineral density or fragility fractures, a bone biopsy is suggested prior to initiating therapy.

8.8.5 Managing Acid-Base and Electrolyte Disturbances

Metabolic acidosis, mostly normal anion-gap and occasionally high-anion-gap in more advanced stage 4–5 CKD or uremic ESKD, complicate CKD in its more advanced stages (usually at an eGFR<25).

Metabolic Acidosis is due to:

1. A decreased nephron mass and thus an impaired ability to excrete a net daily dietary intake of an acid load estimated at 1 mEq per kg,
2. Decreased total ammoniagenesis and ammonia excretion (required as one of the buffers of the excreted acid load) despite an adaptive increase in ammonia production by each of functional renal tubules, and
3. Decreased phosphorus excretion which limits the extent of tubular intra-luminal acid titration.

Adaptive mechanisms also result in the upregulation of aldosterone dependent proton excretion via type-A intercalated cells in the collecting duct. The resultant adaptive mechanisms enhancing ammonia production and aldosterone activity, among others, (a) enhance CKD progression; furthermore, metabolic acidosis is thought to (b) enhance protein catabolism in muscles as well as inhibit albumin synthesis and thus promoting muscle wasting and protein energy wasting and malnutrition, (c) worsen bone disease, (d) promote inflammation (the increased ammoniagenesis in remaining nephrons activates complement system), and (e) increase mortality.

Current recommendations for management of metabolic acidosis in ND-CKD are to initiate oral alkali therapy (e.g oral sodium bicarbonate) to correct the metabolic acidosis to a serum bicarbonate level of 22–24 mEq/L and to endeavor not to overcorrect due to potential adverse CV outcomes. In patients on dialysis, the dialysate bicarbonate is adjusted by the primary nephrologist to correct the metabolic acidosis [226]; and similarly overcorrection and ensuing metabolic alkalosis must be avoided as it accentuates the arrhythmogenic effects of hypokalemia.

8.8.6 Management of Protein Energy Wasting (PEW)/Protein Energy Malnutrition (PEM)

PEW/PEM is a risk factor for mortality and morbidity in stage 3–5D CKD patients.

The K/DOQI recommends assessment of protein and caloric intake in all patients with stage 3–5D CKD. There is no one biochemical marker to quantitate PEW/PEM; surrogates for nutritional status include albumin or prealbumin which serve as biomarkers of visceral protein, whereas anthropometric measurements (e.g. edema-free weight and BMI, waist circumference, waist/hip ratio, % body fat, skin fold thickness) and creatinine production rates serve as biomarkers of somatic/muscle proteins. Other methods to evaluate protein intake include normalized protein nitrogen appearance (nPNA), a subjective global assessment (SGA includes appetite, GI symptoms, food intake, physician's assessment) or food diaries.

PEW is the end of result of multiple pathophysiological processes:

1. Decreased daily caloric intake and dietary protein intake due to CKD clinical manifestations such as poor appetite, nausea or vomiting,
2. Increased branched amino acid catabolism in muscles and inhibition of albumin synthesis due to metabolic acidosis,
3. Diminished visceral protein anabolism due to acute or chronic inflammation.

Dietary protein restriction in patients with ND-CKD is hypothesized to slow down the progression of CKD, but the evidence in the literature is controversial, not always reproducible or uniform. However, protein restriction to 0.8 g/kg per day of healthy body weight (not safe to go below 0.6 g/kg per day) with the addition of daily urinary protein losses is a reasonable and safe recommendation as it would serve not to counter the effects of anti-proteinuric therapy as well as reduce risks of hyperphosphatemia, metabolic acidosis, and azotemia [227–229]. Other goals to minimize PEW/PEM include maintaining serum bicarbonate level of 22–24 mEq/L and targeting an albumin goal above 4 g/dL.

In dialysis patients, protein energy wasting is a risk factor of mortality and a high-protein diet of 1.4 g/kg per day is recommended and often patients may be prescribed oral protein supplements.

8.8.7 Chronic Inflammation

CKD, irrespective of the specific underlying etiology, is invariably associated with a reduction in functional renal

mass and secondary adaptive glomerular hyperfiltration; persistent hyperfiltration and increased intraglomerular capillary pressure promote immune-activation and an inflammatory state, eventually leading to injury and damage in all the kidney compartments, namely, glomerular, vascular endothelial, and tubulointerstitial. Similarly, glomerular podocyte injury and the resultant micro- or macro-albuminuria results in a pro-inflammatory state and tubulointerstitial disease [230, 231].

Chronic inflammation is a risk factor for cardiovascular mortality in patients with CKD. Inflammation is multifactorial:

1. CKD patients have altered gut microbiota (intestinal dysbiosis) and intestinal inflammation with significant disruptions in the functional integrity of the intestinal epithelial barrier, resulting in a "leaky gut" and translocation of bacterial DNA and endotoxins into the systemic circulation. Blood endotoxin levels correlate with severity of CKD and in stage 5D-CKD, said levels predict the severity of inflammation and correlate with atherosclerosis risk. To compound this problem further, dietary restrictions imposed on CKD patients, especially low potassium and low phosphorus, dictate a low plant fiber diet which also result in a secondary change in the gut microbiome. Epidemiological studies suggest that a high-fiber diet promotes the growth of endosymbiotic bacteria, thus preventing gram-negative bacterial overgrowth and the production of endotoxins and gut-derived uremic toxins, and thereby minimizing these triggers of systemic inflammation. Similarly, some observational studies suggest a beneficial role of prebiotics (ingested non-digestible compounds which enhance bacterial growth and activity, e.g. chicory), and probiotics (ingested live organisms, e.g. treated yogurts) [232–234].
2. CKD patients with DM must have regular foot exams to detect any diabetic foot ulcers, which are a significant source of inflammation.
3. Patients with ESKD on RRT have multiple potential sources of inflammation such as presence of dialysis catheters, exposure of blood to dialysis membranes and tubings in HD, exposure of peritoneal cavity to peritoneal dialysate in PD.

There are currently no evidence-based interventions from large clinical trials to stop, decrease or reverse inflammation and CVD risk in patients with CKD. However, it is recommended that a high plant-fiber diet (Dietary Reference Intakes advises 14 g dietary fiber per 1000 kcal per day) be used to restore a more favorable gut microbiota. Furthermore, the use of biocompatible dialysis membranes and PD solutions may also decrease the burden of inflammation.

8.8.8 Dietary Modifications

Patients with CKD are advised to follow the following dietary restrictions, which may also help minimize risk of CVD:

1. Restrict daily sodium intake to 2 grams (or 5 grams of sodium chloride) daily. Unfortunately, this may be a challenge for some in the present time especially that most pre-packaged processed foods are usually high in salt. High salt intake is associated with increased oxidative, which may contribute to CKD and CVD, and a more expanded ECF volume and higher BP thus interfering with effectiveness of BP lowering medications.
2. A protein restriction to 0.6–0.8 g/kg per day of healthy body weight (plus daily urinary protein losses) may help slow down progression of CKD especially in patients with DM, reducing eGFR decline by 0.53 mL/min per annum [235], while preventing PEW/PEM. A high animal-protein diet has been associated with glomerular hyperfiltration [236] as well as worsening metabolic acidosis and is thus not recommended in patients with CKD. In contrast, increasing plant-protein intake does not increase glomerular filtration, does not increase daily acid load, increases daily fiber intake which in turn may decrease inflammation [234].
3. A high fiber diet is recommended for patient with CKD with special attention to potassium and phosphorus imbalances, examples include fruits and vegetables, whole grains and legumes. A high-fiber diet (16–17 grams daily) in elderly Swedish subjects was associated with slower CKD progression assessed by eGFR (cystatin C), less inflammation reflected by CRP and IL6 levels, lower cancer-mortality, and better overall survival in patients with stage 3–5D CKD after a median followup of 10 years [237].

8.8.9 Constant Monitoring for Prescription and Non-Prescription Medications

Patients with CKD and or CVD frequently have a significant pill burden; in fact, patients with ESKD on HD have a median daily pill burden of 19 with 25% of the patients taking more than 25 pills a day [238]. This triggers concerns over medication or dosing errors (e.g. not adjusting dose to eGFR), use of contraindicated agents, drug-drug interactions, risk of adverse reactions, and overall safety. Thus it is

essential that PCPs, nephrologists and other specialists work closely together to simplify dosing regimens (avoid more than twice daily dosing whenever possible) and to ensure safety of medication choice, dosing as well as the whole prescription regimen.

For example, in a cohort of 267 patients with stage 3–5 CKD from the "Safe Kidney Care study", 69.3% of participants had an adverse event, with hypoglycemia being the highest patient-reported adverse event followed by severe dizziness or falls, and hyperkalemia being the highest laboratory-confirmed adverse event [239]. Thus, special care must be offered to choosing and dosing oral hypoglycemics in CKD patients.

Slowing down the progression of CKD and thus avoiding an additional CVD burden risk, requires constant diligence to monitor the intake of potential nephrotoxic medications or herbs. Analgesics, especially non-steroidal anti-inflammatory drugs top the list of the undesirables; high-dose acetaminophen should also be avoided. Alternative medicines and supplements, to this date, are not FDA regulated, and as many as one third been shown to be contaminated with heavy metals at the production site [240]; in addition, the safety of many has not been studied in clinical trials and some are known to be harmful or nephrotoxic. The NKF published a list of 37 harmful herbs that must be avoided in patients with CKD, this list can be accessed at the NKF website [241].

Illicit drug use has been associated with increased CKD as well as CVD risk [242]. For example, cocaine and meth-amphetamines have been associated with hypertensive and ischemic damage resulting in ESKD as well as cardiomyopathy; adulterated cocaine has also been associated with ANCA-vasculitis.

8.8.10 Evidence for Specific CV Conditions

8.8.10.1 Sudden Cardiac Death

As mentioned earlier, sudden cardiac death accounts for 37% of mortality seen in patients with ESKD on HD. A meta-analysis of seven RCTs (2867 patients) evaluated the benefits of primary prevention implantable cardioverter-defibrillator (ICD) in CKD and found that the survival benefit attributed to ICDs is GFR dependent and retained its statistical significance for a GFR ≥60 mL/min/1.73 m^2 but not lower [243].

8.8.10.2 Percutaneous Coronary Interventions

In patients with an eGFR <60 and when indicated, a meta-analysis of 26 clinical trials with 66,840 patients has shown a survival benefit and lower complication rate (repeat revascularization, myocardial infarction) when using drug-eluting stents when compared to bare-metal stents [244]. The lower restenosis rate with drug-eluting stents was reproduced by another randomized clinical trials in CKD patients [245].

8.8.10.3 Atrial Fibrillation

Atrial fibrillation is associated with an increased risk for all-cause mortality, cardiovascular mortality, stroke namely thromboembolic stroke (but not hemorrhagic stroke), ischemic heart disease, HF, PAD, sudden cardiac death, and CKD [246].

In turn, CKD is associated with a higher risk of non-valvular AF and stroke as well as a higher risk of bleeding.

In patients with ND-CKD, anticoagulation for high risk ($CHADS_1$) non-valvular AF decreases risk of ischemic strokes and all-cause as well as cardiovascular mortality without a significant rise in major bleeding [247–249].

However, the debate of the risk-benefit ratio with the use of anticoagulation for the treatment of high-risk ESKD dialysis patients with non-valvular AF is ongoing. For example, a 2016 meta-analyses reported a significant rise in the risk of major bleeding and no benefit in stroke prevention with warfarin therapy in this patient population [247], while other studies report a benefit with lower thromboembolic risk. Thus, the decision for or against anticoagulation therapy in dialysis patients must be customized to each patient based on a thorough risk-benefit analysis.

8.8.10.4 Cardiorenal Syndromes

The 2013 "American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) Guideline for the Management of HF" recommends that all patients with HF have an initial as well as serial monitoring of kidney function [250]; this reflects the fact that neither CKD nor worsening kidney function are uncommon in HF, and both carry a poorer prognosis. However, whereas albuminuria and eGFR are both useful at quantitating risk in HD, eGFR alone should be used to guide HF therapy at this time and until such evidence emerges for the role of other CKD biomarkers as far as therapy and prognosis [251].

The main challenge in types 1 and 2 cardiorenal syndromes is to achieve the optimal balance between successive diuresis and the maximal benefit of RAAS inhibition to avoid the fluctuation from one extreme and another, namely between acuter decompensated heart failure on the one hand and AKI due to excessive diuresis and effective arterial volume depletion on the other. Furthermore, worsening kidney function may predispose to hyperkalemia and deprive patients with symptomatic HF and reduced LVEF from the survival benefits associated with dual aldosterone receptor antagonist therapy and ACEi therapy.

A meta-analysis evaluated the impact of worsening kidney function (WRF) after initiation of RAAS inhibition in patients with HF and left ventricular systolic dysfunction, and included five clinical trials (SOLVD – Studies of Left Ventricular

Dysfunction, SAVE Survival and Ventricular Enlargement Trial, RALES – the Randomized Aldactone Evaluation Study, Val-HeFT – Valsartan Heart Failure Trial, and EPHESUS – Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) and showed a survival benefit with RAAS inhibition irrespective of whether the patients experienced WRF (Relative Risk RR 0.72, $P < 0.001$) or not (RR 0.91, $P = 0.04$). More patients in the RAAS treatment group developed WRF and WRF was a predictor of increased mortality (RR 1.22, $P = 0.0003$) when compared to the RAAS treatment group with no WRF. However, when the mortality rates in the RAAS treatment group with WRF were compared to the placebo group with WRF, RAAS inhibition was associated with a reduction in mortality; the magnitude of this protective effect was greatest in patients in the treatment subgroup with WRF [119].

8.9 Summary and Conclusions

CKD is associated with increased risk for CVD. Patients with CKD require a specialized focus on multiple clinical parameters that may lead to the progression of CKD, but also need global cardiovascular risk reduction efforts. Estimation of GFR provides a better measure of renal function compared to the serum creatinine, and better informs clinicians of the need for needed intervention and appropriate targets for therapy. Earlier treatment of CKD may slow progression and optimize treatment for renal replacement therapy.

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Part II

Coronary Artery Disease

Evaluation of Chest Pain and Myocardial Ischemia

9

Thorsten M. Leucker, Steven R. Jones, and Seth S. Martin

9.1 Introduction

A 63-year-old man with a history of type 2 diabetes mellitus, dyslipidemia, hypertension, former tobacco abuse, and a family history that is positive for coronary artery disease (CAD) in his brother who underwent coronary artery bypass grafting at age 50 presents to the outpatient center for routine evaluation. He reports exertional retrosternal fullness of gradual onset while mowing his lawn. Associated symptoms are dyspnea and diaphoresis. His symptoms usually resolve within 5 min of resting and are reproducible with similar degree of exertion. He denies prolonged symptoms, rest or nocturnal chest pain. The patient further reports that he first noticed these symptoms last fall and that he has not noticed progression or worsening of his symptoms. His medical regimen at the time of presentation consists of aspirin, metformin, atorvastatin, glyburide, and metoprolol.

When presented with a patient like this with significant CAD risk factors and a typical presentation of anginal chest pain, we need to address several points: (1) What is the patient's diagnosis? (2) What is the prognosis? (3) What further testing will help answer these questions? Following a hierarchical model for CAD risk assessment, we want to start with a thorough clinical evaluation to get a better sense of the patient's global risk for CAD, including history, physical exam, and electrocardiogram (ECG) followed by further testing. The second step of assessing a patient as described above includes some form of stress testing to get a functional assessment of his likely underlying CAD, and finally based on the results from noninvasive testing, we want to assess his coronary anatomy. The following chapter will discuss the approach to patients with chest pain in the presence or absence of established CAD and provide a framework for evaluation, testing, diagnosis, prognosis, and further management.

T. M. Leucker · S. R. Jones · S. S. Martin (✉)
Department of Medicine, Division of Cardiology, Johns Hopkins Hospital, Baltimore, MD, USA
e-mail: smart100@jhmi.edu

9.2 General Considerations

Patients who present with chest pain are a true diagnostic challenge, given the broadness of possible etiologies. The initial goal should be ruling in an acute coronary syndrome (ACS) in a timely manner, as early intervention in patients with ACS leads to better outcomes. Conversely, for patients without an ACS, it is important that time and resources not be spent pursuing the diagnosis of ACS. When evaluating such a patient in the inpatient or outpatient setting, a history and focused physical exam in conjunction with an ECG are valuable tools for the physician to form and narrow down an extensive list of possible differential diagnoses (Table 9.1).

Since "time is myocardium," making quick triage decisions is of the essence. An ECG should be obtained within 10 min of presentation to evaluate for electrical evidence of acute ischemia. Advanced cardiac life support (ACLS) algorithms should be utilized if a critical patient condition dictates. Once acute life-threatening conditions are excluded, a more detailed evaluation for cardiac and non-cardiac etiologies of the chest pain can begin. Ultimately, depending on the initial clinical evaluation, inclusion of laboratory markers of cardiac injury and modern imaging techniques may be warranted to exclude a cardiac source for chest pain.

9.3 Pre-presentation Self-Assessment

In the day and age of universal Internet access, many patients are using search engines to gather initial information about the severity and potential underlying pathophysiology of their symptoms. A sparse body of literature has tried to evaluate if patients searching online receive sufficient information on

P. P. Toth, C. P. Cannon (eds.), *Comprehensive Cardiovascular Medicine in the Primary Care Setting*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-319-97622-8_9

Table 9.1 Differential diagnosis for patients presenting with acute chest pain based on organ system

Cardiovascular	*Chest wall*	*Gastrointestinal*
Ischemic cardiovascular	Sternoclavivular arthritis	Esophageal
Stable angina	Costochondritis	Rupture
Unstable angina	Trauma/Strain	Spasm
Acute myocardial infarction	Neuropathic pain	Reflux
	Fibrositis	Esophagitis
Non-ischemic cardivascular	Cervical disc disease	
Aortic dissection		Pacreatitis
Pericarditis	*Psychiatric*	
Myocarditis	Anxiety disorders	Biliary
	Panic disorder	Colic
Pulmonary	Hyperventilation	Cholecystitis
Pulmonary embolus		Cholangitis
Tension pneumothorax	Somatoform disorders	Choledocholithiasis
Pneumonia	Thought disorders (e.g. delusions)	
Pleuritis		Peptic ulcer disease
Tracheobronchitis	Affective disorders	Nonperforating
	Depression	Perforating

After initial evaluation of a patient with chest pain, forming a differential diagnosis based on available data is crucial to identify and treat potential life-threatening conditions

when to seek urgent professional medical help [1]. The majority of authors appear to agree that search engines have lacked much of the information needed to make decisions about whether a symptom needs urgent attention. The described barriers were lack of complete critical symptom indicators, inconvenient placement of critical information on the web pages, and distracting advertisements.

Addressing these barriers, Google launched its new health feature "Symptom Search" in June of 2016. The Internet search engine has worked with physicians at academic medical centers to build a Symptom Search database. Patients can enter symptoms into the search feature and receive digital cards to swipe through, briefly describing common health problems related to the search term. The American College of Cardiology has partnered with Google to provide guideline-based information to patients. A Google search may very well be the first place patients in the twenty-first century turn for chest pain evaluation prior to seeking medical attention.

9.4 Patient Evaluation

When evaluating patients with chest pain, forming an initial list of differential diagnoses (see Table 9.1) and utilizing models for pretest probability to assess the likelihood of myocardial ischemia are of central importance. Forrester et al. proposed a model based on age, sex, and symptoms, to classify patients into four categories (high, intermediate, low, and very low) [2]. The ACC/AHA guidelines further recommend including risk factors to increase the specificity of having cardiac chest pain [3].

9.4.1 History

CAD risk factors can be broadly divided into two categories: modifiable and non-modifiable. Modifiable risk factors include smoking, hypertension, dyslipidemia, established CAD and non-coronary atherosclerotic arterial disease, diabetes mellitus, chronic kidney disease, obesity, physical inactivity, and stress. Non-modifiable risk factors include age, sex, and family history. The five leading modifiable CAD risk factors (dyslipidemia, diabetes, hypertension, obesity, and smoking) are estimated to be responsible for more than half of all cardiovascular mortality [4]. Combinations of major CAD risk factors place patients at a higher relative and absolute risk of CAD and all-cause mortality [5]. Some patients without established CAD have a risk of subsequent cardiovascular events that is equivalent to that of patients with established CAD. Examples of such high-risk patients include some patients with non-coronary atherosclerotic arterial disease, diabetes mellitus, and chronic kidney disease. All patients with a CAD risk equivalent should be managed as aggressively as those with prior CAD.

If the patient's likelihood of ACS is very low (<1–2%), additional testing for ACS is not likely to be beneficial [6]. All other patients with possible (but not definite) ACS should be further risk stratified by obtaining serum troponin. These patients should be monitored with continuous ECG rhythm monitoring. Any change in clinical condition (e.g., patient complaints or changes in vital signs) should prompt reassessment. Serial ECGs should be performed on patients with continuous pain or changes in symptoms to detect dynamic changes. Patients felt to have definite ACS or deemed high risk should be managed accordingly (see Chap. 11 and Chap. 12).

9.4.2 Typical and Atypical Anginal Symptoms

Symptoms can be misleading, and purely relying on the patient's history is insufficient when triaging a patient with chest pain, as summarized by Swap et al. [7]. However, classical anginal pain, as illustrated in the case history above, is described as a squeezing/tightness ("like a clenched fist") or pressure/heaviness ("like an elephant on the chest"). If stable, the patient may have predictable pain with exertion and relief with rest. However, sudden episodes may occur, and certain chest pain characteristics are associated with an

increased likelihood of ACS or acute myocardial infarction. Namely, chest pain that radiates to one shoulder or both shoulders or arms or is precipitated by exertion was found to have the highest likelihood ratios. A thorough history should include a detailed description of the chest pain characteristics in terms of quality, location and radiation, temporal elements, provocation, palliation, severity, and associated symptoms (cardiac, pulmonary, musculoskeletal, gastrointestinal, psychiatric, and systemic).

A few characteristics of cardiac and non-cardiac chest pain are as follows. Pleuritic chest pain is often described as sharp and "stabbing," which is worse with breathing and coughing. Pain related to pericarditis has a similar sharp characteristic, however, is often described as positional, i.e., sitting up and leaning forward tends to ease the pain, while lying down and breathing worsens it. Patients with aortic dissection classically have sudden, severe chest pain that is tearing in quality and radiates through to the back. Chest pain that is related to gastroesophageal reflux can present especially in the postprandial state, and some patients describe an associated bitter sensation in their mouth related to the reflux. Patients with musculoskeletal-related chest pain often describe reproducibility with chest wall palpation and passive extension, flexion, and rotation of the cervical and thoracic spine. In contrast, patients with psychiatric-related chest pain tend to have palpitations occurring in the setting of an anxiety attack. Keeping extra-cardiac sources for chest pain in mind while having a high index of suspicion for cardiac-related chest pain, especially in the right patient (see risk factor discussion above), is key in encountering the challenging chief compliant of chest pain.

9.4.3 Physical Exam

Physical exam findings of patients with ACS can be difficult to distinguish from non-cardiac chest pain. However, in some instances a physical exam finding can lead us to a specific non-cardiac diagnosis. Patients with a life-threatening cause of their chest pain may appear anxious and may be tachycardic, dyspneic, and diaphoretic. The presence of rales and a S3 gallop indicate left ventricular dysfunction and left-sided heart failure, which is often seen in patients with ACS. Cool or cold extremities, an ashen or cyanotic appearance, and altered mental status are particularly ominous signs indicating low output and cardiogenic shock. Signs of right heart failure include jugular venous distention, hepatojugular reflux, and peripheral edema which can be seen in ACS involving the right coronary artery with extension to the right ventricle or in patients with a pulmonary embolism. Patients evaluated on the tail end of a myocardial infarction may show physical exam findings of mechanical complications, such as a new systolic murmur, which may signify papillary muscle dysfunction or a ventricular septal defect. Pericardial friction rubs can be related to pericarditis. Exam findings in a patient with aortic dissection may include discrepancies in pulse or blood pressure, murmur of aortic insufficiency, signs of shock or cardiac tamponade (low arterial pressure, distended neck veins and distant, muffled heart sounds), acute heart failure, and cerebrovascular accident. Chest pain that is associated with acute respiratory distress, focal wheezing, or asymmetric extremity swelling raises concern for pulmonary embolus.

9.4.4 Risk Scores

As reported by Fanaroff et al. [7], utilizing a combination of history, ECG, age, risk factors, troponin (HEART), and thrombolysis in myocardial infarction (TIMI) risk scores performs well in diagnosing ACS once troponin results are available. The TIMI score (Table 9.2) was initially derived and validated in patients enrolled in clinical trials with ACS, but has since been externally validated [8].

For any patient in whom the diagnosis of ACS is being entertained, cardiac biomarkers should be measured. The common practice is to obtain two sets of cardiac markers separated by either 6 h or 8 h, although one set of negative biomarkers may be adequate if there is more than 8–12 h from onset of symptoms. After the return of the second

Table 9.2 TIMI risk score

Historical	*Points*	Risk of cardiac events (%) by 14 days in TIMI 11B[a]		
Age ≥65 years?	1	Risk score	Death or MI	Death, MI or urgent revasc
≥ 3 risk factors for CAD?	1	0 or 1	3	5
Known CAD (stenosis ≥50%)?	1	2	3	8
Aspirin use in past 7 days?	1	3	5	13
Presentation		4	7	20
Severe angina (≥ 2 episodes w/in 24 h)?	1	5	12	26
ST changes on ECG ≥0.5 mm?	1	6 or 7	19	41
Positive cardiac markers?	1			
Risk score = Total points (0–7)				

[a]Entry criteria: UA/NSTEMI defined as ischemic pain at rest within 24 h, with evidence of CAD (ST segment deviation or positivecardiac marker)

The TIMI risk score was initially developed as a simple prognostication scheme that categorizes a patient's risk of death and ischemic events and provides a basis for therapeutic decision-making. The score was initially validated in patients enrolled in clinical trials with acute coronary syndrome (ACS), but has since been validated in patients suspected to have ACS

troponin, tools such as the above-described TIMI and HEART risk scores in conjunction with established care pathways can guide decisions regarding further testing and disposition, as well as interim medical therapies. In addition, these tools can predict the risk of adverse short-term outcomes (30-day risk of death, nonfatal myocardial infarction, or recurrent ischemia).

9.4.5 Role of Biomarkers

With the wide introduction of high-sensitivity troponin assays on the horizon, much of the recent focus within the published literature has been on the use of these assays in the identification of low-risk patients suitable for early discharge with outpatient follow-up. High-sensitivity troponin assays have a coefficient of variation of 10% or less at the 99th percentile (the upper limit of the reference population) and are able to detect cardiac troponin in at least 50% of the reference population. It is therefore of critical importance to have a clear understanding of the cutoff values to accurately identify low-risk patients for early discharge. Such rapid rule-out strategies may serve to substantially reduce hospital admissions [9]. However, before these abbreviated biomarker strategies are widely implemented and adopted by clinical practice guidelines, they should undergo further prospective validation and should include the diagnostic accuracy for short-term (30 day) ACS events, including the need for revascularization.

9.4.6 Differential Diagnosis

Throughout the evaluation process, it is of critical importance, even if initial suspicion is low for cardiac-related chest pain, to keep other potential life-threatening chest pain etiologies high on your differential list. Pulmonary embolism, pneumothorax, and aortic dissection are among these. Utilizing risk scores for the clinical assessment such as the Wells criteria for pulmonary embolism can be helpful. However, ultimately chest imaging is an important modality if suspicion is high. Helical chest computed tomography (CT) is a powerful technology with an established role in the evaluation of chest pain and myocardial ischemia. Current-generation CT with contrast can exclude the diagnosis of aortic dissection with a sensitivity approaching 100% [10] and exclude pulmonary embolism with a sensitivity of over 90% [11].

9.4.7 Atypical Presentations

Besides considering potential differential diagnoses for chest pain, it is of equal importance to keep a high level of clinical suspicion for atypical presentations of angina. Especially women and diabetic patients are more likely to present with atypical symptoms [12]. The following case study illustrates this concept.

Imagine you are evaluating a 65-year-old woman in the outpatient center with a past medical history significant for morbid obesity, uncontrolled type 2 diabetes mellitus, hypertension, dyslipidemia, 50 pack-year smoking history, and a significant family history for premature CAD in her father and brother. She has been complaining of back, jaw, and neck pain with physical activity which is relieved by rest. Associated symptoms are nausea, loss of appetite, dyspnea, palpitations, indigestion, dizziness, fatigue, and near syncope.

Although, the patient does not describe typical chest pain symptoms, the presentation should raise a high suspicion for underlying significant CAD. ECG, chest x-ray, and basic laboratory evaluation, including troponin, are within normal limits. A subsequent exercise stress ECG reproduced her symptoms at a moderate workload, and the ECG showed 3 mm horizontal ST-segment depression in the infero-lateral leads. A subsequent coronary angiography revealed a high-grade lesion in her right coronary artery as the explanation for her presenting symptoms.

Although CAD in women presents most often as stable angina rather than an acute ST-segment elevation myocardial infarction, outcomes for ACS (post-revascularization complications and inhospital mortality) are worse compared to men [13]. One explanation for these sex differences in outcomes is a delay in treatment and less aggressive invasive and pharmacologic therapies [14], which are potentially related to atypical presentations.

9.5 Noninvasive Stress Testing

If a patient has successfully passed the rule-out portion (i.e., no recurrent ischemic pain, no ECG changes, negative cardiac biomarkers), but still is judged as having an intermediate pretest probability of CAD based on the established risk scores and/or clinical judgment, then subsequent noninvasive provocative testing should be entertained for further risk stratification. In addition, patients in whom there remains a high suspicion of an ACS, despite two normal troponin values, may warrant further testing. The timing of the noninvasive testing is a matter of ongoing debate; however, in general such testing is performed within 72 h of presentation [15]. Choosing the appropriate test modality depends on patient characteristics and comorbidities. The following paragraphs will describe the traditional exercise and pharmacologic stress testing modalities, in addition to, presenting newer and upcoming rule-out imaging modalities (e.g., coronary computed tomographic angiography [CCTA]).

9.5.1 Choosing the Appropriate Stress Test

In general, if the patient is able to exercise, then exercise stress testing is the preferred stress modality since it provides additional information about the patient's functional capacity. However, for women, treadmill ECG testing has a higher false-positive rate (38–67% compared with 7–44% in men) but a lower false-negative rate [16]. Therefore, especially in women, exercise capacity, percentage of age-predicted exercise capacity, chronotropic response, heart rate recovery, blood pressure response, and the Duke treadmill score [DTS = exercise time−(5 × max ST)−(4 × angina index)] can all be used to enhance the diagnostic and prognostic value of exercise ECG [17]. Patients who fit the above risk groups and have an interpretable ECG for ischemic changes can undergo exercise ECG testing. Previous studies have shown that patients with a negative exercise ECG and with a low-risk assignment had 1-year cardiac mortality in the range of less than 0.5% [18]. Patients who are unable to exercise can undergo pharmacologic stress testing combined with imaging, e.g., vasodilator stress radionuclide myocardial perfusion imaging (rMPI) or dobutamine stress echocardiography (DST). Finally, patients who have an uninterpretable resting ECG for ischemic changes (i.e., preexcitation, >1 mm rest ST depression, left bundle branch block, ventricular paced rhythm, left ventricular hypertrophy with strain pattern, or digoxin therapy) should be evaluated with exercise stress testing in combination with echo or nuclear imaging (e.g., DST or rMPI).

The addition of computed tomographic (CT) attenuation correction to rMPI improves the relative uniformity of radionuclide tracer distribution and thereby improves specificity [19]. Furthermore, CT images provide information of coronary artery calcification and allow calculation of the coronary artery calcium score (CAC; see below for further details). An up-and-coming advancement to rMPI is stress-first imaging with attenuation correction. If the stress images are normal, the resting imaging is not required, and the study can be completed in a shorter time frame and with lower radiation exposure. A pretest scoring tool has been created and validated to accurately identify patients who can successfully undergo a stress-first imaging protocol [20].

9.5.2 High-Risk Features on Stress Testing

The major purpose of stress testing with or without imaging is to ultimately identify patients who may merit coronary angiography and consideration for revascularization to improve their prognosis. Certain high-risk features on noninvasive stress testing have been proposed by the AHA/ACC on exercise ECG: (1) exercise-induced ventricular arrhythmias, (2) exercise-induced ST elevations, (3) ST depression at low workload or persisting into recovery, and (4) hypotensive blood pressure response (drop in exercise blood pressure vs. rest blood pressure or peak systolic blood pressure <120 mmHg). In addition, high-risk features on imaging are defined as follows: (1) severe resting left ventricular dysfunction (LVEF < 35%) or decrease in LVEF to <35% with exercise; (2) high-risk Duke treadmill score (score ≤ −11); (3) stress-induced large perfusion defect (particularly if anterior); (4) stress-induced multiple perfusion defects of moderate size; (5) large, fixed perfusion defect with LV dilation or increased lung uptake; (6) stress-induced moderate perfusion defect with LV dilation or increased lung uptake; (7) echocardiographic wall motion abnormality (involving greater than two segments) developing at a low dose of dobutamine (≤10 mg/kg/min) or at a low heart rate (<120 beats/min); and (8) stress echocardiographic evidence of extensive ischemia [21]. Patients exhibiting any of the above high-risk features for ischemic heart disease should be urgently followed up with coronary angiography to assess their coronary anatomy.

Choosing the right stress testing modality can often be a challenge. Basic principles to consider are as follows: (1) symptom-limited exercise is generally the preferred form of stress for patients who can exercise, because it provides the most information concerning symptoms, exercise capacity, and hemodynamic response during exercise. These pieces of information are both diagnostically and prognostically important. Pharmacologic testing is typically performed when a patient is unable to exercise. (2) Exercise ECG should be the initial test for the majority of patients who can exercise adequately, who have an interpretable ECG. (3) Stress testing with imaging should be used if the ECG is uninterpretable or in patients with known coronary stenosis of unclear physiologic significance.

9.6 Coronary Computed Tomographic Angiography

The multicenter ROMICAT II trial evaluated the use of CCTA as an evaluation tool for patients in the ED with suspected ACS versus standard evaluation as outlined above. The results showed that CCTA evaluation decreased the length of stay by 7.6 h ($P < 0.001$) and increased direct ED discharge rates (47% vs. 12%, $P < 0.001$) without an increase in the rate of missed ACS [22]. Other studies have confirmed the strong predictive value of CCTA in excluding risk of major adverse cardiac events (MACE). The radiation exposure of CCTA is comparable to rMPI and slightly higher than stress-first rMPI depending on patient characteristics and the reporting study (exposure relative to naturally occurring annual background radiation exposure for a person living in the United States (~3 mSv): CCTA 1-4, rMPI 3-4, CAC 0.5) [23]. When

selecting rMPI or CCTA as a coronary evaluation tool, clinicians should rule out pregnancy first in women and be more cautious in younger patients who are more susceptible to the potential long-term adverse effects of radiation exposure.

It is well established that among patients presenting to the ED with chest pain, those with no CAC have low cardiac events [22]. Some have proposed that CAC scoring could function as a 'gatekeeper' in low-to-intermediate risk symptomatic patients to further testing with either CCTA or functional imaging [22]. There is an ongoing debate if CAC alone is sufficient to adjudicate chest pain in the ED. However, based on the current ACC/AHA guidelines, this approach is currently not recommended and requires further investigations.

9.7 Patient Disposition

After noninvasive testing, a final disposition can usually be made. Patients with intermediate stress testing or imaging results may benefit from consulting a cardiologist. Many such patients will ultimately be admitted. Patients with positive stress testing or imaging results as well as patients classified as high risk for CAD (see evaluation of patient above) should be evaluated by a cardiologist, admitted to the hospital and ultimately undergo evaluation of their coronary anatomy by coronary angiography. In contrast, if any cardiac source or other life-threatening components of the differential diagnosis have been ruled out, patients can be discharged with a plan for follow-up, ideally within 72 h.

9.8 Conclusion

A conservative estimate by the American Heart Association states that each year roughly 6,200,000 Americans suffer from chest pain symptoms [24]. Physicians in almost any specialty will be confronted with such a patient in their clinical practice at some point. Therefore, it is crucial to develop the clinical skills to quickly assess the severity of a patient's illness and identify life-threatening conditions in a timely manner. Thorough history taking and physical exam as well as attention to the natural history and progression of disease will often reveal the underlying etiology. ECG, laboratory testing, and modern imaging techniques further aid the clinician in forming a diagnosis. In the cases where no immediate diagnosis can be made, life-threatening disease should be excluded by either observation or further diagnostic testing. Arranging for close follow-up is essential. The approach to evaluation and treatment of chest pain, when performed in a systematic but efficient manner (see Fig. 9.1), can safely and positively impact patient outcomes.

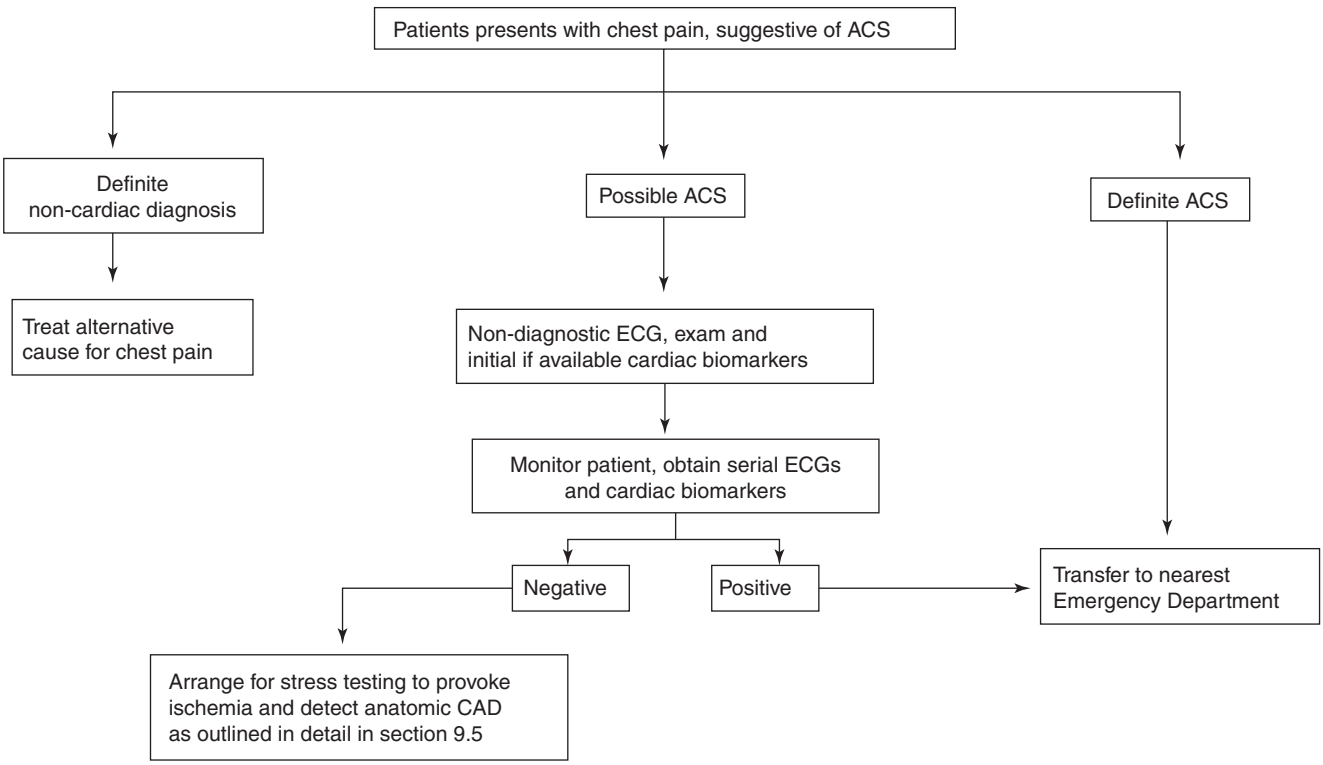

Fig. 9.1 Evaluating a patient with chest pain, suggestive of an acute coronary syndrome

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Myocardial Small Vessel Disease and Endothelial Dysfunction

10

P. Elliott Miller

10.1 Definition and Classification

Whereas CAD is defined as atherosclerosis in the epicardial coronary arteries, CMD is defined as abnormal or impaired blood flow in the coronary microcirculation. There are four previously proposed categories of CMD (Table 10.1) [2] as well as four physiologic categories related to responses of coronary blood flow to acetylcholine (endothelial-dependent mechanism) and adenosine (endothelial-independent mechanism) [8]. While CMD can occur in individuals with obstructive coronary disease, this chapter will specifically review CMD in those with nonobstructive CAD.

10.2 Prevalence

The true prevalence of CMD is unclear due to various definitions and because evaluation of the coronary microvascular is not routine. However, it is likely higher than reported. In the United States alone, the prevalence is believed to be at 3–4 million individuals [3]. Furthermore, CMD appears to be more prevalent in women and by some has been termed "female pattern ischemic heart disease" [9]. The cause for the higher prevalence in women is unclear, but is likely multifactorial given differences in hormones, genetics, and referral bias. In a group 917 women from the Women's Ischemia Syndrome Evaluation (WISE) cohort, researchers have found CMD in approximately 50% of women with chest pain and without obstructive CAD [10]. In a cohort of 405 men and 813 women with suspected CAD but with negative stress testing, Sara et al. found that two-thirds (predominantly women) of their cohort showed signs of CMD on physiologic testing of coronary blood flow.

Table 10.1 Classification of coronary microvascular dysfunction

Type 1	CMD with nonobstructive coronary artery disease
Type 2	CMD with myocardial diseases
Type 3	CMD with obstructive coronary artery disease
Type 4	Iatrogenic CMD

P. E. Miller
Division of Cardiovascular Medicine, Yale University School of Medicine, New Haven, CT, USA
e-mail: elliottmiller@jhmi.edu

10.3 Risk Factors

Traditional risk factors for epicardial atherosclerosis, including diabetes, hypertension, cigarette smoking, dyslipidemia, obesity, and increasing age, are also considered risk factors for CMD [2, 3]. However, evidence from the WISE cohort suggests that traditional risk factors, with the exception of age, do not completely account for the incidence of CMD [11], which suggests residual and unidentified causes. One proposed mechanism is chronic inflammation, which has been shown to correlate with atherosclerosis and CMD in rheumatologic diseases such as systemic lupus erythematosus [12, 13]. In a cohort of individuals with CMD but without traditional CVD risk factors, participants with an elevated high-sensitivity C-reactive protein (hs-CRP) (defined as >3 mg/L) had reduced coronary flow reserve (CFR) compared to those without elevated hs-CRP [14].

Just as diabetes has been linked to microvascular disease in the kidneys, eyes, and neurologic system, diabetes and chronic hyperglycemia are associated with both endothelial-independent and endothelial-dependent CMD. Diabetes-related CMD appears to be similar between type 1 and type 2 diabetics, indicating a shared mechanism despite inherent pathophysiologic differences between the two types of diabetes [15]. Dyslipidemia and tobacco smoking have both shown deleterious effects on CFR as well as a concomitant improvement in endothelial function with treatment and cessation, respectively [16–18]. Finally, some have reported a link between endothelial dysfunction and a family history of CAD [19, 20].

P. P. Toth, C. P. Cannon (eds.), *Comprehensive Cardiovascular Medicine in the Primary Care Setting*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-319-97622-8_10

10.4 Pathophysiology

Several pathophysiologic mechanisms have been reported with conflicting results [4], including the presence or absence of smooth muscle hypertrophy [21, 22]. However, no single mechanism entirely explains the microvascular dysfunction in patients with CMD, suggesting several mechanisms likely playing a role at the same time. Of the reported mechanisms, the most commonly accepted is endothelial-dependent dysfunction resulting in impaired vasodilation to nitric oxide [23, 24]. Recent studies have proposed decreased levels of endothelial progenitor cells, a repair mechanism for coronary endothelium, in those with CMD [25]. Numerous other studies have suggested an endothelial-independent mechanism and impairment in smooth muscle cell relaxation contributing to CMD [24, 26, 27]. Others have reported slow coronary flow secondary to inappropriate constriction in the microvasculature [28]. The end result of these heterogeneous and maladaptive functional abnormalities results in impaired subendocardial perfusion and microvascular angina (MVA).

10.5 Clinical Presentation

Those predominantly affected by CMD, women, frequently present differently than men with ischemic heart disease and, in particular, may not experience chest pain [29], which often leads to delay in seeking medical care [30]. Further, evidence from the WISE cohort indicates that typical vs. atypical angina is not helpful in distinguishing between obstructive and nonobstructive CAD [31]. Once found to have nonobstructive findings on angiography, which can lead to misdiagnosis, patients are often told that the source of their pain is non-cardiac in origin.

Typical angina symptoms are present in roughly 50% of patients with CMD. Classically, CMD takes a prolonged period of time (>15 min) for resolution of chest discomfort and has a poor response to nitrates [32, 33]. Lanza et al. studied the response of nitrates during exercise stress testing in two groups, one with known CAD and the other with CMD. Whereas nitrates improved exercise tolerance and chest discomfort in individuals with CAD, participants with CMD had worsening of their exercise tolerance and lacked improvement in chest discomfort [34]. Patients with CMD undergoing stress testing who develop angina and ST-segment depression often lack echocardiographic wall motion abnormalities [35, 36].

10.6 Diagnosis

In 1910, Sir William Osler described the difficulty of distinguishing non-cardiac chest pain from "true" angina [37]. In the modern era, CMD is still difficult to diagnose, which is perhaps made more difficult by the existence of several chest pain syndromes (e.g., vasospastic or Prinzmetal angina) with normal or nonobstructive coronary arteries. Further, non-cardiac causes of chest pain must be ruled out when nonobstructive CAD is found on angiography [38]. These diagnostic uncertainties often lead to a delay in diagnosis as well as persistent chest pain in many of these patients [39, 40].

Diagnostic strategies for CMD include invasive and non-invasive studies. Through coronary angiography, coronary reactivity testing is the gold standard for diagnosis, and investigated with intracoronary infusion of endothelial-dependent (acetylcholine) and endothelial-independent (adenosine) stimuli [41]. Once these vasoactive agents are instilled, a Doppler flow wire inside the coronaries measures CFR. The risks and benefits of invasive coronary investigation need to be considered thoughtfully. Coronary reactivity testing has been estimated to carry a 0.7–2.4% risk of a non-fatal adverse event [42, 43] and argued by some to include unjustified risk [4]. However, others would disagree and argue the estimated lifetime cost for patients with CMD to be close to $800,000 due to repeated indeterminate exposures to the health-care system [44].

Several noninvasive modalities, including positron emission tomography (PET) [45], cardiac magnetic resonance (CMR) [27, 46], and transthoracic Doppler recording echocardiography (TTE-DR) [47], are available to aid in the diagnosis of CMD. Both PET and CMR are complex, time-consuming, expensive, and not widely available in clinical practice [4]. TTE-DR assesses diastolic coronary blood flow velocity after vasodilation with adenosine and coronary blood flow at rest as a ratio to evaluate coronary microvascular dilator function. CMD is suggested when this ratio is less than 2.0. Notably, only the left anterior descending artery is generally assessed, and mild CMD can be missed [4, 48].

10.7 Management

The mainstay of medical treatment for CMD is beta-blockers (Table 10.2), especially for patients with increased sympathetic activity (i.e., high resting heart rate) [4]. Beta-blockers have been estimated to provide chest pain relief in 19–60% of patients [49]. Of note, therapeutic studies for those with CMD, including with beta-blockers, have been small. In a crossover study of ten patients, atenolol showed less chest pain episodes when compared to amlodipine or nitrates [50]. Similarly, both atenolol (n = 22) and propranolol (n = 16) prevented exercise-induced ST changes when compared with verapamil and placebo [51, 52].

Calcium channel blockers have generally been used as second-line agents or in addition to beta-blockers for those with symptoms that were not well controlled [4]. However, studies have been conflicting, and most likely related to

Table 10.2 Treatment options by category for coronary microvascular dysfunction

Antianginal therapy
Beta-blockers
Calcium channel blockers
Nitrates
Nicorandil
Trimetazidine
Ivabradine
Ranolazine
Microvascular function therapy
Angiotensin-converting enzyme inhibitors
Statins
Metformin
Nitric oxide modulators
Sildenafil
L-arginine
Lifestyle therapy
Smoking cessation
Exercise
Diet (e.g., Mediterranean)
Miscellaneous
Xanthine derivatives (adenosine)
Imipramine
Estrogen
Alpha-blockers
Non-pharmacologic therapy
Spinal cord stimulation
Enhanced external counterpulsation

differences in patient selection and study design [49]. In a group of 26 patients with angina, normal coronary arteries, and abnormal coronary reserve, Cannon et al. found that those receiving calcium channel blockers had less angina and took fewer nitroglycerin tablets compared with placebo [53]. In contrast, Bugiardini et al. found no differences with verapamil compared to propranolol or placebo [52]. Nitrates have similarly been disappointing, but some report improvement in chest pain in roughly 50% of patients [49].

Several drugs, including renin-angiotensin-aldosterone inhibition, statins, and metformin, have targeted microvascular function [54]. Angiotensin II has been shown to stimulate oxidative stress in the endothelium, vascular remodeling, and be a potent vasoconstrictor [54, 55]. Several studies have demonstrated improvement in CFR and ST-segment depression on stress testing with angiotensin-converting enxyme inhibitors (ACE-I), but without additional benefit from aldosterone antagonism such as eplerenone [56–58]. Similarly, statin therapy, through putative pleiotropic and anti-inflammatory effects, has been shown to improve CRF in several studies in those with CMD [59–62]. In a group of 33 nondiabetic women with CMD, women randomized to metformin showed improvement in ST-segment depression on stress testing, Duke score, and chest pain incidence compared with placebo [63].

Two newer antianginals, ranolazine and ivabradine, have shown promise in the treatment of CMD. Mehta et al. found that ranolazine, compared with placebo, decreased anginal episodes and improved quality of life in a group of women with CMD [64]. In a group of 46 patients with persistent CMD symptoms, Villano et al. showed both ranolazine and ivabradine decreased angina compared with placebo. Ranolazine appeared to be superior to ivabradine in this small study of 46 patients and also showed improved time to 1-mm ST-segment depression on stress testing [65].

Non-pharmacologic options for patients with multidrug-"resistant" CMD include spinal cord stimulation (SCS) and enhanced external counterpulsation (EECP). The exact mechanism for improvement in CMD from SCS is unknown. However, SCS is thought to provide improvement in microcirculatory function and perhaps abatement of increased pain perception seen in those with CMD [66–69]. After long-term follow-up with a mean of 36 months, Sgueglia et al. found improvement in angina symptoms, quality of life, and stress test parameters in those receiving SCS [70]. Luo et al. similarly found improvement in angina and CFR in those treated with EECP [71]. While some evidence shows that these treatment options are helpful in those with resistant CMD, it must be noted that they are typically more costly and carry risks of several serious complications.

While beta-blockers are the mainstay of medical therapy, non-pharmacologic lifestyle changes are just as important. Although not studied directly in those with CMD, tobacco cessation has been shown to improve endothelial-dependent dilation [72]. Klonizakis et al. found a Mediterranean diet when combined with regular exercise has also shown endothelial-dependent vasodilation [73]. A low-fat diet with exercise training and exercise training alone has also showed improvement in CFR [74, 75].

10.8 Case Studies

10.8.1 Case 1

A 52-year-old woman visits your office for the third time in the last 2 months. She has a distant history of tobacco smoking as well as hypertension and dyslipidemia. During this time, she has also been to the emergency department twice for chest pain with the first episode resulting in admission to the hospital. She was found to have nonobstructive coronary disease and told the source of her chest pain was likely noncardiogenic. She reports nearly daily chest pain described as substernal, associated with exertion, and relieved with rest over 10–15 min. She denies reflux symptoms, shortness of breath, and wheezing.

She has a pulse of 87 beats/min and a blood pressure of 147/83 mm Hg. Her lungs are clear and cardiovascular exam

unremarkable. An EKG is obtained and unremarkable. Due to the reassuring coronary angiography and negative noncardiac workup, you suspect CMD. The patient would like a more definitive answer for her symptoms, but would prefer not to undergo another invasive procedure. What noninvasive options are available to aid your diagnosis?

Several noninvasive options are available or are being studied, including transthoracic echocardiographic Doppler records (TTE-DR), positron emission tomography, and cardiac magnetic resonance. Given availability and reliability, you order a TTE-DR, which measured the diastolic coronary blood flow in the left anterior descending artery at peak vasodilation and at rest. The ratio returns <2.0 and you make a diagnosis of CMD.

10.8.2 Case 2

A 63-year-old woman with a history of hypertension, type 2 diabetes mellitus, and obesity presents to your office for follow-up of her exertional angina. She was diagnosed with CMD after several episodes of chest pain prompting visits to the emergency department. She was found to have nonobstructive coronary disease and microvascular dysfunction on coronary angiography. Once diagnosed, she was placed on beta-blockers in addition to aspirin, statin, metformin, and titrated to maximum doses. A calcium channel blocker was tried, but the patient self-discontinued the medication due to side effects. Sublingual nitroglycerin does not provide relief of her chest pain.

Her pulse is 62 beats/min and blood pressure 127/82 mm Hg. Her lungs are clear to auscultation, and heart sounds are regular without murmurs. Her EKG shows a normal sinus rhythm with nonspecific T-wave flattening in the precordial leads. While she reports that her anginal events have decreased, she is still experiencing 2–3 episodes weekly. What is the next appropriate step in the management of this patient?

The next best option would be to try ranolazine. She has received maximum doses of beta-blockers and has a well-controlled heart rate and blood pressure. Calcium channel blockers are often considered second line, but this drug class was tried and discontinued by the patient. Ranolazine has been shown to be helpful in chronic stable angina and also for CMD in small studies.

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Unstable Angina and Non-ST Elevation Myocardial Infarction

11

Jeremy Robbins and Eli V. Gelfand

Key Points

- Acute coronary syndromes represent a major public health concern, with over 1.1 million hospitalizations occurring annually in the United States; NSTE-ACS account for the majority of these.
- NSTE-ACS is characterized by anginal chest discomfort accompanied by ischemic electrocardiographic ST-segment abnormalities and/or elevation of cardiac biomarkers.
- The differential diagnosis of NSTE-ACS includes other life-threatening diagnoses, including pulmonary embolism, aortic dissection, tension pneumothorax, esophageal rupture, and cardiac tamponade.
- Rupture of a vulnerable atherosclerotic plaque and subsequent thrombus formation are central to the pathophysiology of acute coronary syndromes.
- Risk stratification for recurrent MI, death, or heart failure is central to decision-making in NSTE-ACS.
- The management of NSTE-ACS includes application of anti-ischemic therapies, antiplatelet therapies, and anticoagulation, as well as selective use of coronary revascularization.
- Secondary prevention includes pharmacologic agents such as aspirin, other antiplatelet agents, beta-blockers, HMG-CoA reductase inhibitors (statins), inhibitors of the renin-angiotensin-aldosterone axis, as well as weight control, smoking cessation, and management of hyperglycemia if present.

11.1 Introduction

Unstable angina (UA) and non-ST elevation myocardial infarction (NSTEMI) represent part of the acute coronary syndrome (ACS) spectrum that also includes ST elevation myocardial infarction (STEMI). Combined, UA and NSTEMI are known as non-ST elevation acute coronary syndrome (NSTE-ACS). Recent estimates suggest that 1.14 million hospitalizations occurred for ACS events in 2010 in the United States, with 813,000 for myocardial infarction (MI) alone [1]. Of those patients with elevated cardiac biomarkers suggestive of MI, at least one-half may be classified as NSTEMI, and its percentage appears to be rising [2, 3] Among the NSTE-ACS, the development of more sensitive cardiac biomarker assays, and in particular cardiac-specific troponin, has led to increased detection of NSTEMI [4, 5].

11.2 Definitions and Classification

Myocardial infarction can be broadly defined as a pathologic process of myocardial necrosis resulting from sustained ischemia. The European Society of Cardiology (ESC), American College of Cardiology (ACC), American Heart Association (AHA), and World Heart Federation (WHF) published an updated classification scheme for MI (Table 11.1) that considers the underlying mechanism of myocardial ischemia and clinical circumstances that have led to infarction [6]. NSTE-ACS are characterized by a syndrome of anginal chest discomfort, accompanied by ischemic electrocardiographic (ECG) ST-segment abnormalities and/or elevation in cardiac biomarkers. The presence of elevated cardiac biomarkers distinguishes NSTEMI from UA, and the development of high-sensitivity troponin assays has led to an increasing prevalence of biomarker-positive NSTE-ACS (e.g., NSTEMI) [4, 5, 7]. The recommendations

J. Robbins · E. V. Gelfand (✉)
Cardiovascular Division, Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA
e-mail: egelfand@bidmc.harvard.edu

P. P. Toth, C. P. Cannon (eds.), *Comprehensive Cardiovascular Medicine in the Primary Care Setting*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-319-97622-8_11

Table 11.1 Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction [6]

Type 1	Spontaneous myocardial infarction related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection
Type 2	Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply, e.g., coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension
Type 3	Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation or new left bundle branch block or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood
Type 4a	Myocardial infarction associated with percutaneous coronary intervention (PCI)
Type 4b	Myocardial infarction associated with stent thrombosis
Type 4c	Myocardial infarction associated with in-stent restenosis
Type 5	Myocardial infarction associated with coronary artery bypass grafting (CABG)

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Table 11.2 ACC and AHA classification scheme for recommendations [7]

Class	Risk-benefit profile	Recommendation
I	Benefit >>> Risk	Procedure/treatment *should* be performed/administered
IIa	Benefit >> Risk Additional studies with focused objectives needed	*It is reasonable* to perform procedure/administer treatment
IIb	Benefit ≥ Risk Additional studies with broad objectives needed; additional registry data would be helpful	Procedure/treatment *may be considered*
III	Risk ≥ Benefit No additional studies needed	Procedure/treatment should *not* be performed/administered *since it is not helpful and may be harmful*

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set forth by the ACC and AHA are classified by the strength of supporting evidence. This classification scheme is outlined in Table 11.2 [7].

11.3 Pathophysiology

ACS is the culmination of an atheroinflammatory process originating at the site of a cholesterol-laden plaque within a coronary artery. Braunwald proposed a pentad of pathophysiologic processes that contribute to the development of an acute atherothrombotic event including (a) rupture of a vulnerable atherosclerotic plaque that disrupts the local balance of thrombosis and endogenous fibrinolysis,

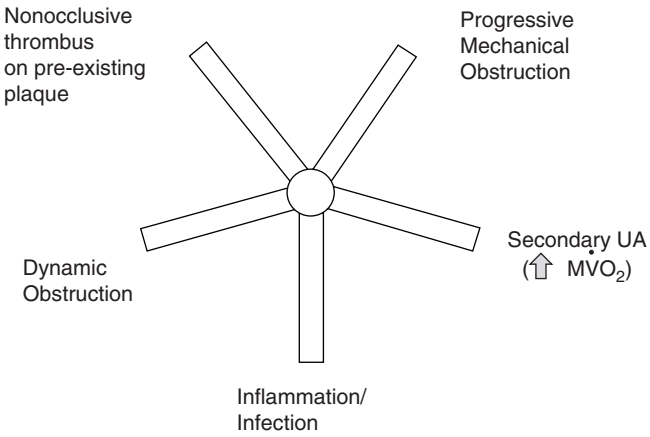

Fig. 11.1 Framework for considering five major causes of unstable angina [5]. (Reproduced from Circulation ©1998 with permission from LWW)

leading to formation of a superimposed nonocclusive thrombus; (b) dynamic obstruction of the vessel such as spasm of a major epicardial coronary vessel in Prinzmetal's angina or constriction of small muscular coronary arteries; (c) progressive mechanical obstruction of the vessel; (d) inflammation; and (e) secondary unstable angina, related to oxygen supply-demand mismatch [8] (Fig. 11.1). These processes are not mutually exclusive, and ACS likely arises as a combination of some or all of these factors [9]. STEMI typically results from transmural infarction due to an occlusive coronary process, whereas UA or NSTEMI are usually caused by non-transmural processes.

11.3.1 Thrombosis

The central role of thrombosis in the pathogenesis of ACS is supported by the presence of thrombi at the site of a ruptured atherosclerotic coronary plaque at autopsy in atherectomy specimens from patients with UA and on angioscopy and angiography of patients with UA. Marked improvement in clinical outcomes of patients with ACS is achieved with specific antithrombotic therapy including aspirin [10], heparin (unfractionated or low molecular weight) [11–13], and platelet $P2Y_{12}$ receptor blockers (e.g., clopidogrel, prasugrel, ticagrelor) [14–16] (Fig. 11.2).

11.3.2 Role of Platelets

When an atherosclerotic plaque ruptures, collagen and tissue factor are exposed to blood. Platelet adhesion occurs through the interaction of the GP Ib receptor with von Willebrand factor. Platelet activation involves a conformational change of platelet shape, degranulation with release of several

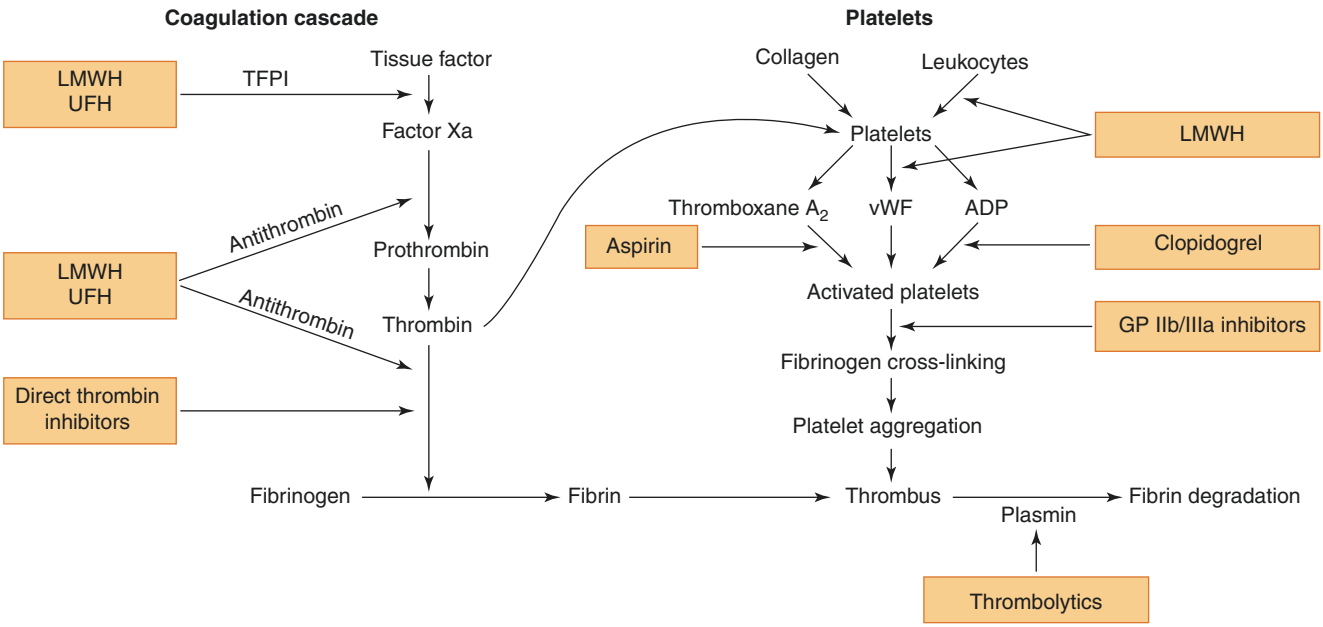

Fig. 11.2 Main sites of action of antithrombotic therapies. ADP adenosine diphosphate, GP glycoprotein, LMWH low-molecular-weight heparin, TFPI tissue factor pathway inhibitor, UFH unfractionated heparin, vWF von Willebrand factor [17]. (Reproduced from American Journal of Cardiology ©2003 with permission from Elsevier)

proaggregatory and chemoattractant mediators, and expression of GP IIb/IIIa receptors on the platelet surface, which binds fibrinogen in their activated conformation. Platelet aggregation is mediated through this interaction. Because of this central role, antiplatelet therapy is a cornerstone of therapy and works by decreasing formation of thromboxane A2 (aspirin), inhibiting the adenosine diphosphate (ADP) receptor pathway of platelet activation ($P2Y_{12}$ receptor blockers), and directly inhibiting platelet aggregation (GP IIb/IIIa inhibitors). The precise sites of antiplatelet therapy activity on the platelet activation cascade are highlighted in Fig. 11.2 [17].

11.3.3 Plasma Coagulation System in Acute Coronary Syndrome

Concurrent with formation of the platelet aggregates, the plasma coagulation system is activated. Atherosclerotic plaque rupture and subsequent release of tissue factor lead to the conversion of factor X to factor Xa, which in turn generates thrombin (factor IIa). Thrombin converts fibrinogen to fibrin in the final common pathway for clot formation. Thrombin stimulates platelet aggregation and activates factor XIII, thereby cross-linking and stabilizing the fibrin clot. At the same time, endogenous fibrinolytic mechanisms are activated including plasmin, which functions to cleave fibrin-specific peptide bonds and break apart the clot. Pharmacological inhibition of thrombin and factor Xa plays an important role in the primary treatment of ACS, and specific anticoagulation targets are highlighted in Fig. 11.2.

11.3.4 Dynamic Coronary Obstruction

Coronary vasoconstriction commonly occurs in the region of atherosclerotic plaque rupture and thrombosis and may result from local vasoconstrictors released by platelets (i.e., serotonin and thromboxane A_2), as well as from mediators present within the thrombus (i.e., thrombin). *Prinzmetal's angina* or variant angina is characterized by coronary artery vasoconstriction that can occur even in the absence of significant atherosclerotic narrowing [18]. Vascular smooth muscle hyperreactivity likely plays a central role in its pathogenesis [19, 20]. Adrenergic stimuli, exposure to cold, cocaine [21], and profound mental stress [22] can also lead to coronary vasoconstriction. *Microvascular angina or cardiac syndrome X* may occur as a consequence of either vasoconstriction in small intramural arteries where coronary flow is slow despite the lack of epicardial stenoses [23] or an abnormal pain response [24].

11.3.5 Progressive Mechanical Obstruction

Angiographic and atherectomy studies have demonstrated that progressive luminal narrowing of the culprit vessel secondary to rapid cellular proliferation may precede the

Table 11.3 Causes of myocardial oxygen supply-demand mismatch that may lead to secondary unstable angina

Conditions that cause *increased oxygen demand*
Tachycardia
Systemic infection/fever
Thyrotoxicosis
Hyperadrenergic states
Elevations of left ventricular afterload (hypertension, severe aortic stenosis)
Conditions that cause *impaired oxygen delivery*
Anemia
Hypoxemia
Hypotension

onset of NSTE-ACS. Progressive narrowing of the coronary lumen has been observed most commonly in the setting of restenosis after percutaneous coronary intervention (PCI) prior to the widespread use of drug-eluting stents. When myocardial damage is detected, this has been termed type 4c MI.

11.3.6 Type 2 Myocardial Infarction

This form of MI is caused by profound imbalances in myocardial oxygen supply and demand and often occurs on a background of underlying coronary stenoses. Examples are given in Table 11.3.

11.4 Clinical Presentation

Patients with NSTE-ACS typically present with one or more of the following features of anginal chest pain: (a) occurring at rest or with light exertion, usually lasting at least 20 min, (b) new onset (i.e., within 2 months), and (c) occurring in an accelerating pattern (i.e., more severe, prolonged, or frequent than previous occurrences and with a lower threshold for occurrence with exertion) [25]. Three features characterize angina: (1) often poorly localized chest discomfort (only infrequently described as "pain") that may radiate to the arm(s), neck, back, or jaw, (2) exacerbation with physical exertion or emotional stress, and (3) relief with rest and/or nitroglycerin. A grading system for angina, developed by the Canadian Cardiovascular Society, is outlined in Table 11.4 [26]. *Unstable angina* has one or more of the following features: Anginal equivalents commonly include shortness of breath, diaphoresis, epigastric pain, and extreme fatigue, and atypical presentations are more common in older age (e.g., >75 years old), women, and patients with long-standing diabetes mellitus [27, 28].

Physical examination may be unremarkable, though signs of a large infarct are highlighted in Table 11.5. A sufficiently large infarction will cause end-organ hypoperfusion and cardiogenic shock, which developed in 2.5% of patients without ST elevation on presentation and carried a mortality rate greater than 70% in the GUSTO-IIb Trial [29]. Right ventricular (RV) infarction is a distinct entity, usually caused by occlusion of the proximal right coronary artery and may occur in conjunction with an inferior left ventricular (LV) MI. Physical signs of RV infarction include hypotension and elevated jugular venous pressure in the absence of signs of LV failure.

Symptoms of ACS must be differentiated from other causes of chest pain, many of which can be life-threatening (Table 11.6). Acute aortic dissection should be considered given the potential ramifications of treating patients for suspected ACS with antithrombotic agents. In cases of suspected RV infarction, care must be exercised in differentiating this scenario from the overlapping presentations of acute pulmonary embolism or cardiac tamponade. Acute pericarditis may be misdiagnosed as acute MI since presentation commonly involves chest discomfort with ST-segment changes on ECG. One study suggests that the following features of chest pain identify a subgroup of patients who are at "low" risk for having ongoing MI (<3%): (1) sharp or stabbing pain, (2) no history of angina or MI, (3) pain with pleuritic or positional components, and/or (4) pain that was reproduced by palpation of the chest wall [30].

Table 11.4 Canadian Cardiovascular Society grading of angina pectoris [26]

Class	*Description*
I	Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation
II	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, and walking or stair climbing after meals or in cold or in wind or under emotional distress or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions
III	Marked limitation of ordinary physical activity. Walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace
IV	Inability to carry on any physical activity without discomfort, anginal syndrome may be present at rest

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Table 11.5 Physical exam findings in a large myocardial infarction

Evidence of low cardiac output
Diaphoresis
Pale cool skin
Sinus tachycardia
Confusion
Evidence of elevated filling pressures
Audible S3 or S4 on cardiac auscultation
Rales on lung auscultation
Jugular venous distention

Table 11.6 Differential diagnosis of chest discomfort

Conditions with immediate life-threatening potential
Acute coronary syndrome
Acute aortic dissection
Pulmonary embolism/infarction
Esophageal rupture
Tension pneumothorax
Cardiac tamponade
Other conditions
Acute pericarditis
Gastroesophageal reflux disease
Costochondritis and related musculoskeletal conditions
Acute myocarditis
Transient apical ballooning syndrome (takotsubo cardiomyopathy)
Esophageal spasm
Pleurisy
Herpes zoster
Pancreatitis
Gallbladder disease

11.5 Initial Evaluation and Risk Stratification

Prompt evaluation of patients with suspected ACS is essential. Patients who contact healthcare providers by phone with symptoms suggestive of accelerating angina or angina at rest should be advised that a full evaluation cannot be performed solely via the telephone and immediate evaluation in an emergency room should be strongly encouraged. Use of emergency medical services rather than private transportation is advised.

An initial, focused history should concentrate on the nature of the anginal symptoms, any prior history of coronary artery disease (CAD), and traditional cardiovascular risk factors. Cocaine use should be addressed, and urine toxicology should be performed when substance abuse is suspected as a cause of, or contributor to, ACS.

Physical examination should be directed toward the assessment of possible precipitants of NSTE-ACS, such as severe hypertension, thyroid disease, gastrointestinal bleeding, or other causes of a potential myocardial oxygen supply-demand mismatch. Evidence for extra-cardiac vascular disease, such as carotid bruits or diminished distal pulses, should be sought. Alternate life-threatening diagnoses should be considered (see Table 11.6), and hemodynamic ramifications of a large MI should also be evaluated as highlighted in Table 11.5.

11.5.1 ECG

A 12-lead ECG should be interpreted within 10 min of the patient's arrival to the emergency department [7]. A recording made during active chest pain is of particular value, and comparison to a prior tracing is particularly helpful. The presence of ST deviation and/or T-wave inversions in contiguous leads (Fig. 11.3), or pathologic Q-waves suggesting prior myocardial infarction (Fig. 11.4), may suggest ongoing or prior myocardial ischemia and/or infarction. If the initial ECG is nondiagnostic, follow-up ECG should be performed every 15–30 min or with episodes of recurrent chest pain. Posterior leads V_7–V_9 should be utilized to enhance the detection of posterior MI because acute MI due to left circumflex coronary artery occlusion may present with an otherwise "silent" electrocardiogram [31]. When RV infarction is suspected based on clinical presentation, right-sided precordial leads (V_3R–V_5R) should be obtained, with ST elevation in lead V_4R being a specific finding [32].

11.5.2 Cardiac Biomarkers

Cardiac-specific troponins (cTn, e.g., troponin I and troponin T) are the most sensitive and specific markers of myocardial cell necrosis [33]. Elevations in cardiac troponin can be detected in the blood as early as 2–4 h after symptom onset and as long as 5–14 days following an MI [34] (Fig. 11.5). Initial evaluation with a troponin assay carries a Class I AHA/ACC recommendation in all patients who present with features consistent with ACS and should be repeated in 3–6 h after symptom onset [7]. In a clinical scenario suggestive of ACS, MI is defined by a rising and/or falling cTn with at least one value above the 99th percentile of the upper reference level [6]. It is important to note that there is wide variability across different troponin immunoassays owing to a lack of standardization and the variability in assay detection of degraded and modified cTn [35, 36]. New, high-sensitivity cTn assays (hs-cTn) have emerged and been shown to facilitate the rapid evaluation of patients with possible ACS [37, 38]. Questions remain, however, about the interpretation of these powerful tools [39], and the need to interpret hs-cTn in the appropriate clinical context and individualize patient care remains paramount.

Though displaced by cTn as a first-line measure of early myocardial injury, creatine kinase-MB (CK-MB) remains important as a measure of infarct size.

B-type natriuretic peptide (BNP) is a cardiac neurohormone released in response to ventricular stretch. While BNP has been used as a diagnostic and prognostic marker in congestive heart failure, it also serves as a strong predictor of short- and long-term mortality in patients with ACS independent of previous heart failure or clinical signs of LV dysfunction [40]. In a 2001 study, plasma BNP levels were measured at a mean of 40 h after symptom onset in patients presenting with NSTE-ACS. Patients with BNP levels above a threshold of 80 pg/mL had an increased incidence of death, new or

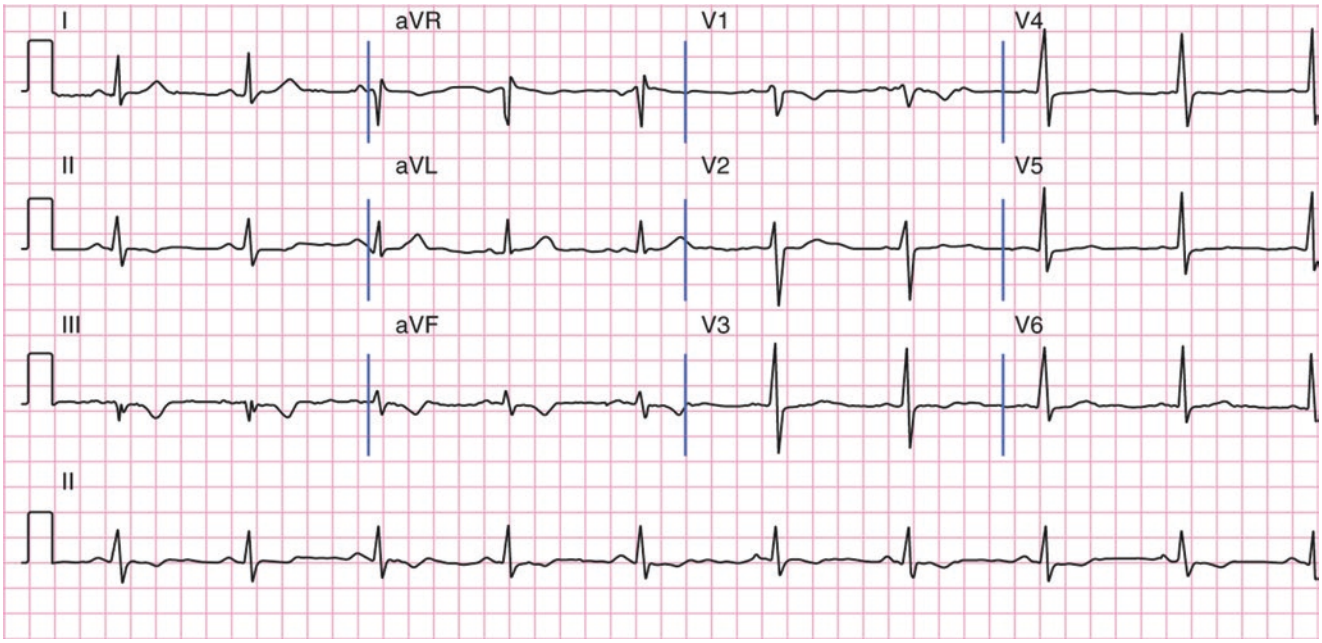

Fig. 11.3 ECG evidence of myocardial ischemia, with T-wave inversions in the inferior leads II, III, and aVF. Subtle ST depression is suggested in lead aVF, though ST deviation is not noted elsewhere on this ECG

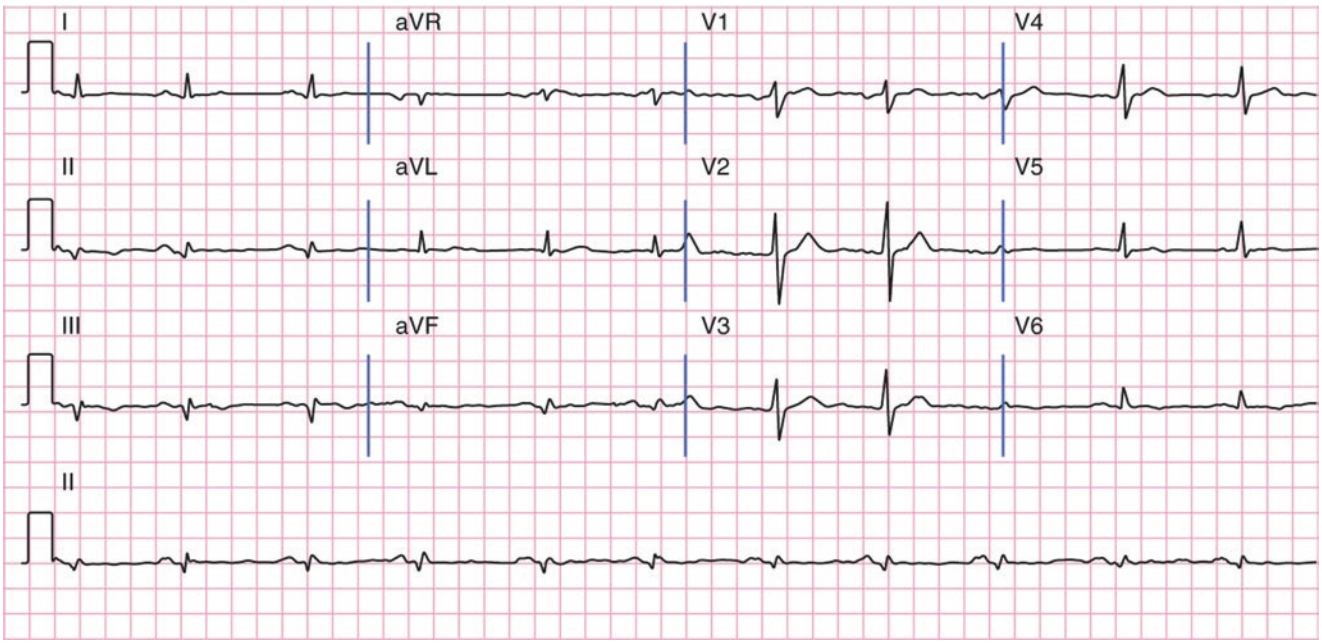

Fig. 11.4 ECG evidence of prior myocardial infarction, with Q-waves in the inferior leads II, III, and aVF. Minimal Q-waves in leads I, aVL, and V6 are also noted

progressive heart failure, and new or recurrent MI at 30 days and 10 months from the index event [41]. N-terminal proBNP (NT-proBNP) has been shown to have similar predictive value in in NSTE-ACS [42]. Routine measurement of BNP or NT-proBNP has not been adopted in clinical practice at this point.

Several novel biomarkers have emerged that have demonstrated improved performance of preexisting predictive models. In a study of over 4000 patients with moderate or high-risk NSTE-ACS, copeptin, midregional pro-adrenomedullin (MR-proADM), and midregional pro-atrial natriuretic peptide (MR-proANP) were all independently

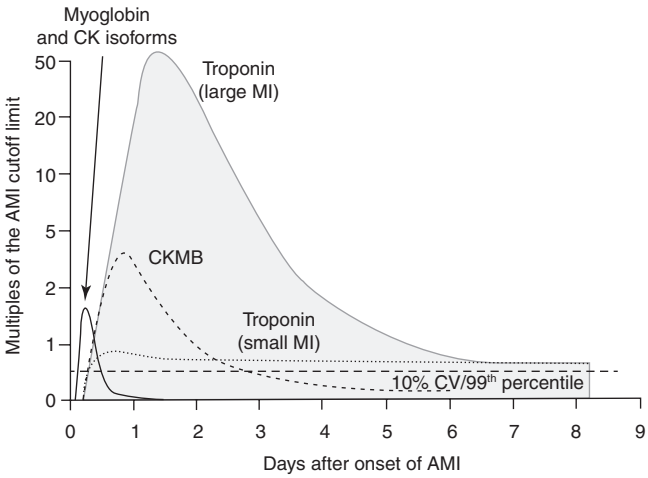

Fig. 11.5 Kinetics of the appearance of cardiac biomarkers after acute MI. Shown are the time concentrations/activity curves for myoglobin and creatine kinase (CK) isoforms, troponin after large and small infarctions, and CK-MB. Note that with the cardiac troponin, some patients have a second peak in addition. CV coefficient of variation [25]. (Reproduced from the Journal of the American College of Cardiology ©2006 with permission from Elsevier)

associated with risk of cardiovascular death or heart failure at 1 year. In addition, combining each biomarker to a predictive model based on clinical variables and preexisting cardiac biomarkers (e.g., cTn-I, BNP, pregnancy-associated plasma protein A, etc.) led to improved prognostic discrimination and patient reclassification for the composite outcome [43]. Similarly, the addition of growth differentiation factor 15 to the Global Registry of Acute Coronary Events (GRACE) score increases its predictive value in patients with NSTE-ACS [44]. It remains to be seen how best to translate these novel biomarkers into clinical benefit [45, 46].

11.5.3 Cardiac Computed Tomography Angiography

Cardiac computed tomography angiography (CCTA) has demonstrated strong negative predictive value for traditional major adverse cardiovascular events (MACE) and may aid in the decision-making surrounding patients with a low- to intermediate risk of NSTE-ACS. CCTA permits the visualization of non-stenotic coronary plaque, both calcified and noncalcified, and has rapid examination times with excellent image quality. Several studies have demonstrated high negative predictive values (~91–100%) in low- to intermediate-risk patients [47–49], thereby making it an attractive tool for "ruling out" CAD and facilitating more rapid triage from the emergency department in select patient groups. Indeed, average length of stay was reduced in patients receiving CCTA as part of their diagnostic evaluation compared to usual care in several randomized controlled trials [50–52].

CCTA is inappropriate in patients with a high pretest probability of CAD presenting with suspected NSTE-ACS, because the posttest probability of CAD will remain unacceptably high despite a negative CCTA scan [53]. Similarly, patients with a very low pretest probability of CAD presenting with chest pain may be subjected to an unnecessary radiation exposure and left with the possibility of a false-positive result given the intermediate positive predictive value for CCTA [54].

11.5.4 Cardiovascular Magnetic Resonance

Cardiovascular magnetic resonance (CMR) is being investigated for its use in early triage of patients presenting with chest pain. CMR can provide a wide range of information including global and regional cardiac function, myocardial perfusion, myocardial viability, and proximal coronary anatomy. CMR has been shown to add diagnostic value over the usual clinical parameters such as ECG, troponin, and thrombolysis in myocardial infarction (TIMI) score in suspected NSTE-ACS [55, 56]. The inability to differentiate nonviable myocardium as acute versus chronic MI previously limited the value of CMR in the triage of patients with chest pain. New protocols including the use of T2-weighted imaging and assessment of LV wall thickness have demonstrated increased specificity, positive predictive value, and overall accuracy compared to the conventional CMR protocol in determining the chronicity of myocardial abnormalities on late gadolinium enhancement (LGE) [57]. An example of myocardial infarction detected by LGE CMR is provided in Fig. 11.6. Disadvantages of CMR include long acquisition times, a steep learning curve, high setup cost, and the potential inability to scan patients with implanted pacemakers/defibrillators.

11.5.5 Risk Stratification in NSTE-ACS

NSTE-ACS is a spectrum of diseases with variable clinical courses and prognoses (Fig. 11.7). Optimal management strategies in NSTE-ACS are, therefore, based on an individual patient's risk of major adverse cardiovascular events. High-risk features of NSTE-ACS are highlighted in Table 11.7. Rapid bedside evaluation of and individual risk prediction can be accomplished using early risk stratification tools. The thrombolysis in myocardial infarction (TIMI) risk score [58] was derived and validated through the TIMI 11B [12, 59] and the ESSENCE [13] trials. It includes seven variables that were independently found to increase the risk of all-cause mortality, new or recurrent MI, or severe recurrent ischemia

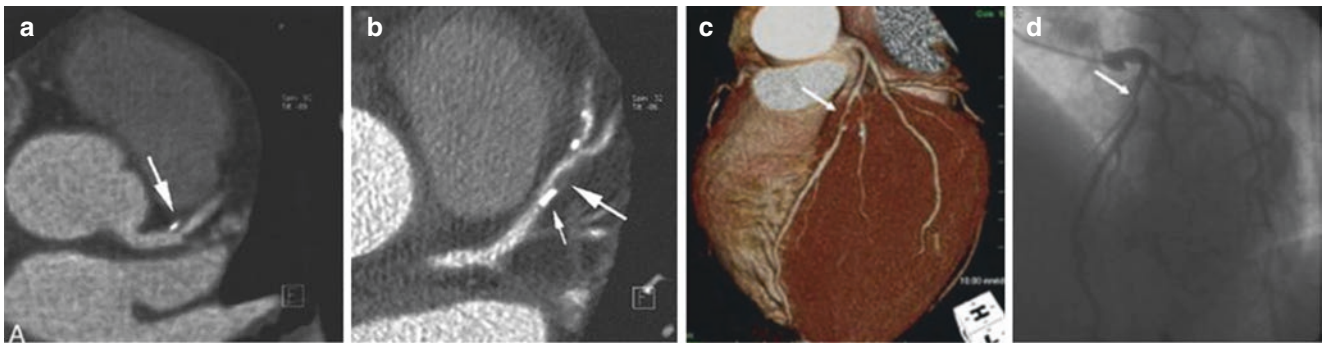

Fig. 11.6 (**a**) LGE CMR image, taken from a sagittal view. Normal myocardium is dark, while infarcted myocardium appears bright in this protocol. This patient has had a prior infarct in the basal and mid-inferior and inferolateral walls (arrow). (**b**) Wall motion analysis from a bull's eye depiction of the left ventricle. Normal segments are blue, while abnormal or hypokinetic/akinetic segments are red. Decreased excursion of the inferior wall is suggested (arrowhead) and correlates with the infarct identified with LGE CMR

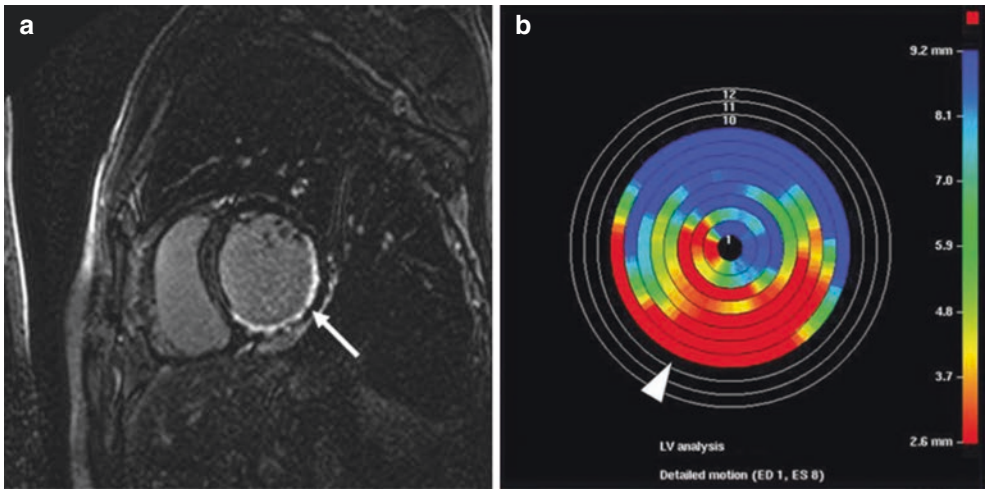

Fig. 11.7 Spectrum of severity in unstable angina and non-ST elevation myocardial infarction

Table 11.7 Indicators of increased risk in patients with NSTE-ACS [61]

1.	Recurrent ischemia at rest or with minimal activity, despite intensive anti-ischemic therapy
2.	Elevated serum troponin level
3.	New ST-segment depression
4.	Recurrent ischemia with heart failure symptoms, an S_3 gallop, pulmonary edema, rales, or new mitral regurgitation
5.	High-risk findings on noninvasive stress testing
6.	LV ejection fraction <40%
7.	Hemodynamic instability or angina at rest accompanied by hypotension
8.	Sustained ventricular tachycardia
9.	Percutaneous intervention within 6 months
10.	Prior coronary artery bypass graft surgery

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prompting urgent revascularization within 14 days in subjects with NSTE-ACS (Table 11.8). Patients with a TIMI risk score ≥3 benefit from low-molecular-weight heparin (versus unfractionated heparin) [12, 58] and an early invasive (versus conservative) strategy [60].

Table 11.8 TIMI risk score for NSTE-ACS [58]

Components	Points
Age ≥ 65 years	1
Documented prior coronary artery stenosis >50%	1
At least three conventional cardiac risk factors	1
Use of aspirin in the preceding 24 h	1
At least two anginal episodes in the preceding 24 h	1
ST-segment deviation	1
Elevated cardiac biomarkers	1
Total possible score	0–7

0–2: low risk, 3–4: intermediate risk, 5–7: high risk

The Global Registry of Acute Coronary Events (GRACE) risk score is another powerful risk prediction tool, validated by the GRACE [62] and GUSTO-IIb [63] cohorts, that can predict both in-hospital, all-cause mortality after ACS [64] and 6-month and 1-year mortality or recurrent MI [65, 66]. The GRACE risk score is based on eight variables including older age, Killip class, systolic blood pressure, ST-segment deviation, cardiac arrest during presentation, serum creatinine level, positive initial cardiac biomarkers, and

heart rate, and, similar to the TIMI score, has an additive effect on risk [65].

11.6 Management of NSTE-ACS

11.6.1 Routine Initial Care in NSTE-ACS

Patients who are hemodynamically stable should be admitted to an inpatient telemetry unit for continuous ECG monitoring. Reliable intravenous access, rapid availability of bedside cardioverters-defibrillators, and frequent monitoring of vital signs are essential. Hemodynamic or electrical instability or ischemia refractory to medical therapy necessitates placement in a coronary care unit for closer monitoring. Bed rest should be implemented during active ischemia, and physical activity should initially be permitted only to the extent that it does not provoke symptom recurrence. Oxygen should be administered to patients with arterial saturation of <90%, patients in respiratory distress, or those with other high-risk features of hypoxemia.

11.6.2 Anti-ischemic and Analgesic Therapies

11.6.2.1 Nitrates

Nitroglycerin increases myocardial oxygen supply through endothelium-dependent coronary vasodilation while also reducing myocardial oxygen demand through venodilation and reduction of LV preload and wall stress. Nitroglycerin can be given sublingually as a tablet or buccal spray; for persistent angina, a continuous intravenous infusion of nitroglycerin may be initiated. Contraindications to nitrates include hypotension (initial systolic BP <90 mmHg or 30 mmHg below baseline) and use of phosphodiesterase-5 inhibitors within the preceding 24 h (sildenafil or vardenafil) to 48 h (tadalafil) [67]. *Nitrates should be avoided in patients with RV infarction, where the decrease in preload that results from nitrate-mediated venodilation may provoke or exacerbate hypotension.* Nitrates appear to have a neutral effect on mortality in MI [68, 69]; therefore, the goal of nitrate therapy is the relief of anginal discomfort.

11.6.2.2 Morphine

Judicious use of morphine is reasonable for patients with persistent anginal discomfort despite nitroglycerin therapy. A dose of morphine sulfate (1–5 mg IV) may be considered in such cases with careful blood pressure monitoring, with repeat doses every 5–30 min as needed. No randomized controlled clinical trials have investigated the impact of morphine administration on mortality during ACS.

11.6.2.3 Beta-adrenergic Blockers

Beta-adrenergic blockers (BBs) competitively block the effects of catecholamines on beta-adrenergic receptors. In NSTE-ACS, the primary benefits of BBs are due to inhibition of beta-1 adrenergic receptors, which results in decreased myocardial contractility and heart rate and, therefore, decreased cardiac work and myocardial oxygen demand. Trials in the pre-thrombolytic era, when both STEMI and NSTEMI were included, demonstrated reduction in infarct size, reinfarction, and mortality with BBs [70]. Several placebo-controlled trials in NSTE-ACS have shown the benefit of BBs in reducing progression to MI and/or recurrent ischemia [71, 72]; however more modern trials have not demonstrated reductions in short-term mortality [73, 74].

The COMMIT trial, which evaluated 45,852 patients with acute MI (93% with STEMI, 7% with NSTEMI), suggested a modest reduction in reinfarction and ventricular fibrillation with metoprolol after day 1 but was counterbalanced by an increase in cardiogenic shock, primarily occurring in hemodynamically unstable patients or those in acute heart failure who received intravenous BB [73].

Therefore, BBs are recommended for patients with ACS who do not have contraindications to beta-adrenergic blockade (Table 11.9). Particular caution must be exercised in unstable patients at risk for cardiogenic shock [7].

11.6.2.4 Calcium Channel Blockers

Calcium channel blockers (CCBs) have been shown to relieve or prevent ischemic symptoms to a degree similar to BBs [75–77], though meta-analyses have not found any beneficial effect of CCBs in reducing mortality or subsequent reinfarction [68, 78]. Diltiazem and verapamil have been shown to be harmful to patients with acute MI with LV dysfunction or CHF [75, 79, 80]. Likewise, short-acting nifedipine, a dihydropyridine CCB that can cause a reflex tachycardia from blood pressure-lowering effects, has been shown to be harmful in patients when administered without a BB [81]. Non-dihydropyridine CCBs may thus be used in patients with ACS for recurrent ischemia despite beta-adrenergic blockade or in patients in whom BBs are contraindicated, primarily because of bronchospasm. They should be avoided in patients with LV dysfunction and/or CHF, and nifedipine should be avoided altogether in ACS when a BB is not being

Table 11.9 Contraindications to beta-adrenergic blockers

History of severe bronchospasm
Bradycardia
Second- or third-degree atrioventricular (AV) block
Persistent hypotension
Previously known systolic dysfunction with *acute* pulmonary edema
Cardiogenic shock
Suspected cocaine-associated MI *(nonselective alpha/beta-blockers may be used with caution)*

concurrently administered. When atrial fibrillation with rapid ventricular response complicates NSTE-ACS, BBs may be considered for rate-control strategies if CCBs are being avoided.

11.6.2.5 Angiotensin-Converting Enzyme Inhibitors

The benefits of angiotensin-converting enzyme (ACE) inhibition after STEMI are considerable but less well-established in NSTE-ACS. Both early and late administration of ACE inhibitors have proven to be beneficial after acute MI [82–84] Three large trials showed a 0.5% absolute reduction in mortality with early ACE inhibition in patients with acute MI, with particular benefit in those with LV systolic dysfunction, heart failure, and diabetes mellitus [69, 85–87]; however no benefit was observed in patients with NSTEMI in the ISIS-4 study [69] Two large RCTs have demonstrated reductions in composite outcomes including cardiovascular death and MI with ACE inhibition in patients with established coronary heart disease (CHD) or those at high risk for CHD [88, 89]. Results from the HOPE and EUROPA trials (stable CAD) and from earlier trials mostly involving patients with STEMI have led many clinicians to prescribe ACE inhibitors to all patients after NSTE-ACS. In the absence of contraindications, ACE inhibitors may be seen as first-line therapy in NSTE-ACS for systemic hypertension despite the use of BBs and certainly in patients with LV dysfunction or congestive heart failure.

11.6.2.6 Lipid-Lowering Therapy

Long-term lipid-lowering therapy, especially with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), has been shown to be beneficial in patients following ACS [90–92]. In the landmark 4S trial, simvastatin reduced mortality by 30% and coronary deaths by 42% in patients with hypercholesterolemia with a history of angina or prior MI. Recurrent MI and the need for coronary revascularization were likewise decreased by 37% [90, 93].

The benefit of early statin initiation in the setting of NSTEMI has been investigated in several studies [94–97]. The MIRACL trial found that a 4-month course of atorvastatin 80 mg/day, initiated between 24 and 96 h after hospital admission for NSTEMI, reduced the incidence of cardiovascular death, nonfatal MI, resuscitated sudden cardiac death, or urgent rehospitalization for recurrent ischemia by 16% [98]; similar results were demonstrated in the longer-term A-to-Z TIMI 21 trial of early aggressive simvastatin treatment [99].

The role of intensive lipid-lowering therapy (atorvastatin 80 mg/day) was compared to standard lipid-lowering therapy (pravastatin 40 mg/day) in patients with ACS in the landmark PROVE-IT TIMI 22 study [78]. Standard therapy led to a median low-density lipoprotein cholesterol (LDL-C) value of 95 mg/dL, while intensive therapy lowered LDL to a median value of 62 mg/dL. The risk of death, MI, UA, revascularization, or stroke was reduced by 16% with intensive therapy, with rates at 2 years (mean time of follow-up) falling from 26.3 to 22.4% in the standard versus intensive therapy groups. Benefits were seen within 30 days of randomization and continued throughout 2.5 years of follow-up. These studies form the basis for the AHA/ACC Class I recommendation to initiate and continue high-intensity statin therapy in patients with NSTE-ACS and without clear contraindications to its use [7].

In a small, but significant, population of patients who are unable to tolerate statins because of adverse effects or those in which LDL-C remains elevated despite statin therapy, treatment with inhibitors of cholesterol absorption in the small intestine (ezetimibe) and/or proprotein convertase subtilisin/kexin type 9 (PCSK9) may provide modest and significant reductions in LDL-C, respectively. While IMPROVE-IT (The Improved Reduction of Outcomes: Vytorin Efficacy International Trial) demonstrated that the addition of ezetimibe to statin therapy compared to statin therapy alone led to a significant reduction in LDL-C (53.7 mg/dL vs. 69.5 mg/dL, $p < 0.001$) and a modest reduction in MI (HR 0.87, 95% CI 0.80–0.95) and stroke (HR 0.86, 95% CI 0.73–1.00) in ACS patients [100], we await the long-term outcomes of treatment with PCSK9 inhibitors in patients with ACS [101].

11.6.3 Antiplatelet Therapies

11.6.3.1 Aspirin

Aspirin serves as the cornerstone of antiplatelet therapy in ACS and works by decreasing platelet aggregation by irreversibly modifying the enzyme cyclooxygenase (COX)-1 and attenuating thromboxane release. The Antithrombotic Trialists' Collaboration included over 5000 patients with NSTE-ACS enrolled in 12 trials treated with antiplatelet therapy (mostly aspirin) and demonstrated that the combined end point of MI, stroke, or death from cardiovascular disease was reduced by 46% with antiplatelet therapy [102]. The optimal dosage of aspirin during the acute phase of ACS appears to be at least 160 mg/day, based on the mortality benefit seen among STEMI patients enrolled in the ISIS-2 trial [103]. For long-term treatment of ACS, several large RCTs have demonstrated that a dose of 75–100 mg/day is equally effective to higher doses and has lower bleeding risk [104–106]. In the absence of contraindication, aspirin should be continued indefinitely in patients with NSTE-ACS.

Aspirin resistance has been reported in 5–8% of patients during chronic therapy and is not dose dependent [107, 108], though this phenomenon may simply reflect inadequate blockade of the thromboxane pathway.

Contraindications to aspirin are rare but include documented aspirin allergy (e.g., bronchoconstriction), active life-threatening bleeding, or a known platelet disorder. Clopidogrel or ticagrelor may be considered as alternative therapies in the presence of a documented aspirin allergy (see subsequent discussion); however, strong consideration should be given to performing aspirin desensitization in an intensive care unit [7].

11.6.3.2 Clopidogrel

Clopidogrel, a thienopyridine, causes platelet inhibition by irreversibly blocking the binding of platelet ADP to its P2Y12 receptor and inhibiting activation of the glycoprotein GP IIb/IIIa complex (Fig. 11.2). It is a pro-drug that is 85% hydrolyzed by human carboxylesterase-1 into an inactive metabolite and 15% metabolized by various enzymes within the hepatic cytochrome P450 (CYP450) into its active form [109]. The CAPRIE trial compared clopidogrel to aspirin for secondary prevention in a broad range of patients with atherosclerotic disease, finding that clopidogrel resulted in an 8.7% relative reduction in the long-term combined end point of stroke, MI, or cardiovascular death [110]. The benefit of dual antiplatelet therapy (DAPT) with clopidogrel and aspirin in NSTE-ACS was demonstrated in the landmark Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, in which over 12,000 patients with NSTE-ACS were randomized to receive aspirin alone or with clopidogrel in addition to standard medical therapies. The combined end point of cardiovascular death, MI, or stroke at 9 months was reduced by 20%, and the benefit persisted for 1 year. This benefit was seen in patients managed medically, with a percutaneous coronary intervention (PCI), or undergoing coronary artery bypass grafting (CABG) [14]. Similar findings were observed in the PCI-CURE trial, which specifically evaluated CURE patients who underwent PCI [111]. In CURE, DAPT was associated with a 38% increased risk of major bleeding compared to aspirin alone; however the absolute increase was 1% (3.7 vs. 2.7%), and the rates of life-threatening bleeding or intracranial hemorrhage were similar [14].

An initial loading dose of 300 or 600 mg should be administered, followed by 75 mg daily in patients with NSTE-ACS. While pharmacologic studies have demonstrated more rapid achievement of steady-state platelet inhibition with a 600 mg loading dose, the CURRENT-OASIS 7 trial demonstrated that high-dose clopidogrel (600 mg load followed by 150 mg daily for 1 week and 75 mg daily thereafter) did not decrease a composite of cardiovascular death, MI, or stroke at 30 days. It did, however, increase the absolute risk of major bleeding by ~0.5% and the need for blood cell transfusion [105]. A substudy of CURRENT-OASIS 7 did find a decrease in MACE and stent thrombosis in patients undergoing PCI in the higher-dose clopidogrel arm [112]; thus, it may be reasonable to give a 600 mg loading dose to those patients likely to undergo an invasive strategy and/or those with low bleeding risk.

Perioperative bleeding is increased in patients undergoing CABG surgery within 5 days of clopidogrel treatment compared to patients treated with aspirin alone. In CURE, 9.6% of patients treated with clopidogrel had significant bleeding (defined as receipt of ≥2 units of blood) compared to 6.3% of patients treated with aspirin. No excess bleeding risk was seen after surgery in patients who had received clopidogrel ≥5 days prior [14]; this finding supports the recommendation to discontinue clopidogrel at least 5 days before CABG when possible [7].

11.6.3.3 Prasugrel

Prasugrel, like clopidogrel, is a thienopyridine that inhibits platelet aggregation by irreversibly binding to the platelet P2Y12 receptor. Unlike clopidogrel, prasugrel is rapidly oxidized to its active form within 30 min and has greater bioavailability, leading to greater platelet inhibition [113]. TRITON-TIMI 38 compared prasugrel (60 mg load plus 10 mg daily maintenance dose) to clopidogrel (300 mg load plus 75 mg daily maintenance load) in 13,608 moderate- to high-risk patients with ACS planned to undergo PCI, including 10,074 with NSTE-ACS [15]. The composite end point of cardiovascular death, nonfatal MI, or stroke was reduced by 19% (95% CI, 0.73–0.90; $p = 0.0004$) in the prasugrel arm. Rates of probable and definite stent thrombosis were also significantly (>50%) reduced in patients receiving prasugrel versus clopidogrel after PCI. More potent platelet inhibition came at the expense of an increased bleeding risk; the prasugrel arm had a 32% higher risk (0.6% absolute risk) of major bleeding, including fatal bleeding, compared to clopidogrel, and this finding was most striking in patients ≥75 years old. Thus, prasugrel should be avoided in the elderly (≥75 years old) and those with low body weight (<60 kg) due to an increased bleeding risk. Additionally, prasugrel is contraindicated in patients with a history of cerebrovascular accident (CVA) or transient ischemic attack (TIA) due to net clinical harm found on a post hoc exploratory analysis of TRITON-TIMI 38 [15].

The ACCOAST (A Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients with Non-ST-Elevation Myocardial Infarction) trial found no reduction in a composite of MACE and rescue glycoprotein IIb/IIIa inhibitor therapy with "upfront" prasugrel administration at the time of randomization compared to administration at the time of PCI; however there was an increased risk of bleeding complications [114]. In the TRILOGY-ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) trial, >7000 patients were randomized to medical management

of NSTE-ACS with aspirin plus prasugrel (10 mg daily) or clopidogrel (75 mg daily). No differences in MACE or rates of severe bleeding were seen in the two arms [115]. Thus, prasugrel is not recommended as "upfront" therapy in NSTE-ACS but receives an AHA/ACC Class IB recommendation in those undergoing PCI. Prasugrel should be discontinued at least 7 days prior to elective CABG when possible [7].

11.6.3.4 Ticagrelor

Ticagrelor is a cyclopentyl-triazolopyrimidine; in contrast to the thienopyridines, ticagrelor is bioactive in its parent drug state and acts directly to block the platelet P2Y12 platelet receptor. Ticagrelor (loading dose 180 mg plus 90 mg twice daily maintenance dose) was compared to clopidogrel (300 or 600 mg loading dose plus 75 mg daily maintenance dose) in >18,000 patients with ACS (>11,000 with NSTE-ACS) [16]. There was a significant reduction in the composite end point of cardiovascular death, MI, or stroke (16% relative risk reduction) in the ticagrelor group that was largely driven by reductions in MI (16% relative risk reduction) and death from CV causes (21% relative risk reduction). Total mortality (22% relative risk reduction) and stent thrombosis (0.6% absolute risk reduction) were also reduced in the ticagrelor group. Rates of major bleeding, as well as CABG-related bleeding, were similar across the ticagrelor and clopidogrel groups. Interestingly, ticagrelor showed no benefit over clopidogrel in the subgroup of patients enrolled in the United States; the possibility that this finding was related to higher maintenance doses of aspirin (e.g., 325 mg daily) has led to the Federal Drug Administration (FDA) warning that only low-dose (75–100 mg) aspirin be used with ticagrelor [7]. Like clopidogrel, ticagrelor should be discontinued 5 days prior to elective CABG.

11.6.3.5 Cangrelor

Cangrelor, a rapidly acting, non-thienopyridine, reversible ADP receptor antagonist, is the only intravenous P2Y12 receptor inhibitor approved for use in the United States. Cangrelor has been compared against clopidogrel in three RCTs. CHAMPION (Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition) PLATFORM found that the addition of periprocedural cangrelor to downstream clopidogrel (600 mg) was not superior to placebo in reducing a composite of death, MI, and need for revascularization in >5000 patients with NSTE-ACS who underwent PCI [116]. CHAMPION PCI looked at the same outcome in ~8000 patients randomly assigned to cangrelor versus clopidogrel (600 mg) given 30 min before PCI; similar to CHAMPION PLATFORM, there was no difference in the primary outcome [117]. More recently, a third RCT demonstrated a reduction in a composite of death, MI, need for revascularization, and stent thrombosis in patients with either stable angina or ACS assigned to the cangrelor and clopidogrel (600 mg) arm compared to those receiving clopidogrel alone prior to or during PCI. These results were driven by reductions in MI and stent thrombosis and should be interpreted with the understanding that only 44% of the study population had an ACS and half of the clopidogrel monotherapy arm received a 300 mg versus 600 mg dose [118].

11.6.3.6 Glycoprotein IIb/IIIa Inhibitors

GP IIb/IIIa inhibitors (tirofiban, eptifibatide, and abciximab) reversibly bind the platelet GP IIb/IIIa receptor and block the final common pathway for platelet aggregation and may be useful in selected patients with NSTE-ACS undergoing an early invasive strategy. All three drugs are available only in intravenous formulations and have short half-lives (~2 h for tirofiban and eptifibatide; ~12 h for abciximab) allowing rapid "on and off" time of action. Dose reductions are necessary for renal insufficiency when administering tirofiban and eptifibatide, and their use is discouraged in patients with a creatinine >4.0 mg/dL. Abciximab may be used in patients with renal insufficiency, including those on hemodialysis. An important side effect of GP IIb/IIIa inhibitors is thrombocytopenia (incidence ranging 0.2–2% in clinical trials), and routine measurement of platelet count is indicated prior to initiation, 6–8 h later, and daily thereafter until infusion is terminated. If the platelet count drops below 50,000 per μL, the GP IIb/IIIa inhibitor should be discontinued. Platelet transfusion should be considered if the platelet count is <10,000 per μL, if there is severe bleeding, or if an emergency invasive procedure is needed.

Several RCTs and meta-analyses have examined the role of GP IIb/IIIa inhibitors in NSTE-ACS and yielded the following findings: (1) The greatest benefit of GP IIb/IIIa inhibitors is seen in high-risk patients, those with elevated cardiac biomarkers, TIMI risk score ≥3, or continued ischemic discomfort despite maximal medical therapy [119]. In the second Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT 2) trial, the addition of abciximab to aspirin, clopidogrel (600 mg load), and UFH in patients with ACS who underwent PCI with stenting led to a reduction in adverse ischemic events; however this benefit was confined to patients who had elevated troponins [120]. (2) Major bleeding was significantly increased (1% absolute risk) in patients receiving GP IIb/IIIa therapy compared to placebo in a meta-analysis of major placebo-controlled trials [119]. (3) There was no mortality benefit and an increased rate of major bleeding in patients assigned to "upstream," routine early use of GP IIb/IIIa inhibitors compared to its use just prior to PCI [121]. Thus, current ACC/AHA guidelines give a Class IIB recommendation for the use of GP IIb/IIIa inhibitors, along with DAPT, in NSTE-ACS with

intermediate-/high-risk features in whom catheterization with PCI is planned [7]. It should be noted that GP IIb/IIIa are commonly employed during PCI in patients with large thrombus burden or in case of intra-procedural thrombotic complications.

11.6.4 Anticoagulation

The addition of intravenous UFH, subcutaneous LMWH, bivalirudin, or fondaparinux is an ACC/AHA Class I recommendation for all patients with NSTE-ACS, regardless of the initial treatment strategy [7].

11.6.4.1 Unfractionated and Low-Molecular-Weight Heparin

Heparin is an intravenous mixture of polysaccharide chains that inhibits factors IIa (thrombin) and Xa in the coagulation cascade. Several trials have demonstrated the superiority of combined therapy with intravenous UFH and aspirin versus aspirin alone for preventing death or MI in ACS. A meta-analysis by Oler et al. found a one-third reduction in death or MI in patients with UA who received UFH in addition to aspirin compared to aspirin alone [11]. The dosing regimen of UFH that results in the best aPTT control and highest safety is 60 units/kg bolus, followed by 12 units/kg infusion with subsequent drip rate adjustments based on aPTT; measurement of aPTT is done 6 h after starting the IV infusion of heparin and then every 12–24 h during the infusion, with goal aPTT 50–70s. UFH should be continued for 48 h or until PCI is performed in patients with NSTE-ACS [7]. Potential complications beyond bleeding risk include heparin-induced thrombocytopenia, a rare but potentially devastating immunogenic disorder that can lead to venous and arterial thrombosis in addition to thrombocytopenia [122].

The pharmacokinetics of enoxaparin provide several advantages over UFH in ACS. Enoxaparin has a higher anti-Xa to anti-IIa activity ratio (which results in less thrombin generation), higher bioavailability (allowing for subcutaneous administration), and more predictable and potent antithrombin activity. Monitoring of anticoagulation levels (e.g., aPTT) is not necessary due to its consistent bioavailability and effect. In several trials of enoxaparin versus either placebo or UFH, enoxaparin decreased the risk of death or MI, while bleeding rates were overall equivalent between LMWH and UFH [123, 124]; similar findings have been observed in studies employing GP IIb/IIIa inhibitors and an early invasive approach [125, 126]. In a meta-analysis of contemporary trials of enoxaparin versus UFH in NSTE-ACS, enoxaparin resulted in a statistically significant 9% reduction in the odds of death or MI at 30 days [123]. Potential disadvantages of LMWH include the need for dose reductions in patients with renal dysfunction and less effective reversal with protamine than with heparin.

Both LMWH and enoxaparin receive an ACC/AHA Class I recommendation in patients with NSTE-ACS undergoing either an ischemia-guided or early invasive strategy (see Sect. 11.6.6) [7].

11.6.4.2 Direct Thrombin Inhibitors

The direct thrombin inhibitors, bivalirudin and argatroban, have favorable anticoagulation profile and are mainly reserved for use in patients with ACS and a history of HIT and/or those undergoing PCI. In patients undergoing coronary angiography and PCI DTIs can be monitored using activated clotting time. The Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial tested bivalirudin alone or with a GP IIb/IIIa inhibitor versus UFH or LMWH plus GP IIb/IIIa inhibitor in 7789 patients undergoing PCI for NSTE-ACS [127]. Bivalirudin with or without GP IIb/IIIa inhibitor was found to be non-inferior to UFH/LMWH plus GP IIb/IIIa inhibitor, and bivalirudin monotherapy had a superior net clinical benefit driven primarily by a reduction in bleeding. Patients needed to be pretreated with clopidogrel to have the clinical benefit. Results from ACUITY have made bivalirudin (0.10 mg/kg load followed by 0.25 mg/kg/hr) an option for NSTE-ACS patients treated with DAPT with planned coronary angiography and particularly attractive for those with high bleeding risk [7]. Argatroban may be used in patients with HIT undergoing PCI and because of its hepatic metabolism may be used as an alternative to bivalirudin in patients with severe renal dysfunction in which bivalirudin is contraindicated.

11.6.4.3 Fondaparinux

Fondaparinux is a synthetic polysaccharide that directly inhibits factor Xa activity. Potential advantages over UFH include decreased binding to plasma proteins, dose-independent clearance, a longer half-life with more predictable and sustained anticoagulation, and fixed, once-daily subcutaneous dosing. Fondaparinux, like enoxaparin, does not require laboratory monitoring and is renally excreted. In the Organization to Assess Strategies in Ischemic Syndromes (OASIS-5) trial, >12,000 patients with NSTE-ACS were randomized to standard medical therapy and either fondaparinux 2.5 mg daily or enoxaparin 1 mg/kg twice daily for 8 days [128]. The two treatment groups had similar rates of death, MI, or refractory ischemia at 9 days; however fondaparinux had a significantly lower rate of bleeding, which was also seen in a subgroup analysis of patients who underwent PCI [129]. This analysis also found a threefold increase in catheter-related thrombosis (0.9% vs. 0.3%) in the fondaparinux vs. LMWH groups, respectively, and thus an additional anticoagulant with anti-IIa activity (e.g., UFH or bivalirudin) should be used during PCI in patients treated

with fondaparinux [7]. Fondaparinux remains a reasonable option for patients with NSTE-ACS treated noninvasively or at high risk for bleeding.

11.6.4.4 Oral Anticoagulation

The combination of aspirin plus warfarin in MI appears to be more effective than aspirin alone for long-term secondary prevention but carries a significantly increased risk of major bleeding [130]. Given the similar benefit seen with DAPT, the added convenience of less frequent laboratory monitoring, as well as the common use of PCI in the patient population, the clinical use of warfarin in addition to aspirin is limited. Currently, such an approach should be taken in patients with a separate clinical indication for warfarin (e.g., anticoagulation for atrial fibrillation).

Limited data exist on the impact of novel, oral direct anti-Xa inhibitors in patients with ACS. The Apixaban for Prevention of Acute Ischemic Events 2 (APPRAISE-2) trial investigated the addition of apixaban 5 mg twice daily to standard medical regimens for >7000 subjects with ACS (60% NSTE-ACS). Approximately 81% of the subjects were taking DAPT, and all patients were considered high risk for a recurrent event (at least two of the following: diabetes mellitus, history of MI within 5 years, history of either cerebrovascular or peripheral artery disease, heart failure or LVEF<40%, impaired renal function, or no revascularization for the index event). The trial was stopped early (median, 241 days) because apixaban was associated with a significantly higher rate of TIMI major bleeding compared to placebo (1.3% vs. 0.5%) [131]. There was no significant difference in a composite primary outcome of cardiovascular death, MI, or ischemic stroke between the two groups.

In contrast, the Rivaroxaban in Patients with a Recent Acute Coronary Syndrome (ATLAS ACS-2, TIMI 51) randomized >15,000 patients with ACS (~50% NSTE-ACS) to either twice daily rivaroxaban 2.5 mg or 5 mg doses in addition to standard ACS medical regimens (93% patients received DAPT) [132]. Death from cardiovascular causes or any cause was significantly reduced in the low-dose rivaroxaban group but not the high-dose compared to the placebo group (2.7% and 2.9% vs. 4.1% and 4.5%, respectively). There was no significant difference in the rate of fatal bleeding; however there was an increased risk of intracranial hemorrhage in the rivaroxaban groups compared to placebo. A more recent trial of Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease (COMPASS) trial randomized >27,000 patients with established stable atherosclerotic disease to twice daily rivaroxaban 2.5 mg with aspirin, twice daily rivaroxaban 5 mg without aspirin, or aspirin monotherapy. The trial demonstrated that at a mean follow-up of 23 months, rivaroxaban plus aspirin was associated with a 1.3% absolute risk reduction in cardiovascular death, nonfatal MI or stroke compared with aspirin alone, at the expense of a 1.2% absolute increase in the risk of major bleeding [133]. At this time, rivaroxaban is not FDA approved for treatment of ACS, or for secondary prevention of vascular events following ACS.

11.6.5 Fibrinolysis

Several trials, including TIMI-IIIB, showed conclusively that fibrinolytic therapy was associated with *more* fatal and nonfatal MI and a higher rate of intracranial hemorrhage than heparin alone in NSTE-ACS [134]. Coronary arteriography during NSTE-ACS has shown that the culprit artery is not occluded in 60–85% of cases [135] and nonocclusive thrombus is often platelet rich and therefore less likely to respond to fibrinolytic therapy in contrast to the fibrin-rich occlusive thrombus often seen in STEMI [136, 137]. In addition, lytic-associated hemorrhage into ruptured plaque may potentially convert the nonocclusive thrombus to a complete arterial occlusion. Therefore, fibrinolytic therapy is *contraindicated* in patients with NSTE-ACS [7].

11.6.6 *Invasive* Versus *Conservative Strategy*

An *invasive strategy* generally refers to routine diagnostic coronary angiography and, when indicated, percutaneous intervention within the first 24 (early) to delayed (25–72) hours after NSTE-ACS presentation. A suggested algorithm for this strategy from the *ACC/AHA guidelines* is shown in Fig. 11.8. A *conservative (or ischemia-guided) strategy* encompasses full medical management, followed by coronary angiography and revascularization only in patients with high-risk clinical signs or symptoms or intermediate- to high-risk findings on a functional evaluation such as an exercise or pharmacologic stress test. A suggested algorithm for this strategy from the *ACC/AHA guidelines* is shown in Fig. 11.9.

Several large randomized trials have compared invasive to conservative strategies in NSTE-ACS, and all trials except for the VANQWISH trial have demonstrated benefits of an early invasive strategy in patients with moderate to high risk in regard to nonfatal MI, heart failure, or death [60, 134, 138–140]. Markers of increased risk differed between the trials and included age in TIMI-IIIB, elevated serum troponin in FRISC II and TACTICS-TIMI 18, and ST depression in TIMI-IIIB, FRISC II, and TACTICS-TIMI 18.

The timing of an invasive strategy has been investigated in RCTs and a recent meta-analysis of contemporary trials. Both RCTs demonstrated significant reductions in a composite of death and MI with an early versus delayed invasive strategy in the highest-risk (highest tertile) patients (defined by a GRACE score >140 in Mehta et al.) [141, 142].

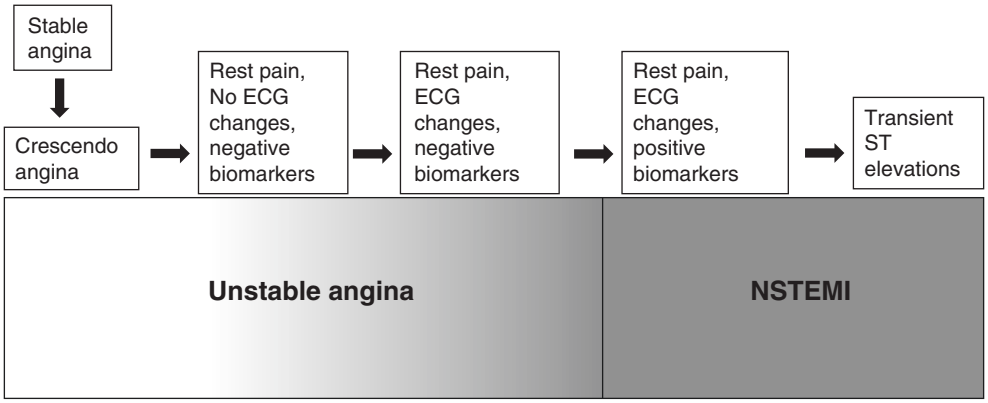

Fig. 11.8 Algorithm for patients with NSTE-ACS managed by an initial invasive strategy. When multiple drugs are listed, they are in alphabetical order and not in order of preference (e.g., Boxes B1 and B2) [7]. ASA aspirin, GP glycoprotein, I intravenous, LOE level of evidence, UA/NSTEMI unstable angina/non-ST elevation myocardial infarction, UFH unfractionated heparin. (Reproduced from the Journal of the American College of Cardiology ©2014 with permission from Elsevier)

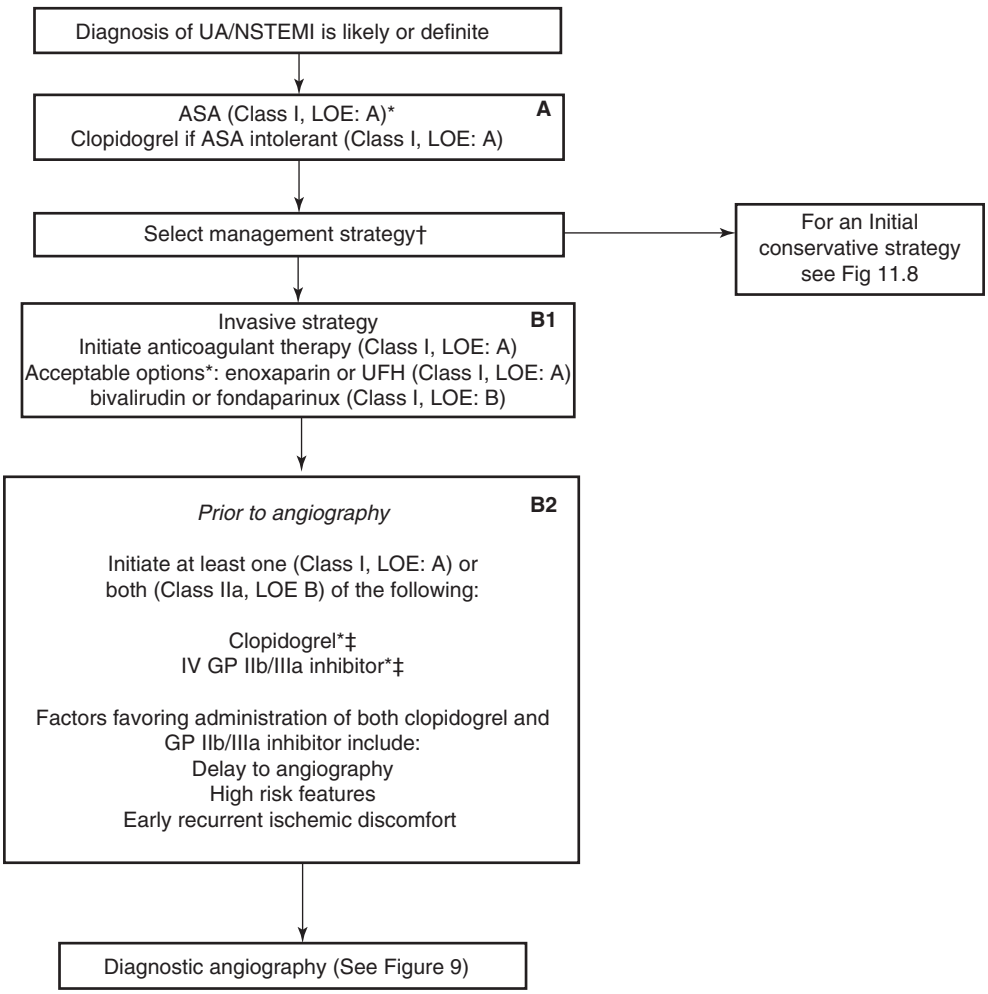

Fig. 11.9 Algorithm for patients with NSTE-ACS managed by an initial conservative strategy. When multiple drugs are listed, they are in alphabetical order and not in order of preference (e.g., Boxes C, C1, and C2). ‡Recurrent symptoms/ischemia, heart failure, and serious arrhythmia [4]. ASA spirin, EF ejection fraction, GP glycoprotein, IV intravenous, LOE level of evidence, LVEF left ventricular ejection fraction, UA/NSTEMI unstable angina/non-ST elevation myocardial infarction, UFH unfractionated heparin. (Reproduced from the Journal of the American College of Cardiology ©2014 with permission from Elsevier)

A more recent meta-analysis of several RCTs and observational studies found a nonsignificant trend toward a survival benefit (17% relative risk reduction, 95% CI, 0.64–1.09; $p = 0.18$) and no difference in rate of MI. Because of small sample size among the RCTs (5370 patients) and differences in study design, Navarese et al. concluded that there was insufficient evidence whether or not to support an early invasive strategy over a delayed invasive strategy [143].

Thus, based in part of the above studies in addition to patients with signs/symptoms of clinical deterioration during ACS (e.g., HF, evidence of worsening mitral regurgitation, hemodynamic instability) who warrant immediate coronary angiography, an early invasive strategy is recommended in patients with a rising pattern of cTn, new ST-segment depressions, or a GRACE risk score >140. In those not at intermediate/high risk, either a delayed invasive or ischemia-guided strategy is reasonable, and in some subgroups (e.g., cTn-negative, low-risk women), an ischemia-guided strategy is preferred [7, 144].

If PCI is performed as a post-angiography management strategy in NSTE-ACS, several recommendations exist regarding drug therapies that have been covered in their respective sections above; however several new guidelines were provided from the ACC/AHA Guideline Focused Update on the Duration of DAPT in Patients with CAD [7, 145]. Low-dose (75–100 mg) aspirin should be continued during DAPT therapy due to the increased bleeding risk with higher doses. A P2Y12 receptor should be continued for at least 12 months; after that, the benefits (fewer ischemic events) versus the risks (bleeding) of continuing DAPT for up to 30 months postcoronary stent placement should be considered based on findings from the Dual Antiplatelet Therapy (DAPT) study [146]. A validated risk prediction tool ("DAPT score") may be helpful in determining the risks vs. benefits of this decision [147]. In patients already on DAPT who undergo CABG, DAPT should be resumed postoperatively in order to complete a 12-month course of therapy.

11.6.7 Pre-discharge Noninvasive Risk Stratification After UA/NSTEMI

Several situations may arise where noninvasive risk stratification would be helpful in patients with suspected or definite NSTE-ACS prior to discharge from the hospital:

1. To diagnose or rule out ACS in patients with a low-intermediate probability for this diagnosis
2. To diagnose exercise-induced ischemia in patients in whom a conservative (ischemia-guided) strategy has been employed and to risk stratify them based on ischemia extent and severity
3. To diagnose and localize residual ischemia in patients in whom complete percutaneous or surgical revascularization has not been fully accomplished (e.g., patient with multivessel coronary disease, who underwent PCI of a culprit vessel)
4. To assess myocardium for left ventricular function and viability

Treadmill exercise tolerance testing (ETT) is a cost-effective, reliable means to assess a patient's functional status and prognosis. In general, it remains the modality of choice in patients that do not have an abnormal resting ECG (e.g., ST shifts, left bundle branch block) that may interfere with interpretation. In those patients and in certain subgroups (e.g., women), the addition of an imaging modality, most commonly echocardiography or myocardial perfusion imaging, is appropriate [7]. Pharmacologic stress testing with a vasodilator (e.g., adenosine or dipyridamole) may be performed if patients cannot exercise and is safe as early as 48 h after presentation with a definite ACS if the ECG is stable for 24 h prior to the test, biomarkers are downtrending, and the patient is free of anginal discomfort at rest.

If an early invasive strategy has been employed and revascularization is complete, there is generally no need for functional testing prior to hospital discharge. Such testing may be undertaken later, primarily to determine the patient's functional exercise capacity, provide a new "baseline" study, and prescribe an appropriate exercise program for cardiac rehabilitation.

11.7 Secondary Prevention Measures After NSTE-ACS

Diagnosis of ACS is commonly perceived as a "life-changing" event, and risk factor modification and secondary prevention measures become central to long-term management. Table 11.10 provides a comprehensive checklist of issues to be addressed at the first outpatient appointment following a hospital discharge for NSTE-ACS.

11.7.1 Pharmacologic Measures

11.7.1.1 Aspirin

Following ACS, aspirin reduces the risk of recurrent MI, stroke, or cardiovascular death by approximately 25% [102]. A dose of 81–365 mg/day should be continued indefinitely unless contraindicated, with new recommendations for lower-dose aspirin (75–100 mg/day) in patients on DAPT [145].

Table 11.10 Outpatient visit checklist for patients discharged with diagnosis of NSTE-ACS

Demographics Name:_____ DOB:_____ Age:_____ PCP:_____ Cardiologist:_____ Cardiologist Phone #:_____ Date of ACS:_____	**Coronary Anatomy at Discharge** Date:_____ LMCA:_____ LAD:_____ LCx:_____ RCA:_____ LIMA:_____ SVG:_____ SVG:_____ SVG:_____ LVEF:_____ by Echo/Cath/Nuclear/CMR
Risk Factor Modification Diabetic: Yes/No Smoker: Yes/No Hypertension: Yes/No Hyperlipidemia: Yes/No Overweight: Yes/No Chronic renal insufficiency: Yes/No Congestive heart failure: Yes/No Depression: Yes/No	**Stents Used (circle all that apply)** Bare-metal Drug-eluting Bioresorbable Type_____ Date implanted:_____
Follow-Up Issues to Be Addressed Reinforce dual antiplatelet therapy Aspirin for life P2Y12 inhibitor per guidelines Beta-blocker indefinitely ACE inhibitor if CHF/LVEF <40%, diabetic, hypertensive, renal insufficiency High-dose statin therapy post-ACS Check HbA1c, goal <7.0 Goal BP <130/80 Check weight, BMI, waist circumference goal BMI 18.5–24.9, goal waist circumference <40 in. (men) or <35 in. (women) Smoking cessation NTG Rx as needed; refill regularly Stop HRT Avoid NSAIDs Dietary changes – ADA, DASH diets Cardiac rehabilitation program	**Labs** Hemoglobin:_____ Platelets:_____ Creatinine:_____ Fasting glucose:_____ HbA1c:_____ Total cholesterol:_____ LDL:_____ HDL:_____ Triglycerides:_____ CRP:_____ **Antiplatelet Therapy Dosing Guidelines** Aspirin: 81 mg/day **indefinitely** Clopidogrel: 75 mg/day or ticagrelor 90 mg/BID or prasugrel 10 mg/day for _____ months **mandatory uninterrupted therapy**

11.7.1.2 P2Y12 Inhibitors

P2Y12 inhibitor therapy recommendations following ACS are outlined in the right of Fig. 11.10 [145]. In general, all patients with NSTE-ACS should receive a minimum of 12 months of DAPT regardless of whether or not they undergo coronary stenting; however earlier discontinuation may be reasonable in individual cases after a discussion of the risks and benefits of such a decision [7, 145].

11.7.1.3 Vorapaxar

Vorapaxar is a novel antiplatelet agent that antagonizes protease-activated receptor 1 (PAR-1) and inhibits thrombin-induced platelet aggregation. It has been evaluated in both the ACS population and as secondary prevention in patients with a history of MI; however it is only approved for the latter group after the TRACER (Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome) trial failed to show a benefit in reducing a composite of cardiovascular death, MI, stroke, ischemia, or need for revascularization in patients with ACS despite demonstrating an increased risk of bleeding [148]. Vorapaxar's role in post-MI management was evaluated in TRA 2P (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events) TIMI 50 in which >26,000 patients with a recent (2–12 months prior to enrollment) ischemic stroke or MI or symptomatic peripheral arterial disease treated with at least one additional antiplatelet agent (mostly clopidogrel) were assigned to vorapaxar versus placebo. While the vorapaxar arm demonstrated a statistically significant 13% reduction in the composite primary end point (cardiovascular death, MI, or stroke), moderate-significant bleeding, including intracranial bleeding, was significantly increased (4.2 vs. 2.5%; HR 1.66, 95% CI, 1.43–1.93) leading to vorapaxar's discontinuation among

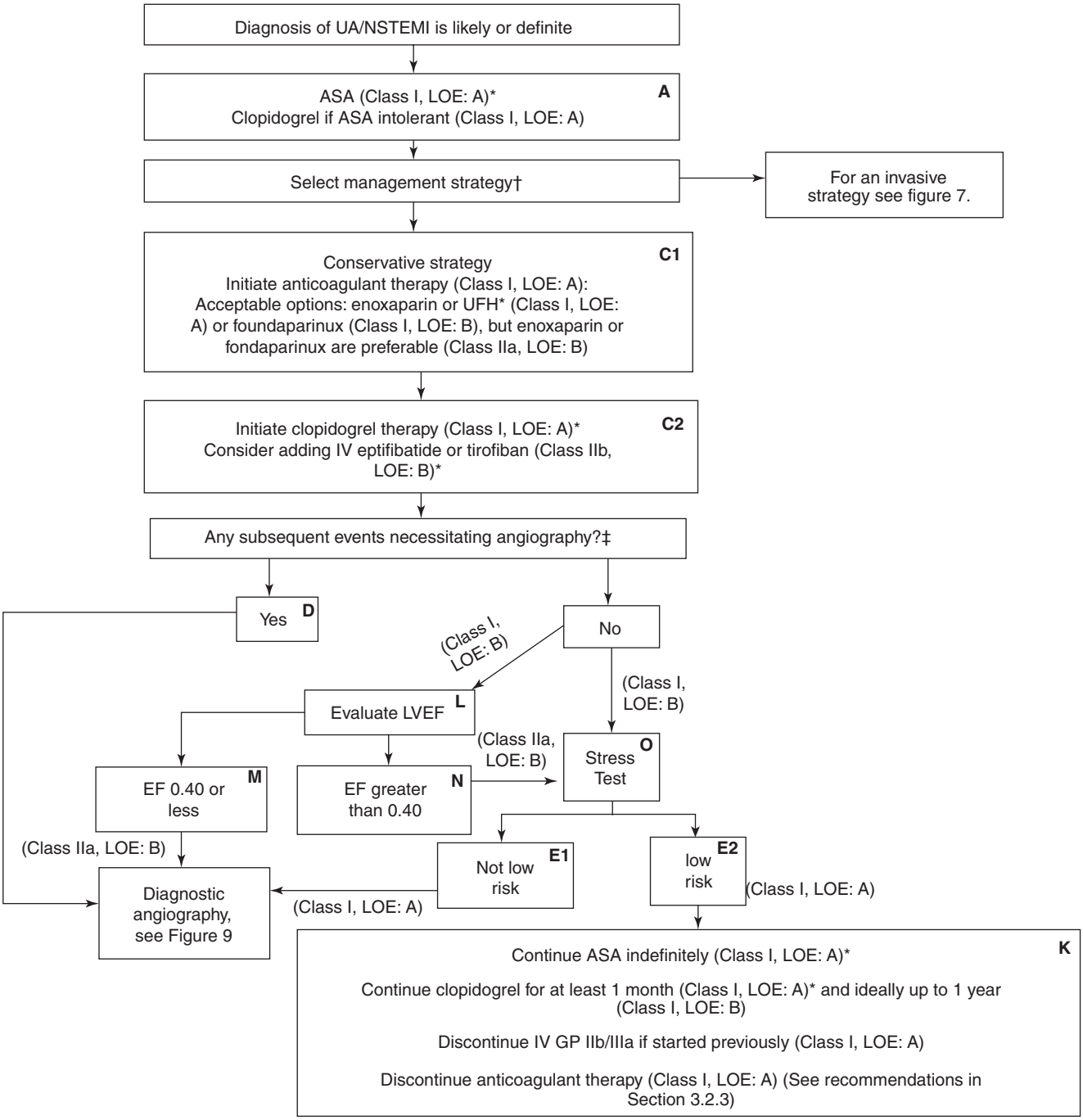

Fig. 11.10 Overall management strategy for patients with likely or definite non-ST elevation acute coronary syndromes

patients with a history of stroke or TIA [149]. These findings were reproduced among high-cardiovascular risk patients with type II diabetes mellitus [150]. Vorapaxar's role in post-ACS management remains limited to very high-cardiovascular risk patients with prior MI, low bleeding risk, and taking clopidogrel (vs. ticagrelor or prasugrel).

11.7.1.4 Beta-Adrenergic Blockers

BBs reduce mortality after ACS by as much as 23%, mainly by reducing the incidence of fatal ventricular tachyarrhythmia and blocking the effects of adverse cardiac remodeling in patients with LV systolic dysfunction [74]. Unless contraindicated, BBs should be continued indefinitely in all patients with NSTE-ACS.

11.7.1.5 Angiotensin-Converting Enzyme Inhibitors

The greatest benefit of ACE inhibitors is seen in post-MI patients with depressed LV ejection fraction (LVEF) or large anterior MI. Thus, all patients with NSTE-ACS with these conditions and/or diabetes mellitus, chronic renal insufficiency, and uncontrolled hypertension should be provided ACE inhibition in the absence of contraindication [7]. Angiotensin receptor blockers may be prescribed in cases of ACE inhibitor intolerance (e.g., persistent cough, history of angioedema).

11.7.1.6 Statins and Lipid-Lowering Therapy

Multiple studies have demonstrated that statins reduce CAD death and recurrent MI post-ACS through a wide range of pretreatment levels [90, 92, 95, 97, 151]. The PROVE-IT TIMI 22 and MIRACL trials demonstrated that early, high-intensity statin therapy confers additional benefits after MI in comparison to even moderate doses [98, 151]. ACS patients should be started on high-intensity statin therapy as soon as possible and, at a minimum, before hospital discharge. IMPROVE-IT demonstrated a modest benefit in reducing recurrent MI and stroke with the addition of ezetimibe to statin therapy [100], while ongoing trials are evaluating the role of PSCK9 inhibitors after ACS.

11.7.2 Medications of No Benefit or Harm Following ACS

11.7.2.1 Vitamins/Antioxidants

Elevated homocysteine (HCY) levels are associated with CAD; however a reduction in HCY levels through folic acid supplementation has not proven effective in several trials [152–154]. Similarly, trials of antioxidant therapy have not proven effective in both the primary and secondary prevention of cardiovascular events [155, 156]. Thus, folic acid and antioxidant supplementation should not be used for secondary prevention of NSTE-ACS [7].

11.7.2.2 Hormone Replacement Therapy

The Heart and Estrogen/Progestin Replacement Study (HERS) trial of estrogen/progestin therapy for secondary prevention of CAD in postmenopausal women failed to find benefit and in fact demonstrated a pattern of early increased risk of CAD events [157]. The Women's Health Initiative (WHI) also identified an increased risk of coronary events associated with hormone replacement therapy (HRT), especially within the first year after beginning HRT [158, 159]. These studies were stopped early in light of these observed risks. Postmenopausal women receiving HRT at the time of NSTE-ACS should discontinue its use from a strictly cardiovascular perspective, and HRT should not be initiated for secondary prevention of coronary events [7].

11.7.2.3 Nonsteroidal Anti-inflammatory Drugs

Selective COX-2 inhibitors and other nonselective, nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with increased cardiovascular risk, particularly in patients with established CAD [160, 161]. The risk of cardiovascular events is proportional to COX-2 selectivity [162]. Thus, a stepwise pharmacologic approach to the management of chronic musculoskeletal pain has been proposed that recommends alternative agents, including acetaminophen, tramadol, and/or even short-term narcotic analgesics [163]. Nonselective NSAIDs such as naproxen should only be used very sparingly for refractory pain.

11.7.3 Therapy for Comorbidities Following NSTE-ACS

11.7.3.1 Diabetes Mellitus

Almost 1/3 of patients with NSTE-ACS have diabetes mellitus; there is a strong relationship between serum glucose levels and mortality among ACS patients with diabetes mellitus [164–166]. Meticulous control of serum glucose becomes paramount following discharge. A target hemoglobin A1c of <7% is recommended by the ACC/AHA for diabetics post-MI through diet, physical activity, oral hypoglycemics, and/or insulin [167]. Thiazolidinedione drugs should be used with caution, however, since they may cause substantial sodium and fluid retention and are therefore contraindicated in patients with decompensated (NYHA Class III–IV) heart failure after ACS. Conflicting data exist about the cardiovascular effects of newer antihyperglycemic agents including the glucagon-like peptide 1 (GLP-1) agonists and dipeptidyl peptidase 4 (DPP-4) inhibitors in patients with established cardiovascular disease [168–170]. However, the addition of liraglutide, a GLP-1 agonist, to standard of care in patients with type II diabetes mellitus recently demonstrated a decreased composite of cardiovascular death, myocardial infarction, and stroke compared to placebo [171].

11.7.3.2 Hypertension

Blood pressure control through lifestyle modification and pharmacologic therapy is an essential part of the core principles of risk factor modification for secondary prevention after NSTE-ACS. There is insufficient evidence from RCTs to propose specific blood pressure treatment goals post-MI, and standard management guidelines apply [172].

11.7.3.3 Depression

Major depression is common among patients hospitalized for CAD and, in an older study, was associated with a 5.7-fold increase in cardiac mortality within 6 months after MI [173]. A combination of short-term individual cognitive behavioral therapy and selective serotonin reuptake inhibitors (SSRIs), when needed, may reduce depressive symptoms over the 6-month post-MI period in depressed or socially isolated patients.

11.7.4 Lifestyle Modifications

11.7.4.1 Smoking Cessation

Patients should be advised to quit smoking at every visit. Assistance through counseling and developing a plan for quitting is essential and can be done by arranging follow-up, referral to special programs, and/or pharmacotherapy (including nicotine replacement therapy, bupropion, or varenicline). Patients should be encouraged to reduce their exposure to secondhand smoke.

11.7.4.2 Diet/Nutrition and Weight Management

Diabetics should consider the American Diabetes Association (ADA) diet, and general dietary principles and patterns of eating should be recommended to all patients with CAD as well as those with preexisting hypertension or dyslipidemia [174].

Body mass index (BMI), including height and weight measurements, and waist circumference should be assessed at each visit. Weight maintenance and/or loss should be encouraged through a combination of physical activity, caloric intake modification, and dietary changes. A BMI of 18.5–24.9 kg/m2 and a waist circumference (measured horizontally at the iliac crest) of <40 in. for men and <35 in. for women is recommended. When weight loss is necessary, even modest (3–5%), sustained weight loss should be encouraged along with specific weight loss strategies [175].

11.7.4.3 Alcohol

Dietary studies have consistently demonstrated a J-shaped relationship between the amount of routinely consumed alcohol and cardiovascular events including ACS and stroke. Moderate consumption (0.5–1 drink daily for women, 1–2 drinks daily for men) increases HDL levels and has a positive effect on postprandial glucose and insulin levels while also reducing the risk of recurrent events after MI. The 2006 AHA/ACC diet and lifestyle guidelines reinforced that alcohol consumption cannot be recommended solely for cardiovascular disease risk reduction and did not recommend initiating alcohol consumption in persons who do not already consume alcohol as a means to prevent cardiovascular disease [176], and the most recent guidelines did not specifically comment on alcohol and NSTE-ACS [174].

11.7.4.4 Physical Activity

Resumption or initiation of regular, physical activity, and in particular aerobic exercise, should be encouraged in all patients after NSTE-ACS. Aerobic exercise training can generally begin within 1–2 weeks after NSTE-ACS treated with PCI or CABG, whereas resistance training should commence after 2 weeks. Referral to a comprehensive cardiac rehabilitation program either at discharge or after the initial posthospitalization outpatient visit is an AHA/ACC Class I recommendation [7]. Decisions regarding returning to work may be influenced not only by a patient's cardiac functional status but also by factors such as job satisfaction, financial stability, and company policies and should be assessed on an individual basis.

In stable patients without complications after NSTE-ACS, sexual activity can be resumed within 7 days [177]. Driving can begin 1 week after discharge, though this may also depend on individual state laws. Patients whose MI was complicated by cardiac arrest or other complications, such as high-degree heart block or serious arrhythmias, should delay driving for 2–3 weeks after symptoms have resolved. Air travel within the first 2 weeks after MI should be undertaken only if there is no angina, dyspnea, or hypoxemia at rest, and the patient should have a companion with them at all times [7]. Patients who had UA but no infarction can return to these activities sooner (often within a few days) than those who experienced NSTEMI.

11.8 Case Studies

11.8.1 Case 1

A 54-year-old male with type 2 diabetes mellitus, hypertension, hyperlipidemia, and a 30 pack/year smoking history presents to the emergency room with central non-radiating chest pressure while watching television. The symptoms have been intermittent over the past 3 months but usually occur after exertion or brisk walking. He takes aspirin chronically, including on the day of symptom onset. Physical examination reveals a blood pressure 160/85 mm Hg, heart rate 85, O_2 saturation 95% on room air; he has a normal S1 and S2 without murmurs, and his lungs are clear. Peripheral pulses are intact and equal, and the exam is otherwise unremarkable. His initial ECG demonstrates T-wave inversions in the inferior leads (Fig. 11.3). Chest x-ray is unremarkable. Cardiac bio-

markers show a CPK 400 ng/mL, CK-MB 85 ng/mL, and troponin T 1.36 ng/mL. He is given aspirin 325 mg by mouth. His pain is initially responsive to sublingual nitroglycerin but later intensifies, requiring an intravenous nitroglycerin drip.

11.8.1.1 Management Decisions

This patient's clinical presentation is consistent with an NSTEMI. Initial risk stratification is important in guiding further management decisions. In this case, his TIMI risk score (Table 11.8) is 3 (points for multiple cardiac risk factors, using aspirin within 24 h, and elevated cardiac biomarkers), classifying him as at least intermediate risk for major adverse events.

Appropriate anti-ischemic therapy for this patient includes intravenous nitroglycerin titrated to symptoms and limited by blood pressure effect or adverse effects (e.g., headache); beta-adrenergic blockade given the absence of hemodynamic instability, heart failure, or signs of RV infarction; and intravenous morphine if the first two agents are unsuccessful in controlling the patient's pain. Given his high TIMI risk score, he should receive immediate anticoagulation with unfractionated heparin, low-molecular-weight heparin, or bivalirudin if he were at high risk for bleeding. An early invasive strategy should be pursued given his elevated cTn-T and overall high-risk profile. In addition to aspirin, a P2Y12 receptor inhibitor should be administered either prior to or during coronary angiography, in the absence of surgical coronary disease necessitating CABG. Strong consideration should be given to administering a GP IIb/IIIa inhibitor as adjunctive antiplatelet therapy. If his symptoms were refractory to anti-ischemic therapies, performing immediate (within 2 h) cardiac catheterization would be appropriate.

11.8.2 Case 2

A 75-year-old female with obesity, hypertension, hyperlipidemia, and a 40 pack/year smoking history presents for an office visit. She was recently admitted to the hospital for an inferior NSTEMI and underwent drug-eluting stent placement for a 90% lesion in her mid-RCA. Coronary angiography otherwise revealed diffuse, nonobstructive disease in her left coronary artery system. A transthoracic echocardiogram prior to discharge revealed preserved biventricular systolic function (LVEF 55%) and mild left ventricular hypertrophy, with no significant valvular disease seen. Her current ECG demonstrates inferior Q-waves consistent with her myocardial infarction (Fig. 11.4). She is taking aspirin 81 mg/day, clopidogrel 75 mg/day, atorvastatin 80 mg/day, and metoprolol succinate 100 mg/day. Her resting heart rate is 60; however her blood pressure remains elevated at 155/90 mm Hg, correlating with her home readings. She continues to smoke 10 cigarettes/day.

11.8.2.1 Management Decisions

This patient had a recent NSTEMI in the setting of having several cardiac risk factors. She should remain on DAPT for at least 12 months, after which the risks and benefits of continued DAPT for up to 30 months should be weighed.

She remains hypertensive with evidence of pathologic cardiac remodeling (left ventricular hypertrophy) on her echocardiogram. An ACE inhibitor would be a reasonable therapy for this patient, not only for management of her hypertension but also for long-term reduction of recurrent ischemic events. Her beta-blocker therapy appears to be working effectively and has little room for uptitration given her resting heart rate.

She should remain on a high-intensity statin indefinitely, and should her LDL remain elevated (e.g., >100), first the addition of ezetimibe and if needed a PCSK-9 inhibitor would be appropriate to achieve this goal.

Further risk factor modification should also be addressed at this visit. Smoking cessation is imperative, and all available options should be reviewed in order to develop a plan for quitting. Weight maintenance should be encouraged to achieve a goal BMI of 18.5–24.9 and a waist circumference of <35 in. for a female patient.

Table 11.11 Suggested online resources for further information

Name	Web address	Features
CardioSource	http://www.cardiosource.com/	American College of Cardiology site with extensive library of images, reviews of current literature, and references to ACC/AHA guidelines
TheHeart.org	http://www.theheart.org/	An independent website with news updates from current clinical trials as well as streaming discussions, educational programs, and slide downloads
Clinical trial results	http://www.clinicaltrialresults.org/	Current clinical trials, with streaming interviews with clinical investigators, slide downloads
ACC guidelines database	http://www.acc.org/qualityandscience/clinical/topic/topic.htm	Index of ACC clinical guidelines
AHA statistics	http://www.americanheart.org/presenter.jhtml?identifier=3055922	Latest cardiovascular disease statistics from the American Heart Association
ECG wave maven	http://ecg.bidmc.harvard.edu/maven/mavenmain.asp	A leading free online ECG education tool, with many ECGs pertaining to acute coronary syndrome diagnosis and complications

Physical activity should be encouraged; it would be reasonable to refer this patient to a comprehensive cardiac rehabilitation program.

Further Reading

Several online resources are available for further detailed information regarding management of patients with NSTE-ACS. These resources can be found in Table 11.11.

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ST-Elevation Myocardial Infarction

12

Eric R. Bates and Brahmajee K. Nallamothu

Key Points

- Age, blood pressure, heart rate, congestive heart failure, and ECG findings allow early risk stratification for patients presenting with acute ST-segment elevation myocardial infarction (STEMI).
- Expeditious reperfusion therapy should be the goal for all patients with STEMI.
- Primary PCI is superior to fibrinolytic therapy if performed in a timely manner (less than 90 min) in an excellent interventional cardiology laboratory.
- Echocardiography should be performed in hemodynamically unstable patients to exclude mechanical complications.
- All patients should receive dual antiplatelet therapy with aspirin for life and a platelet $P2Y_{12}$ inhibitor for 1 year.
- Patients should acutely receive anticoagulation therapy with either unfractionated heparin, enoxaparin, fondaparinux, or bivalirudin.
- Patients should receive an oral beta-blocker within 24 h unless contraindications exist.
- Aspirin, beta-blockers, statins, and ACE inhibitors have each been shown to reduce long-term mortality.
- Aldosterone blockade is indicated in patients with LVEF ≤40% and either symptomatic heart failure or diabetes mellitus, unless they have renal dysfunction or hyperkalemia.
- Risk stratification should be performed to select high-risk patients for elective coronary artery revascularization and ICD therapy.
- Patients should be referred to a cardiac rehabilitation program subsequent to discharge from hospital.
- Long-term adoption of American Heart Association Step II diet, exercise, and smoking cessation is indicated. Control of hypertension, hyperlipidemia, diabetes mellitus, and weight to target values should be aggressively pursued.

12.1 Introduction

Acute ST-elevation myocardial infarction (STEMI) is the leading cause of death in the United States. The American Heart Association estimated that there were 750,000 Americans with acute myocardial infarction (MI) in 2016 [1]. Approximately 30–45% of these were STEMI. Excellent societal guideline recommendations exist for STEMI care [2–4].

Atherosclerotic coronary artery disease and plaque rupture with resultant thrombosis remain the most common cause of MI. Other, less common, causes include arteritis, spontaneous dissection, embolization, congenital anomalies, hypercoagulable states, and substance abuse.

12.2 Patient Evaluation

12.2.1 History

The risk for STEMI increases with age. Patients often have a family history of coronary artery disease or risk factors including smoking, hypertension, diabetes mellitus, dyslipidemia, or obesity. The classic symptom is crushing retrosternal chest discomfort with radiation to the left arm. Some individuals may present with epigastric discomfort

E. R. Bates (✉) · B. K. Nallamothu
Division of Cardiovascular Medicine, University of Michigan Medical Center, Ann Arbor, MI, USA
e-mail: ebates@umich.edu

P. P. Toth, C. P. Cannon (eds.), *Comprehensive Cardiovascular Medicine in the Primary Care Setting*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-319-97622-8_12

that can lead to the misdiagnosis of heartburn or another abdominal disorder. Elderly individuals may not have any chest discomfort but may present with symptoms of left ventricular failure, marked weakness, or syncope. Postoperative patients and diabetic patients are other subgroups that may not experience classic symptoms. Patients may also present with neck, jaw, back, shoulder, or right arm discomfort as the sole manifestation. Other associated symptoms can include diaphoresis, dyspnea, fatigue, weakness, dizziness, palpitations, acute confusion, nausea, or emesis.

12.2.2 Physical Examination

The physical examination is more important in excluding other diagnoses and in risk-stratifying patients than in establishing the diagnosis of MI. Patients presenting with STEMI often appear anxious and distressed. All patients should have a thorough cardiovascular examination as a baseline to monitor for complications that may develop, such as ventricular septal rupture or acute mitral regurgitation. A fourth heart sound is almost universally present in patients who are in sinus rhythm. Systolic blood pressure, heart rate, rales, and a third heart sound are important prognostic determinants. A baseline neurologic examination is important, particularly before fibrinolytic therapy is initiated.

12.2.3 Electrocardiogram

The electrocardiographic diagnosis of STEMI requires at least 1 mm of acute ST-segment elevation in two or more contiguous leads. The presence of prior left bundle branch block may confound the diagnosis, but striking ST-segment deviation that cannot be explained merely by conduction abnormality is suggestive of STEMI. The electrocardiogram (ECG) also is a valuable clinical tool for determining infarct location and estimating potential infarct size.

12.2.4 Cardiac Biomarkers

The serum cardiac markers used in the diagnosis of MI include creatine kinase (CK), creatine kinase–myocardial band (CK–MB) isoenzyme, and cardiac-specific troponins. The diagnosis of MI includes any elevation of serum cardiac biomarkers (preferably troponin) combined with symptoms, ECG signs, or cardiac imaging evidence consistent with myocardial ischemia [5].

12.2.5 Echocardiography

The portability of echocardiography makes it a valuable clinical tool. This technique can add useful information to confirm or exclude the diagnosis and to help with risk stratification. The echocardiogram is very helpful in diagnosing the mechanical complications of STEMI.

12.3 Differential Diagnosis

Pulmonary embolism can present with chest discomfort associated with severe shortness of breath without clinical or radiographic evidence of pulmonary edema. Echocardiography may be useful by demonstrating normal left ventricular wall motion and right ventricular dilatation and strain, although spiral computed tomography has more recently routinely been used. Patients with pneumothorax and pleuritis may also present with substernal chest discomfort, but the character of the pain is different, and the pain is often worse with inspiration.

Acute aortic dissection pain is typically central, severe, and often described by the patient as a tearing sensation. The pain is maximal at onset and persists for many hours. It is extremely important to diagnose this condition because fibrinolytic therapy usually results in death. Chest radiography often shows a widened mediastinum. The diagnosis is usually confirmed with transesophageal echocardiography, computed tomography, or magnetic resonance imaging.

Pericardial pain is usually aggravated by inspiration and lying supine. It is important to distinguish pericarditis from STEMI because inadvertent fibrinolysis in patients with pericarditis may lead to hemopericardium. The ST-segment changes in pericarditis are diffuse, with a concave upward slope. Other important diagnostic features include PR-segment depression and absence of reciprocal ST-segment depression.

Myocarditis typically presents with more gradual onset of symptoms and prior upper respiratory tract symptoms in a relatively young patient. Serum cardiac markers usually remain elevated rather than peaking and returning to baseline levels.

Patients with hypertrophic cardiomyopathy may present with chest discomfort similar to angina, related to increased myocardial oxygen demand. Transthoracic echocardiography is a useful test for diagnosing this condition. Use of nitroglycerin or dobutamine may precipitate hypotension and syncope in affected patients.

Patients with acute cholecystitis may present with symptoms and occasionally ECG findings suggestive of inferior MI. The presence of fever, marked leukocytosis, and right upper quadrant tenderness favors the diagnosis of cholecystitis. Esophageal and other upper gastrointestinal symptoms may also mimic ischemic chest discomfort.

Costochondritis pain is usually associated with localized swelling and redness, and the character of the pain is usually sharp with marked focal tenderness.

Patients with a hyperventilation or panic attack present with chest discomfort, panic/acute anxiety, lightheadedness, air hunger, and paresthesias.

12.4 Therapy

12.4.1 Prehospital Care

There is increasing emphasis on establishing a regional prehospital system of care network of hospitals connected with efficient ambulance services [6]. Early activation of the emergency medical system, public education in cardiopulmonary resuscitation, and a well-trained ambulance service are important components. Shared written protocols, prehospital diagnosis and treatment, and rapid transport to the most appropriate hospital facility by ambulance or helicopter are crucial for optimal management. The ability to treat out-of-hospital cardiac arrest with prompt cardiopulmonary resuscitation, early defibrillation, and advanced cardiac life support is the greatest opportunity for increasing survival with STEMI. Rapid diagnosis and early risk stratification of patients with acute chest pain more quickly identify patients who are candidates for reperfusion therapy.

12.4.2 General Treatment Measures

Several interventions should quickly be undertaken while patients are being evaluated for reperfusion therapy (Table 12.1). First, patients with overt pulmonary congestion and arterial oxygen desaturation (saturation less than 90%) should be given supplemental oxygen, as should all patients with MI during the first 2–3 h. Second, sublingual nitroglycerin every 5 min for a total of three doses should be given, with intravenous therapy considered for ongoing ischemic discomfort, control of hypertension, and management of congestive heart failure. Patients should first be asked about recent use of sildenafil because administration of nitroglycerin within 24 h of sildenafil ingestion, or a similar agent, may cause severe hypotension. Third, morphine sulfate is the analgesic of choice to manage pain.

12.4.3 Reperfusion Therapy

Patients within 12 h of symptom onset are candidates for reperfusion therapy for survival benefit, although little myocardial salvage occurs after 3–4 h of myocardial ischemia. Therefore, the overarching goal in STEMI is to initiate reperfusion therapy within 2 h (ideally within 60 min) of symptom onset (Fig. 12.1). An underutilized strategy for improving systems of care for STEMI patients is to expand the use of prehospital 12-lead electrocardiography programs by emergency medical systems [2].

It is increasingly clear that two types of hospital systems provide reperfusion therapy: those with PCI capability and those without PCI capability. STEMI patients presenting to a hospital with PCI capability should be treated with primary PCI within 90 min of first medical contact as a systems goal. The best outcomes are achieved by offering this strategy 24 h/day, 7 days/week.

Because of the critical importance of time to treatment, fibrinolytic therapy is generally preferred, if there are no

Table 12.1 Diagnostic and treatment measures in patients with ST-elevation myocardial infarction

Initial diagnostic measures	
1.	Use continuous ECG; automated BP, HR monitoring
2.	Take targeted history (for MI inclusions, fibrinolysis exclusions). Check vital signs, perform focused examination
3.	Start IV(s); draw blood for serum cardiac markers, hematology, chemistry, lipid profile
4.	Obtain 12-lead ECG
5.	Obtain chest X-ray
General treatment measures	
1.	Oxygen 2–4 L/min by nasal cannula
2.	Nitroglycerin 0.4 mg sublingual every 2–5 min three times
3.	Morphine (2–4 mg) as needed
Specific treatment measures	
1.	Reperfusion therapy
	Primary PCI: door-to-balloon time <90 min
	Fibrinolytic therapy: door-to-needle time <30 min
	Alteplase: 15 mg IV bolus, infusion 0.75 mg/kg over 30 min (max 50 mg), then 0.5 mg/kg over 60 min (max 35 mg)
	Reteplase: 10 U IV over 2 min, repeated in 30 min
	Tenecteplase: 0.5 mg/kg IV bolus
2.	Antiplatelet therapy
	Aspirin: 81 mg daily (160–325 mg load)
	Clopidogrel: 75 mg daily (600 mg load with primary PCI, 300 mg load if age ≤75 year)
	Prasugrel: 10 mg daily (60 mg load)
	Ticagrelor 90 mg twice daily (180 mg load)
3.	Antithrombotic therapy
	Unfractionated heparin: 60 U/kg (max, 4000 U), 12 U/kg/h (max, 1000/h) adjusted to keep aPTT 50–70 s × sec × 48 h
	Enoxaparin: 30 mg IV load, 1 mg/kg SC twice daily if age ≤75 year; no bolus, 0.75 mg/kg SC twice daily if age >75 year
	Fondaparinux: 2.5 mg IV bolus, 2.5 mg SC once daily
	Bivalirudin: 0.75 mg/kg bolus, 1.75 mg/kg/h infusion

ECG electrocardiogram, *BP* blood pressure, *HR* heart rate, *MI* myocardial infarction, *IV* intravenous administrations, *PCI* percutaneous coronary intervention, *S* subcutaneous

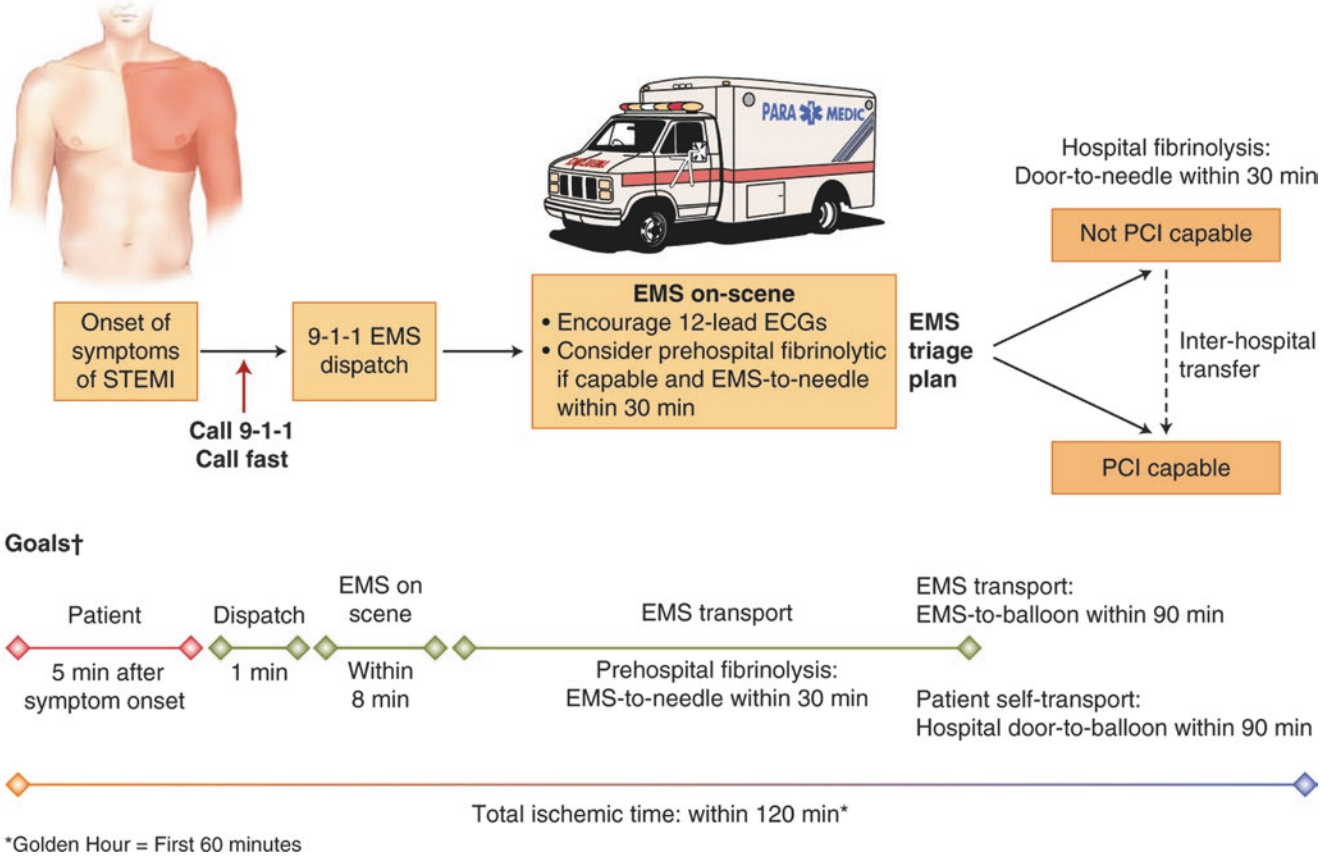

Fig. 12.1 Transportation options and initial reperfusion treatment [2]

contraindications (Table 12.2), in hospitals without PCI capability who cannot transfer the patient for PCI within a door-to-balloon time of 120 min. There need to be transfer protocols in place for arranging rescue PCI when clinically indicated. For fibrinolytic therapy, the systems goal is to deliver drug within 30 min of hospital presentation.

12.4.4 Primary PCI

In unstable patients, such as those with cardiogenic shock (especially those less than 75 years of age), severe congestive heart failure/pulmonary edema, or hemodynamically compromising ventricular arrhythmias (regardless of age), a strategy of immediate coronary angiography with intent to perform PCI is a useful approach regardless of symptom duration or prior therapy. In stable patients, primary PCI has been associated with better outcomes than fibrinolytic therapy, when performed quickly in an excellent interventional cardiology laboratory [7]. Routine coronary stent implantation decreases the need for subsequent target vessel revascularization but does not reduce death or reinfarction rates. Drug-eluting stents further reduce the risk of reintervention,

Table 12.2 Absolute and relative contraindications for fibrinolytic therapy [2]

Contraindications
Previous hemorrhagic stroke at any time, other strokes or cerebrovascular events with 1 year
Known intracranial neoplasm
Active internal bleeding (does not include menses)
Suspected aortic dissection
Cautions/relative contraindications
Severe uncontrolled hypertension on presentation (blood pressure >180/110 mmHg)
History of prior cerebrovascular accident or known intracerebral pathology not covered in contraindications
Current use of anticoagulants in therapeutic doses (INR 2.0–3.0), known bleeding diathesis
Recent trauma (within 2–4 weeks), including head trauma or traumatic or prolonged (>10 min) CPR or major surgery (<3 weeks)
Non-compressible vascular punctures
Recent (within 2–4 weeks) internal bleeding
For streptokinase: prior exposure (especially within 5 days–2 years) or prior allergic reaction
Pregnancy
Active peptic ulcer
History of chronic severe hypertension

INR international normalized ratio, *CPR* cardiopulmonary resuscitation

compared with bare metal stents, without changing the risk for stent thrombosis, reinfarction, or death. However, they might be avoided in selected patients who need oral anticoagulation (atrial fibrillation, left ventricular thrombus, mechanical valves) because of the bleeding risk associated with long-term triple antithrombotic therapy. PCI may be considered in stable patients from 12 to 24 h after symptom onset but is contraindicated after 24 h if the artery is totally occluded and there are no signs of ischemia [2]. PCI of a hemodynamically significant stenosis in a patent infarct artery greater than 24 h after STEMI may be considered as part of an invasive strategy to maintain long-term patency.

12.4.5 Rescue PCI

Failed fibrinolysis can be assumed when there is <50% ST-segment resolution 90 min following initiation of therapy in the lead showing the greatest degree of ST-segment elevation at presentation. Rescue PCI should be considered if there is clinical or ECG evidence of a moderate or large infarct and the procedure can be performed within 12 h of symptom onset [8]. Facilitated PCI, defined as a pharmacological reperfusion treatment delivered prior to planned PCI in order to improve coronary patency, has not been shown to reduce infarct size or improve outcomes [9].

12.4.6 Coronary Angiography

When it is likely that fibrinolysis was successful (ST-segment resolution >50% at 90 min, typical reperfusion arrhythmia, resolution of chest pain), coronary angiography within 3–24 h is recommended if there are no contraindications [2]. Early PCI decreases the risk and complications of infarct artery reocclusion. In patients who did not receive reperfusion therapy, angiography is recommended before hospital discharge [2].

12.4.7 Antiplatelet Therapy

Platelet $P2Y_{12}$ inhibitor therapy should be added to aspirin as dual antiplatelet therapy in all STEMI patients. With fibrinolytic therapy, a 300-mg oral loading dose of clopidogrel should be administered if age is ≤75 year, but not if age is >75 year [10]. The clopidogrel loading dose with primary PCI should be 600 mg. Prasugrel or ticagrelor is preferred for primary PCI [3]. Nonsteroidal anti-inflammatory drugs (NSAIDs) and selective cyclooxygenase (COX-2) inhibitors increase the risk of death, reinfarction, cardiac rupture, and other complications and should be discontinued.

12.4.8 Antithrombin Therapy

Bivalirudin [11] is an alternative to unfractionated heparin with primary PCI, but fondaparinux [12] should be avoided as the sole anticoagulant because of the risk of catheter thrombosis. Enoxaparin [13] and fondaparinux are alternatives to unfractionated heparin [14] with fibrinolytic therapy or in patients not receiving reperfusion therapy. For age >75 years, enoxaparin should be started at a reduced dose (0.75 mg/kg) without an intravenous bolus. If PCI is not performed, enoxaparin and fondaparinux should be administered for the duration of the hospital stay, but unfractionated heparin should only be administered for 48 h because of the risk of heparin-induced thrombocytopenia.

12.4.9 Routine Prophylactic Therapies in the Acute Phase

There is no mortality benefit for the early routine use of intravenous beta-blocker therapy, although it can be useful in treating hypertension [15]. Oral beta-blockers, statins (irrespective of baseline total cholesterol or low-density lipoprotein cholesterol), and ACE inhibitors should be started in stable patients within 24 h, if no contraindications are present. No benefit has been demonstrated with routine use of calcium channel blockers, magnesium, lidocaine, or glucose–insulin–potassium infusions.

12.5 Complications

Sudden cardiac death before hospital admission is the most common cause of mortality in STEMI. In-hospital mortality is primarily due to circulatory failure resulting from either severe left ventricular dysfunction or one of the mechanical complications. The complications of STEMI may be broadly classified as hemodynamic, mechanical, electrical, ischemic, embolic, and pericardial.

12.5.1 Hemodynamic Complications

12.5.1.1 Hypotension

Hypotension (systolic pressure <90 mmHg or 30 mm below previous pressure) can result from hypovolemia, hemorrhage, arrhythmia, heart failure, mechanical complications, or other complications such as sepsis or pulmonary embolism (Fig. 12.2). Rapid volume loading and correction of underlying etiologies are recommended. Persistent hypotension should be evaluated with echocardiography to define cardiac anatomy. Vasopressor and inotropic agents may be required for inotropic failure.

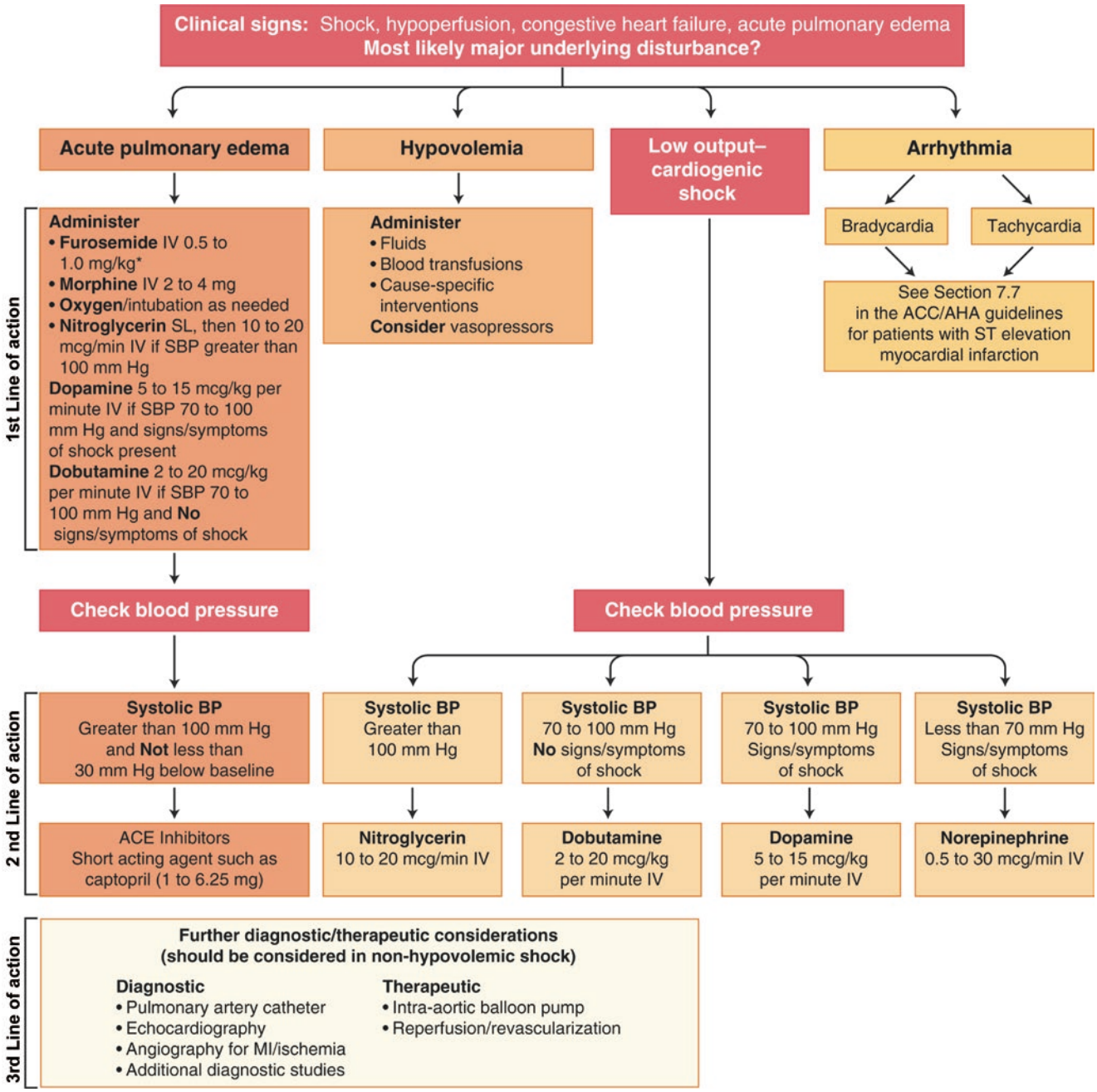

Fig. 12.2 Emergency management of complicated ST-elevation myocardial infarction [2]

12.5.1.2 Left Ventricular Failure

The degree of left ventricular failure can be categorized by the Killip classification: class 1, no rales or third heart sound; class 2, pulmonary congestion with rales over <50% of the lung fields or third heart sound; class 3, pulmonary edema with rales over 50% of the lung fields; and class 4, cardiogenic shock. Therapeutic measures for Killip class 2 and 3 heart failure include oxygen, nitrates, morphine, diuretics, vasodilator therapy, and correction of arrhythmia and electrolyte abnormalities.

12.5.1.3 Right Ventricular Failure

Mild right ventricular dysfunction is common after inferior MI, but hemodynamically significant right ventricular impairment is seen in only 10% of patients. The triad of hypotension, jugular venous distention, and clear lungs is very specific but has poor sensitivity for right ventricular infarction. Patients with severe right ventricular failure have symptoms of low cardiac output, including diaphoresis, clammy extremities, and altered mental status. Patients are often oliguric and hypotensive. The ECG usually shows

an inferior injury current. ST-elevation in V4R in the setting of suspected right ventricular infarction has a positive predictive value of 80%. Hemodynamic monitoring with a pulmonary artery catheter usually reveals high right atrial (RA) pressures relative to the pulmonary artery wedge pressure (PCWP). Acute right ventricular failure results in underfilling of the left ventricle and the low cardiac output state. An RA pressure higher than 10 mmHg and an RA/PCWP ratio of 0.8 or higher are strongly suggestive of right ventricular infarction. Treatment of right ventricular infarction involves volume loading, inotropic support with dobutamine, and maintenance of atrioventricular synchrony. Patients who undergo successful reperfusion of the right coronary artery and the right ventricular branches have improved right ventricular function and decreased 30-day mortality rates.

12.5.1.4 Cardiogenic Shock

Cardiogenic shock is a clinical state of hypoperfusion, hypotension, and low cardiac output due to extensive loss of viable myocardium. Urgent echocardiography and placement of a pulmonary artery catheter can confirm the diagnosis and exclude other conditions. Mechanical ventilation and intra-aortic balloon counterpulsation (IABP) assist in stabilizing the patient. Vasopressor agents and dobutamine are required to improve perfusion. Emergency revascularization of viable myocardium with PCI or surgery can be lifesaving.

12.5.2 Mechanical Complications

12.5.2.1 Free Wall Rupture

Left ventricular free wall rupture occurs in 3% of patients and accounts for about 10% of deaths from STEMI. Advanced age, female gender, hypertension, first MI, and poor coronary collateral vessels are risk factors for free wall rupture. Emergency thoracotomy with surgical repair is the definitive therapy, but most patients die within minutes. Pseudoaneurysm results from a contained rupture of the left ventricular free wall by the pericardium and mural thrombus. Spontaneous rupture occurs without warning in approximately one-third of patients; therefore, surgical resection is recommended for both symptomatic and asymptomatic patients, irrespective of the aneurysm size.

12.5.2.2 Ventricular Septal Rupture

Ventricular septal rupture occurs in 0.5–2% of patients. The diagnosis should be suspected with sudden hemodynamic deterioration and a new loud pansystolic murmur. Echocardiography with color flow imaging or an increase in oxygen saturation in the right ventricle can confirm the diagnosis. An IABP should be inserted as early as possible, unless there is significant aortic regurgitation. Nitroprusside can be used with close hemodynamic monitoring. Early surgical repair is the treatment of choice.

12.5.2.3 Mitral Regurgitation

Mitral regurgitation is common and is usually caused by mitral valve annulus dilatation due to left ventricular dysfunction or to papillary muscle dysfunction. However, rupture of the papillary muscle trunk or tip occurs in 1% of patients and contributes to 5% of the deaths. It is more common with inferior MI. Sudden hemodynamic deterioration and a new soft pansystolic murmur at the cardiac apex are the usual clinical presentation. Two-dimensional echocardiography with Doppler and color flow imaging is the diagnostic modality of choice. Hemodynamic monitoring with a pulmonary artery catheter may reveal large V waves in the PCWP tracing. Vasodilator and IABP therapy should be initiated, and immediate surgery should be performed.

12.5.2.4 Left Ventricular Aneurysm

An acute aneurysmal segment expands in systole, wasting contractile energy generated by the normal myocardium. Chronic aneurysms develop in 10% of patients without reperfusion therapy and are more commonly seen after anterior MI. Heart failure, ventricular arrhythmias, and systemic embolism of mural thrombus are possible sequelae. Heart failure with acute aneurysm is treated with intravenous vasodilators and IABP. Anticoagulation with warfarin is indicated for patients with mural thrombus. In patients with refractory heart failure or ventricular arrhythmias, surgical resection of the aneurysm should be considered. Revascularization may be beneficial in patients with a large amount of viable myocardium in the aneurysmal segment.

12.5.3 Electrical Complications

Arrhythmias are the most common complications after STEMI, affecting approximately 90% of patients. Conduction abnormalities causing hypotension may necessitate temporary or permanent pacemaker therapy. These are briefly summarized in Table 12.3. An implantable cardioverter defibrillator is indicated in patients with sustained ventricular fibrillation or ventricular tachycardia more than 2 days after the MI if recurrent ischemia or transient causes have been excluded and may be implanted for primary prevention if left ventricular function is significantly reduced 1 month after STEMI.

12.5.4 Ischemic Complications

Infarct extension is a progressive increase in the amount of myocardial necrosis within the same arterial territory as

Table 12.3 Electrical complications of acute myocardial infarction and their management

Category	Arrhythmia	Objective	Treatment
1. Electrical instability	Ventricular premature beats	Correct electrolyte deficits and decrease sympathetic tone	Potassium and magnesium replacement; beta-blockers
	Ventricular tachycardia	Prophylaxis against ventricular fibrillation, restoration of hemodynamic stability	Antiarrhythmic agents; cardioversion
	Ventricular fibrillation	Urgent reversion to sinus rhythm	Defibrillation
	Accelerated idioventricular rhythm	Observation unless hemodynamic function is compromised	Increase sinus rate (atropine, atrial pacing); antiarrhythmic agents
	Nonparoxysmal atrioventricular junctional tachycardia	Search for precipitating causes (e.g., digitalis intoxication); suppress arrhythmia only if hemodynamic function is compromised	Atrial overdrive pacing; antiarrhythmic agents; cardioversion relatively contraindicated if digitalis intoxication is present
2. Pump failure/ excessive sympathetic stimulation	Sinus tachycardia	Reduce heart rate to diminish myocardial oxygen demand	Antipyretics; analgesics; consider beta-blocker unless congestive heart failure is present; treat latter with diuretics and afterload reduction
	Atrial fibrillation and/or atrial flutter	Control ventricular rate; restore sinus rhythm	Diltiazem, verapamil, digitalis; anticongestive measures (diuretics, afterload reduction); cardioversion; rapid atrial pacing (for atrial flutter)
	Paroxysmal supraventricular tachycardia	Reduce ventricular rate; restore sinus rhythm	Vagal maneuvers; verapamil, digitalis, beta-adrenergic blockers; cardioversion; rapid atrial pacing
3. Bradyarrhythmias and conduction disturbances	Sinus bradycardia	Acceleration of heart rate only if hemodynamic function is compromised	Atropine; atrial pacing
	Junctional escape rhythm	Acceleration of sinus rate only if loss of atrial "kick" causes hemodynamic compromise	Atropine; atrial pacing
	Atrioventricular block and intraventricular block	–	Ventricular pacing

Adapted from [16]

the original MI. Recurrent angina within a few hours to 30 days after MI is defined as postinfarction angina. The frequency of postinfarction angina is higher after fibrinolytic therapy than after primary PCI. Patients with postinfarction angina have an increased incidence of sudden death, reinfarction, and acute cardiac events. Either PCI or surgical revascularization improves prognosis in these patients. It may be difficult to differentiate ECG changes of reinfarction from the evolving ECG changes of the index MI. Recurrent elevations in CK–MB after normalization or to more than 50% of the prior value are diagnostic of reinfarction.

12.5.5 Embolic Complications

The incidence of systemic embolism after MI is approximately 2%; the incidence is higher in patients with anterior MI. Patients with large anterior MI or mural thrombi should be treated with intravenous heparin for 3–4 days with a target partial thromboplastin time of 50–70 s. Oral therapy with warfarin should be continued for at least 3 months in patients with mural thrombus and in those with large akinetic areas detected by echocardiography.

12.5.6 Pericardial Complications

Early pericarditis usually develops within 24–96 h. The pain is constant, worse with lying supine, alleviated by sitting up and leaning forward, usually pleuritic in nature, and worsened with deep inspiration, coughing, and swallowing. Postinfarction pericarditis is treated with aspirin in doses of 650 mg every 4–6 h. Nonsteroidal anti-inflammatory agents and corticosteroids should not be administered to these patients because they may interfere with myocardial healing and contribute to infarct expansion. Colchicine may be beneficial in patients with recurrent pericarditis. Dressler's syndrome (post-MI syndrome) occurs in 1–3% of patients and is seen 1–8 weeks after MI. Patients present with chest discomfort suggestive of pericarditis, fever, arthralgia, malaise, elevated leukocyte count, and elevated erythrocyte sedimentation rate. Treatment is similar to that for early postinfarction pericarditis.

12.6 Prognosis

The thrombolysis in myocardial infarction (TIMI) risk score for STEMI is a simple tool for bedside risk assessment [17]. The elements of the TIMI score are shown in Fig. 12.3 and

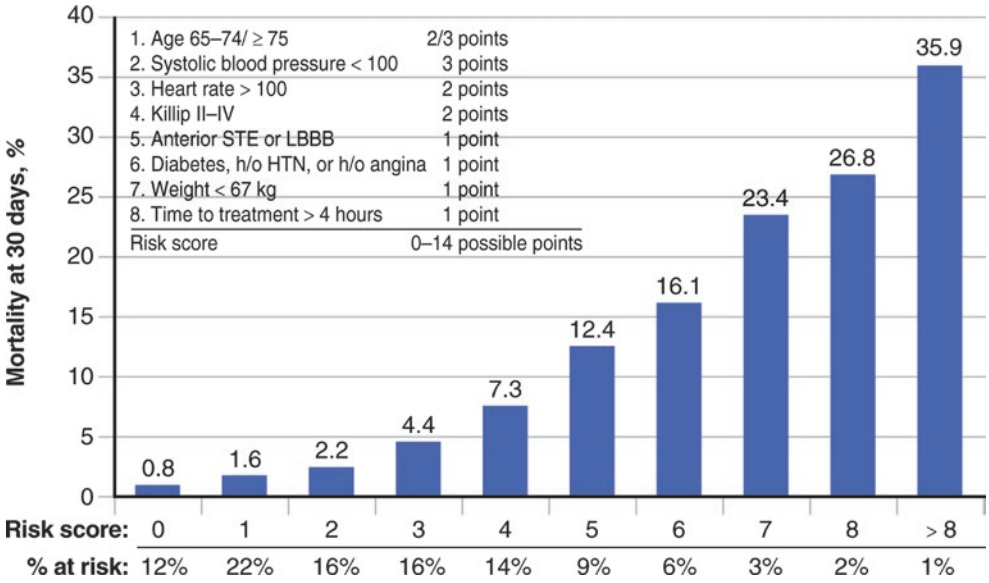

Fig. 12.3 Prediction of 30-day mortality with thrombolysis in myocardial infarction (TIMI) risk score after fibrinolytic therapy for STEMI [17]

include history, physical examination, and electrocardiographic findings on presentation. The actual score is a summed weighted integer score based on eight characteristics. With current therapy, patients treated with early reperfusion therapy have a 4–6% hospital mortality and a 2–4% risk for death in the year following discharge. However, long-term prognosis is variable and depends on left ventricular function, ischemic burden, revascularization status, and comorbidities.

12.7 Follow-Up

All patients should have a return clinic visit in 2–4 weeks and be considered for a cardiac rehabilitation program. Aspirin 81 mg daily should be continued for life. Clopidogrel, prasugrel, or ticagrelor should be continued daily for 12 months. Oral anticoagulants should be given to patients who do not tolerate aspirin and clopidogrel and to those with clinical indications. Oral beta-blockers, ACE inhibitors or angiotensin receptor inhibitors, and statins should be administered to all patients without contraindications. Aldosterone blockade may be considered with left ventricular ejection fraction <40% and heart failure or diabetes, if the creatinine is <2.5 mg/dL in men and <2.0 mg/dL in women and the potassium is ≤5.0 mEq/L. Elective stress testing can be performed as clinically indicated to evaluate patients with multivessel disease for elective coronary revascularization. Assessments for cardiac resynchronization therapy or implantation of an implantable cardioverter defibrillator are made after 1 month of treatment in patients with significant left ventricular dysfunction. All patients should receive yearly influenza immunizations.

Aggressive targets for managing hypertension (blood pressure <140/90 mmHg), diabetes mellitus (HbA1c <7.0%), and LDL cholesterol (<70 mg/dL) have been established. Smoking cessation, diet, weight control, and aerobic exercise at least five times per week are important lifestyle interventions.

12.8 Case Studies

12.8.1 Case 1

A 76-year-old man presents to the emergency department with a 2-h history of retrosternal chest tightness, lightheadedness, and nausea. Medications include aspirin, lisinopril, and simvastatin. On physical examination, the blood pressure is 100/60 mmHg, heart rate 50 bpm, and respirations 20 per min. The jugular venous pressure is 10 cm with a positive Kussmaul sign, the lungs are clear, the heart sounds are normal without extra sounds or murmurs, and degenerative joint disease is present in the hands and knees. The ECG shows sinus bradycardia, 3-mm ST-segment elevation in the inferior leads, 2-mm ST-segment depression in leads V_1–V_3, and 1-mm ST-segment elevation in lead V_4R. A diagnosis of acute inferior/right ventricular STEMI is made, and the patient is immediately referred to the interventional cardiology laboratory for primary PCI. During the informed consent process, the patient states that he is scheduled for total knee replacement surgery in 1 month.

12.8.2 Management Decisions

Although the standard STEMI protocol includes administering nitroglycerin and morphine, these drugs should be withheld in a patient with right ventricular infarction because they decrease ventricular filling pressures. Adequate preload and maintenance of atrioventricular synchrony are important to assure hemodynamic stability.

The ECG would predict a large right coronary artery with a proximal occlusion, and that was what angiography demonstrated. Although the patient was on chronic aspirin, an additional 325-mg dose would be reasonable. Prasugrel and ticagrelor are new platelet $P2Y_{12}$ receptor inhibitors. Compared with clopidogrel, they have faster onset of action, more complete platelet inhibition, and almost no nonresponders, so they are the preferred agents for primary PCI.

A guidewire was easily passed into the distal artery, and balloon angioplasty successfully restored coronary blood flow. The ST-segment changes resolved quickly, suggesting microvascular reperfusion and salvage of ischemic myocardium. Stent implantation reduces the risk of infarct artery reocclusion during the first days and weeks after PCI and decreases the risk of restenosis over the following months. Given the large diameter of the artery and the need for elective surgery in the near future, a bare metal stent was implanted without complication. Dual antiplatelet therapy can be discontinued in 4 weeks, and surgery can be performed 7 days after stopping the $P2Y_{12}$ inhibitor. Implantation of a drug-eluting stent would require at least 6 months of uninterrupted dual antiplatelet therapy. When surgery is required in patients on dual antiplatelet therapy after stent implantation, the first option is to continue dual antiplatelet therapy, the second option is to stop only aspirin, and the last option is to stop both drugs. Therapy should be resumed as soon as possible after surgery to decrease the risk of subacute stent thrombosis.

12.8.3 Case 2

A 65-year-old woman collapses in a shopping mall after feeling ill for 30 min. A bystander notes the patient is apneic and pulseless and so starts cardiopulmonary resuscitation. An automated external defibrillator successfully restores her heart rate and consciousness, and she is emergently transported to the emergency department of a hospital without primary PCI capability. On physical examination, she is ashen and restless. Blood pressure is 80/40 mmHg, heart rate 115 bpm, respirations 32 per min, and oxygen saturation 85% on a face mask. Rales are heard in both lung bases, heart sounds are distant, and extremities are cool. The ECG shows ST-segment elevation in leads $V_{2–6}$, I, and aVL. A diagnosis of acute anterior STEMI complicated by cardiogenic shock is made.

12.8.3.1 Management Decisions

Several interventions must immediately be pursued to stabilize the patient. Oxygenation and airway support may require tracheal intubation and mechanical ventilation. Rhythm control may require an external pacemaker for bradycardia or cardioversion/defibrillation for tachyarrhythmias. Inotropic support with dobutamine and vasopressor support with norepinephrine should be titrated to maintain perfusion pressure. Nasogastric and urinary catheters need to be inserted. Initiation of intra-aortic balloon counterpulsation can offer mechanical support of the circulation.

Hospitals without PCI capability should give fibrinolytic therapy to patients with STEMI when interhospital transfer and primary PCI cannot be accomplished within 120 min. A transfer plan needs to be in place for patients needing rescue PCI or primary PCI when fibrinolytic contraindications are present. With cardiogenic shock, however, emergency transfer for PCI must occur regardless of treatment delays, unless further treatment is considered futile. Fibrinolytic therapy can be administered, but reperfusion rates are low because of hypotension. Only early revascularization with PCI or CABG has been shown to significantly decrease the mortality risk.

The hospital mortality rate with cardiogenic shock is approximately 50%. More than 80% of 1-year survivors are in NYHA functional class I or II. In addition to the routine recommendations for post-discharge care and additional treatment if heart failure is present, these patients require measurement of left ventricular ejection fraction at least 1 month after presentation; an implantable cardioverter defibrillator is usually indicated for values less than 35%.

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Coronary Artery Stenting

13

Michela Faggioni, Eric A. Heller, and George D. Dangas

Key Points

- Percutaneous coronary intervention (PCI) has been proven to be safe and effective in the treatment of coronary artery disease.
- PCI improves survival and prevents recurrent infarction in patients with acute MI.
- An early invasive strategy for ACS that includes PCI reduces major adverse coronary events.
- PCI in stable angina should be used as an adjunct to optimal medical therapy for symptom relief and ischemia reduction.
- PCI may be equivalent to CABG as the revascularization treatment of choice for selected patients with multivessel disease.
- Emerging evidence suggests the benefits of revascularization may be driven by ischemic burden and not symptom severity.
- In-stent restenosis (ISR) is the Achilles heel of PCI's efficacy and has been markedly reduced by drug-eluting stents (DES) and the introduction of novel antiplatelet therapies.
- Stent thrombosis is a rare but serious complication of PCI and is reduced by optimization of stent placement and adherence to dual antiplatelet therapy.

M. Faggioni
Mount Sinai Heart, Mount Sinai Medical Center, New York, NY, USA

Cardiothoracic Department, Division of Cardiology, University Hospital of Pisa, Pisa, Italy

E. A. Heller
Columbia University Medical Center, New York, NY, USA

G. D. Dangas (✉)
Cardiovascular Innovation, Mount Sinai Medical Center, New York, NY, USA
e-mail: gdangas@crf.org

13.1 Introduction

When Andreas Gruentzig performed the first percutaneous coronary angioplasty on an awake patient in 1977 (Zurich, Switzerland), he created the nascent field of interventional cardiology and ushered in a new era of coronary revascularization. Percutaneous coronary transluminal angioplasty (PTCA) was positioned to serve as an alternative and complement to coronary artery bypass grafting (CABG) and optimal medical therapy. As in many medical fields, the advancement of percutaneous coronary interventions (PCI) has been punctuated by innovations and pitfalls.

The refinement of PTCA for the treatment of ischemic coronary artery disease during the 1980s and 1990s led to a procedural success rate of >90%; however, while dilatation of the vessel wall led to improved clinical outcomes and augmented myocardial perfusion, PTCA also resulted in endothelial denudation, plaque modification, elastic recoil, and negative remodeling. The clinical correlates of controlled vessel injury were acute/subacute vessel closure (often requiring emergent CABG) and clinical restenosis (~30%). Laser angioplasty and directional or rotational atherectomy failed to improve on PTCA alone.

The concept of metal scaffolds that could prop open dilated arteries was conceived as early as 1912 by Nobel Laureate Alexis Carrel. The first human coronary stent was implanted after PTCA by Ulrich Sigwart in Lausanne, Switzerland (1986). Juan Palmaz and Richard Schatz, also pioneers in early stent design and implantation, worked with the concept that these scaffolds could help prevent abrupt/threatened vessel closure and restenosis. BENESTENT and STRESS, two pivotal trials published in 1994, demonstrated the improved clinical efficacy and significantly better restenosis rates as compared to PTCA [1, 2]. These data established bare-metal stents (BMS) as the gold standard for PCI.

The major initial concern with BMS was an unacceptably high rate of acute and subacute stent thrombosis. The optimization of a dual antithrombotic regimen consisting of aspirin

P. P. Toth, C. P. Cannon (eds.), *Comprehensive Cardiovascular Medicine in the Primary Care Setting*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-319-97622-8_13

and a thienopyridine (clopidogrel or ticlopidine) helped reduce BMS thrombosis rates to <1%. The Achilles heel of BMS has proven to be in-stent restenosis – neointimal formation driven by smooth muscle cell proliferation. Restenosis rates of approximately 15% (further increased in patients with comorbidities such as diabetes mellitus and renal insufficiency) led to repeat revascularization and, less often, acute coronary syndromes.

Drug-eluting stents (DES) were developed to reduce neointimal hyperplasia, thereby improving the efficacy while maintaining or improving the safety of PCI. First-generation DES contained sirolimus or paclitaxel, drugs that inhibit smooth muscle proliferation and migration through different mechanisms. These drugs are embedded into a polymer that is mounted onto a bare-metal scaffold. Multiple randomized trials showed that DES markedly reduced target lesion revascularization (TLR), target vessel revascularization (TVR), and major adverse coronary events (MACE). First-generation DES restenosis rates were 7–8% at 1 year. Over the past several years, registry data and meta-analyses have pointed to an increased rate of stent thrombosis, particularly very late stent thrombosis (>1 year) with DES as compared to BMS. Controversy has arisen as to how this may affect stent safety, in particular death and myocardial infarction. In 2008, the FDA approved second-generation DES that utilize everolimus and zotarolimus as antiproliferative agents. These compounds have been incorporated into stents with new polymers and bare-metal platforms in a concerted effort to improve the safety and efficacy of PCI. Most recently, third-generation DES have been approved by the FDA. This class comprises everolimus-eluting metallic stents with an absorbable coating polymer and completely bioresorbable scaffolds that are gradually reabsorbed by the body and completely disappear in 18–24 months.

This chapter will review the state of PCI in the DES era, including indications, controversies, adjunctive pharmacology, and the role of intravascular imaging.

13.2 Stent Technique

First-generation BMS, such as the Palmaz–Schatz and Gianturco–Roubin stents, have given way to second- and third-generation stents that exhibit superior conformability, flexibility, tracking, and positioning with a wider variety of diameters and lengths. This has resulted in higher procedural success for a wider variety and complexity of coronary lesion subsets including small vessels (<2.75 mm in diameter), diffuse disease, long lesions, bifurcation lesions, and chronic total occlusions.

Essentially all coronary stents are delivered and then deployed on balloons using guiding catheters and coronary guidewires. Femoral artery catheterization is most common, and brachial artery technique is rare, while radial artery technique has grown in the past few years as it is associated with significantly fewer bleeding and vascular complications. Although direct stenting may be performed in straightforward lesions, most coronary stenoses are pre-dilated with PTCA. High-pressure non-compliant balloons or rotational atherectomy may be used for plaque modification in "non-dilatable" (heavily calcified, diffusely diseased) lesions. Balloon inflation after stent deployment may be used to increase lumen diameter. Stent expansion, vessel apposition, and residual lumen stenosis are the most important factors in stent efficacy. These factors correlate directly with restenosis and thrombosis. The current *ACC/AHA guidelines on percutaneous coronary interventions* recommend a residual stenosis of <10% with an optimal goal of as close to 0% as possible with a final TIMI flow grade 3 [3].

Existing data have demonstrated a discrepancy between the trained eye of the interventionalist and quantitative coronary angiography in determining pre- and post-stent percentage of coronary stenosis. Intravascular ultrasound (IVUS) is a simple catheter-based imaging technique that may be used for diagnostic and interventional purposes. IVUS images cross sections of the arterial wall and can determine minimal lumen area, plaque burden, lesion length, plaque morphology, stent expansion, and stent apposition. In addition, IVUS may be used to diagnose complications of stenting such as coronary artery dissection and stent fracture. The benefit of routine IVUS guidance for stent placement remains controversial. A recent meta-analysis comprising over 11,000 IVUS-guided and 13,000 angiography-guided PCI suggested that IVUS-guided PCI was associated with significantly lower rates of target vessel revascularization and stent thrombosis and myocardial infarction [4]. Nevertheless, IVUS is not indicated in all PCI procedures. According to current AHA/ACC clinical guidelines, IVUS may be considered for guidance on coronary stent implantation particularly in case of left main coronary artery stenting [3]. Another useful technique for the evaluation of coronary lesions is the coronary pressure wire-derived fractional flow reserve (FFR). FFR is a simple and safe way to determine the functional severity of a lesion or efficacy of stent deployment. It measures the coronary artery pressure distal to a given lesion relative to aortic pressure at maximal hyperemia (achieved with intracoronary or intravenous adenosine). Abnormal FFR is a significant predictor of adverse coronary events. Multiple studies support the deferral of intervention in non hemodynamically significant lesions as measured by FFR (>0.80) or IVUS (>4.0 cm^2 for proximal epicardial vessels and > 6.0 cm^2 for the left main artery) [5–9]. Data from the FAME trial suggest that FFR-guided PCI in multivessel coronary artery disease may be superior to angiographically guided interventions with respect to hard clinical outcomes

such as death, MI, and repeat revascularization [10]. However, the subsequent FAME 2 trial received controversial reviews. All patients with any coronary artery disease with angiographic evidence of severe stenosis were evaluated with FFR. In case of positive FFR <0.80, patients were randomized to optimal medical therapy or PCI. Despite being interrupted early for excess of the primary composite endpoint in the optimal medical therapy (OMT) arm, the difference was driven solely by urgent revascularization in 49 (11%) patients in the OMT group compared to 7 (1.6%) in the PCI-treated arm. It could be argued, however, that the remaining 89% of the patients with positive FFR assigned to the OMT did not require any urgent intervention despite the positive FFR [11]. Therefore, some concerns still remain on the routine use of FFR. Nonetheless, FFR has found a role in the AHA/ACC guidelines as a reasonable tool to assess and guide PCI in angiographic intermediate coronary lesions (50–70% diameter stenosis) [3].

13.3 PCI in ACS

Unstable angina and biomarker-positive non-ST-segment elevation MI represent a continuum on the spectrum of acute coronary syndromes. Both conservative and invasive treatment strategies have been developed for the treatment of ACS. Based on the clinical presentation, the baseline characteristics, and the estimated TIMI and GRACE risk scores, patients can be assigned to either (1) conservative strategy/ischemia-driven revascularization or (2) invasive strategy. The conservative strategy employs intensive medical therapy utilizing antithrombotic, antiplatelet, and anti-ischemic agents over a period of several days. If the patient responds, pharmacologic therapy is often followed by stress testing with myocardial perfusion imaging. Either a positive stress test or persistent/recurrent angina is followed by cardiac catheterization with revascularization.

An invasive strategy involves early intensive therapy within 24 h or a delayed invasive therapy 25–72 h following admission with prompt cardiac catheterization and revascularization if indicated. The early invasive strategy involves targeting the culprit lesion, often with PCI, in hopes of limiting myocardial damage and improving overall prognosis [12]. A flowchart of the treatment strategies according to the AHA/ACC guidelines can be found in Fig. 13.1.

Multiple randomized trials have compared conservative versus early invasive strategies in the treatment of ACS patients. The preponderance of the evidence supports early intervention. In FRISC II, TACTICS-TIMI 18, and RITA 3, an early invasive strategy during ACS was associated with a sustained reduction in death and MI, primarily driven by the latter endpoint [13–15]. An early invasive strategy was also associated with a reduction in angina and hospital readmissions. In the TIMACS trial, for instance, there was no difference in the primary endpoint of death, myocardial infarction, and stroke between early (<24 h) and delayed (>36 h) invasive strategy. However, the early invasive therapy was associated with a significant reduction in the secondary composite endpoint of death, myocardial infarction, or refractory ischemia compared to delayed intervention in high-risk patients [16]. Data from meta-analyses have been consistent with these trials [17, 18]. The ICTUS trial was one of the few studies that failed to show a benefit of an early invasive strategy toward the composite endpoint of death, MI, or rehospitalization for anginal symptoms at 1–3- and 5-year follow-up [19]. However, when data from the 5-year follow-up of the FRISC II, TIA-3, and ICTUS were combined, a routine invasive strategy significantly reduced long-term rates of cardiovascular death or MI, with the largest benefit in higher-risk patients [20]. Subgroup analyses indicate that patients who may derive the most benefit from an early invasive strategy are those with positive troponin, new ST depression, LVEF <40%, prior PCI within 6 months or CABG, new heart failure or worsening mitral regurgitation, and high TIMI or GRACE risk scores [12].

The *ACC/AHA guidelines* recommend that ACS patients who are hemodynamically unstable or have refractory angina and malignant ventricular arrhythmias or have very high TIMI and GRACE risk scores undergo immediate catheterization and revascularization. Low-risk patients (i.e., TIMI risk score ≤2) may undergo a conservative strategy, called ischemia-guided strategy, at the discretion of the caring physician (Table 13.1) [12]. Attention should be paid to intermediate risk (TIMI risk 3–4) females who may have increased bleeding complication with an invasive strategy [13].

PCI is clearly indicated in ACS for the treatment of one vessel CAD; however, the majority of ACS patients will have multivessel disease. Multivessel stenting and complete revascularization are often preferred to culprit lesion PCI. There is a wealth of data indicating complete revascularization is superior to incomplete revascularization regardless of the clinical setting [13, 21]. Multivessel stenting is often staged to prevent the use of a large amount of contrast dye or radiation in one setting. However, recently published results from the SMILE trial showed that complete 1-stage coronary revascularization is superior to multistage PCI in terms of major adverse cardiovascular events driven by target vessel revascularization and cerebrovascular events [22]. There are scant and conflicting data as to whether PCI or CABG is preferable when both are viable options and most decisions are made on a case by case basis (patients' wishes, concomitant valvular disease, coronary anatomy, comorbidities). Some objective data can be derived from the SYNTAX trial that randomized an all-comer population with three-vessel disease or left main

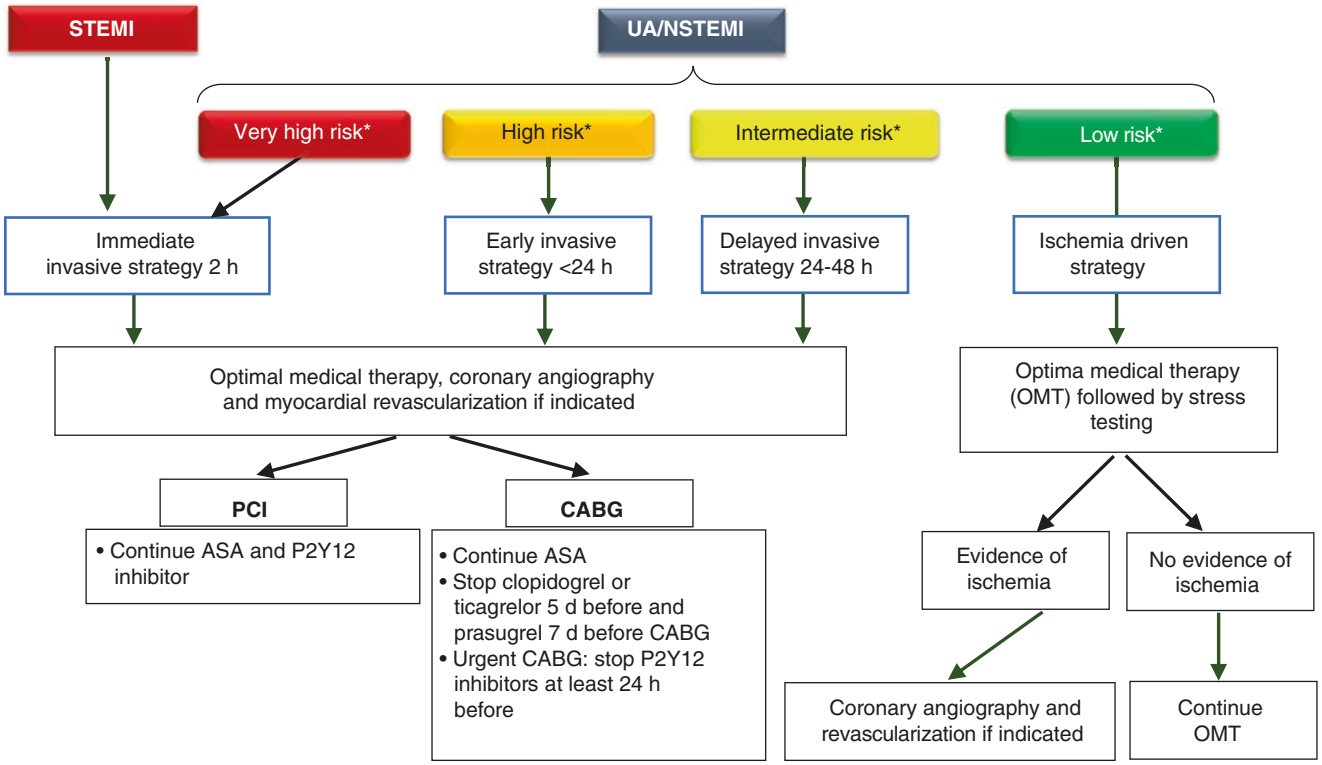

Fig. 13.1 Treatment strategies for acute coronary syndromes. *For risk stratification, please refer to Table 13.1

Table 13.1 Indications for early invasive and conservative strategies in the treatment of ACS [12]

Preferred strategy	Patient characteristics
Immediate invasive (within 2 h)	Recurrent angina or ischemia at rest or with low-level activities despite intensive medical therapy
	Refractory angina
	Signs or symptoms of heart failure or new or worsening mitral regurgitation
	Hemodynamic instability
	Sustained ventricular tachycardia or ventricular fibrillation
	High-risk score (e.g., TIMI, GRACE)
Ischemia-guided strategy	Low-risk score (e.g., TIMI 0 or 1, GRACE <109)
	Low-risk troponin-negative females
	Patient or physician preference in absence of high-risk features
Early-invasive (within 24 h)	None of the above, but GRACE risk score >140
	Temporal change in troponin
	New or presumably new ST-segment depression
Delayed invasive (25–72 h)	None of the above but diabetes mellitus
	Renal insufficiency (eGFR < 60 ml/min/1.73 mm^2)
	Reduced left ventricular systolic function
	PCI within 6 months
	Prior CABG
	GRACE risk score 109–140; TIMI score ≥2

disease to PCI with paclitaxel-eluting stents or CABG. At 1 year, CABG, as compared with PCI, led to lower rates of major adverse cardiac or cerebrovascular events in this population [23]. To provide guidance on the best treatment strategy after coronary angiography, clinical practice guidelines recommend the use of the SYNTAX score. This score is based solely on anatomic criteria of CAD and significantly predicts the risk of 1-year major adverse cardiovascular and cerebrovascular events [24]. Nevertheless, patients' clinical characteristics and patients' wishes should also be considered in the evaluation. When PCI is preferred, drug-eluting stents appear to be safe in ACS and reduce restenosis and the need for repeat revascularization [19]. In particular, second-generation DES might help close the gap with CABG toward long-term outcomes. While the SYNTAX trial was led with paclitaxel-eluting stent (first-generation DES), observational data from the New York registry showed that in contemporary clinical practice, second-generation DES (everolimus-eluting stents) are associated with similar risk of death compared to CABG. Although PCI-treated patients had a higher risk of repeat revascularization and of myocardial infarction, when revascularization was incomplete, they had a lower risk of stroke [25].

13.4 Acute ST-Segment Elevation Myocardial Infarction (STEMI)

Primary PCI with stenting of the culprit lesion is the revascularization therapy of choice in acute MI with time to reperfusion resulting in incremental benefit. Multiple randomized trials have demonstrated the clinical benefit of primary stenting as opposed to thrombolysis [26]. The largest of these trials were DANAMI-2 and PRAGUE-2. DANAMI-2 randomized 1572 AMI patients to primary PCI versus thrombolysis with alteplase [27]. Patients had to have a symptom duration <12 h and be transferred to a PCI center within 3 h of randomization. Primary PCI was associated with a significant reduction in death, MI, or stroke at 30 days. PRAGUE-2 randomized 850 AMI patients with a duration of symptoms <12 h to primary PCI versus thrombolysis with streptokinase [28]. Primary PCI was associated with a trend toward reduced mortality at 30 days and a significant reduction in all-cause mortality, recurrent MI, stroke, or repeat revascularization at 5 years. Several randomized trials have demonstrated a significant decrease in repeat revascularization in primary PCI with no increase in stent thrombosis for DES as compared to BMS. Meta-analyses have shown similar results [29, 30]. HORIZONS-AMI randomized 3600 AMI patients to receive BMS versus paclitaxel-eluting stents [31]. DES were associated with a significant reduction in target lesion revascularization and no difference in the rate of stent thrombosis. A recent meta-analysis comprising trials with second-generation DES found a significantly lower incidence of cardiovascular events, myocardial infarction, target vessel revascularization, and stent thrombosis with second-generation DES compared to BMS [32].

The *ACC/AHA guidelines* recommend primary PCI as the preferred method of revascularization for patients within 12 h of symptom onset [33]. The guidelines also suggest that the preponderance of the evidence favors primary PCI in patients who present within 12–24 h of symptom onset and who have persistent angina, cardiogenic shock, malignant arrhythmias, or severe CHF. Primary PCI should only be performed on the culprit vessel. Intervention on other lesions is contraindicated in the AHA/ACC guidelines on the management of patients with STEMI unless a patient presents in cardiogenic shock. However, since the publication of the guidelines, two main trials, PRAMI and CvLPRIT, have been published which support the use of complete revascularization during primary PCI or at least during index hospitalization vs a culprit-only approach [34, 35]. Both studies showed that immediate complete revascularization was associated with a reduction in cardiovascular outcomes. Results from recent meta-analysis confirmed that immediate or staged complete revascularization results in a significant reduction in major adverse cardiovascular events, cardiovascular mortality, and repeat revascularization without significant harm compared to the culprit-only approach [36, 37]. This data is consistent with what observed in NSTEMI patients and might lead to a re-evaluation of the official indication for the treatment of multivessel disease during primary PCI in the next guidelines.

Finally, PCI following failure of thrombolysis (rescue PCI) has demonstrated clinical benefit. Facilitated PCI with full-dose thrombolytics is contraindicated, and the same is true for repeat thrombolysis [38]. The most recent *ACC/AHA guidelines* recommend PCI as adjunctive therapy to fibrinolysis for patients with cardiogenic shock, recurrent MI, or significant post-infarct ischemia [39]. Adjunctive PCI may be reasonable in patients who develop malignant ventricular arrhythmias, CHF, have an ejection fraction <40%, or have a critical stenosis in an infarct-related artery >24 h after AMI.

13.5 Stable CAD

13.5.1 Role and Limitations of Medical Therapy

The goals of therapy in stable CAD are to ameliorate symptoms and improve quality of life, delay/prevent/reverse progression of atherosclerotic coronary disease, and prevent hard clinical endpoints such as death and myocardial infarction. All of these objectives can be accomplished with aggressive risk factor modification and secondary prevention with a medical regimen that includes aspirin, P2Y12 inhibitor, beta-blockers, ACE inhibitors/ARBs, statins, nitrates, calcium channel blockers, and aldosterone antagonists. Revascularization with PCI or CABG is indicated in selected groups of patients, such as those whose angina is refractory to medical therapy, those who cannot tolerate medical therapy, and those in whom the evidence supports a survival benefit with revascularization (left main disease, three-vessel disease with decreased LV function).

A number of clinical trials have compared medical therapy to percutaneous and/or surgical revascularization; however, up until recently, these trials have had significant limitations. In most trials, patients had focal coronary disease and preserved LV function, limiting generalizability. Studies comparing PCI and CABG are dated and mostly

used vein grafts for surgical revascularization as opposed to the accepted current standard of arterial conduit (i.e., internal mammary artery) to bypass the left anterior descending (LAD) vessel, the intermediated branch or marginal branches. Even when the mammary artery is used, in several studies it is often a single conduit to the LAD which does not reflect the complexity of most of the patients treated with CABG in contemporary practice. Recently the STICH trial tested the efficacy and safety of surgical revascularization in patients with stable CAD and heart failure. This study did not find a significant reduction of all-cause mortality and cardiovascular death in patients treated with CABG compared to medical therapy only [40].

A number of trials compared PCI to "optimal" medical therapy, including RITA-2 and MASS II [41, 42] (Table 13.2). These studies demonstrated a symptomatic improvement in favor of PCI or CABG but no difference in death or myocardial infarction. ACIP was a small study in patients with silent ischemia which demonstrated favorable clinical outcomes with revascularization; however, all of these trials were performed before the drug-eluting stent era and before the advent of the current concept of optimal medical therapy.

The COURAGE trial compared medical therapy to PCI with BMS. COURAGE randomized 2287 patients with stable CAD to optimal medical therapy (OMT) or OMT plus PCI with bare-metal stenting [43]. All subjects were required to have objective evidence of ischemia and angiographic evidence of significant CAD (stenosis ≥70%). The vast majority of patients (87%) were symptomatic and had Canadian Cardiovascular Society (CCS) class II or III angina (58%). High-risk patients (LM disease ≥50%, EF <30%, high-risk stress test, CCS class IV angina) and those with unsuitable coronary anatomy for PCI were excluded from the trial.

At a mean follow-up of 4.6 years, there was no significant difference in all-cause mortality or nonfatal MI. There was also no significant difference in hospitalization for ACS. PCI was associated with decreased angina and improved quality of life up to 3 years; however, the results in the OMT group caught up thereafter. PCI was also associated with the ability to pare down a patient's antianginal pharmacologic regimen (calcium channel blockers, nitrates). Overall, the quality of life benefit in the PCI group was associated with more severe baseline ischemia.

The COURAGE nuclear substudy addressed whether a patient's quantitative ischemic burden during stress testing affected prognosis based upon treatment randomization [44]. Three hundred and fourteen patients within the COURAGE study population received baseline myocardial perfusion scans before and then 6–18 months following randomization. PCI was associated with a significant reduction in ischemic myocardium as compared to OMT alone. Those patients with moderate to severe ischemia at baseline received the greatest benefit from PCI. Patients with ≥5% ischemia reduction had significantly lower unadjusted (but not adjusted) rates of death and myocardial infarction. This subgroup analysis suggests that the extent and severity of ischemic burden in patients with CAD should influence an initial strategy of OMT versus OMT plus PCI. Of note, almost one-third of patients in the OMT arm of COURAGE eventually crossed over to have PCI, and the results were analyzed on an intention-to-treat basis.

It should be noted, though, that most of the listed trials utilized bare-metal stents and antithrombotic regimens that would be considered substandard as compared with current *ACC/AHA guidelines*. Nevertheless, recent meta-analysis has confirmed the results of the COURAGE trial displaying that PCI for stable coronary artery disease does not reduce the risk of mortality, cardiovascular death, nonfatal myocardial infarction, or revascularization compared to medical therapy. However, PCI seemed to provide a greater angina relief compared with medical therapy alone [45, 46].

13.5.2 Multivessel Disease

Revascularization in multivessel coronary disease has traditionally fallen under the purview of CABG; however, with refinements and advancements of PCI, there have been multiple efforts to compare the percutaneous strategy to the surgical gold standard. In the mid-1990s, studies such as BARI, RITA, and CABRI compared CABG versus PTCA in multivessel disease [47–50]. The ARTS I and SOS trials compared CABG to PCI with bare-metal stents [51–54]. These trials concluded that the hard clinical endpoints of death and myocardial infarction were similar between the two treatment strategies; however, PCI was associated with a significant increase in repeat revascularization which was ameliorated by the introduction of bare-metal stents.

The ARTS II registry was conducted in the DES/GP IIB/IIIA era and compared 607 patients treated with sirolimus-eluting stents for multivessel disease with the ARTS I PCI and CABG populations [55]. At 1 year of follow-up, major adverse cardiovascular and cerebral events were similar between the ARTS II registry and ARTS I CABG populations; however, PCI with DES was associated with a statistically significant increase in repeat revascularization (8.4% versus 4.1%) but with much narrower gap than the one observed between bare-metal stents and CABG in ARTS- I trial.

Most recently, the SYNTAX trial made an ambitious attempt to compare PCI versus CABG in moderate- to high-risk patients with multivessel disease [23]. Eighteen hundred patients with three-vessel or left main disease were randomized 1:1 to either CABG or PCI with paclitaxel-eluting stents (PES). Anatomy was suitable for either means of revascular-

Table 13.2 Patient characteristics **(a)** and results **(b)** of randomized trials comparing PCI versus medical therapy for the treatment of stable angina [61]

	AVERT	RITA-2	TIME	MASS II	SWISSI II	COURAGE	Fame 2
(a) Patient characteristics							
Patients, no.	341	1018	301	611	201	2287	888
Women, no. (%)	53(16)	183(18)	131(44)	187(31)	25(12)	338(15)	194(21)
Mean age, year	59	58	80	60	55	62	63
Angina, Canadian class	Nearly all 0 to II	53% II, III, or IV	100% II, III, or IV	81% II or III	None (silent ischemia)	58% II or III	81% I, II, or III; 6.9 IV
Prior MI no. (%)	136(40)	471(46)	141(47)	269(44)	201(100) (first in preceding 3 months)	836(38)	329(37)
Diabetes, no. (%)	51(15)	90(9)	68(23)	177(29)	23(11)	766(34)	240(27)
Mean LVEF, %	61	54	53	67	57	62	<50 in 139 (16)
LVEF exclusion, %	<40	None	"Predominant CHF"	40	None	30; 35 if 3-vessel disease	<30
Ischemia by treadmill test	Excluded	Not required	Not required	Required	Required	Required	
Fractional flow reserve (FFR)	N/A	N/A	N/A	N/A	N/A	N/A	Yes, 0.80 cutoff
Vessels diseased %[a]							
1	57	60	14	Excluded	1- or 2-vessel disease required	35	58
2	43	33	19	42	See above	39	34
3	Excluded	7	60	58	Excluded	25	8
Previous CABG or PCI	Excluded if PCI in the last 6 months or if history of CABG	Excluded	18% PCI 20% MT	Excluded	Not reported	16% PCI 11% MT	18% PCI 17% MT
(b) Results							
Primary endpoint	Ischemic event: cardiac death, cardiac resuscitation, nonfatal MI, stroke, CABG, PCI, or angina with hospitalization	Death, nonfatal MI	Freedom from MACI[b]	Death, nonfatal MI, or refractory angina requiring revascularization	Survival free of MACEs; cardiac death, nonfatal MI, or symptom-driven revascularization	Death, nonfatal MI	MACE: all-cause death, nonfatal MI, urgent revascularization

(continued)

Table 13.2 (continued)

	AVERT	RITA-2	TIME	MASS II	SWISSI II	COURAGE	Fame 2
Results (most recent follow-up published)	PCI 21% MT 13% *P* = 0.048	PCI 14.5% MT 12.3% *P* = 0.21	Freedom from MACE INV 39% MT 20% *P* < 0.001; no difference in mortality or other quality-of-life measures at 4 years	PCI 32.7% MT 36% CABG 21.2% *P* = 0.003; pairwise comparison: no difference between PCI and MT	Adjusted HR (favoring PCI 0.33; 95% CI. 0.20–0.55; *P* < 0.001 [using person-years])	PCI 19.0% MT 18.5% *P* = 0.62 and no difference in angina at 5 years	PCI 4.3% MT 12.7% HR = 0.32[0.19–0.53] p < 0.001
Main result for primary endpoint	Longer time to and fewer ischemic events with MT + high-dose statin	No advantage of PCI over MT	Revascularization improves freedom from MACEs for the elderly no effect on mortality	If revascularization is needed, favor CABG	Patients with silent ischemia after MIT may benefit from PCI	No advantage of PCI over MT	FFR-guided PCI reduces MACE driven by urgent revascularization compared to MT

AVERT Atorvastatin Versus Revascularization Treatment, *CABG* coronary artery bypass grafting, *CHF* congestive heart failure, *COURAGE* Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation, *LVEF* left ventricular ejection fraction, *MASS II* Medicine, Angioplasty, or Surgery Study, *MI* myocardial infarction, *MT* medical therapy, *PCI* percutaneous coronary intervention, *RITA-2* Second Randomized Intervention Treatment of Angina, *SWISSI II* Swiss Interventional Study on Silent Ischemia Trial II, *TIME* Trial of Invasive Versus Medical Therapy in the Elderly, *CI* confidence interval, *HR* hazard ratio, *INV* interventional arm, including percutaneous coronary intervention (PCI) and CABG, *MACE* major adverse cardiac event, *MASS II* Medicine Angioplasty, or Surgery Study, *MI* myocardial infarction, *MT* medical therapy; *RITA-2* Second Randomized Intervention Treatment of Angina, *SWISSI II* Swiss Interventional Study on Silent Ischemia Trial, *TIME* Trial of Invasive Versus Medical Therapy in the Elderly, *FAME 2* Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2

[a]In the TIME trial, the percentage of vessels diseased pertains only to individuals in PCI group; MT group not assessed

[b]Initial primary outcome was improvement in measures of quality of life, including relief of angina and lower rates of MACEs (death, nonfatal MI, or hospitalization for angina or acute coronary syndrome a: 6 month). Freedom from MACEs was reported in the 1-year follow-up

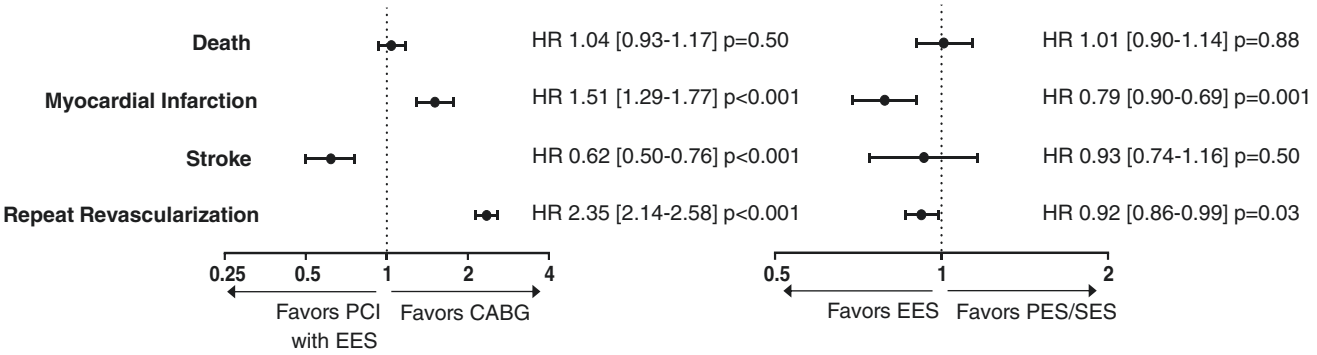

Fig. 13.2 Treatment strategies for stable patients with multivessel coronary disease. Comparison between PCI with everolimus eluting stents (EES) and CABG in the left panel and between PCI with econd (EES) and first generation stents (PES=paclitaxel eluting stents, SES=sirolimus eluting stents) in the right panel using registry data (25).

Table 13.3 Results of the SYNTAX trial (Kaplan–Meier Curves) [44]

	12-month follow-up		
Outcome	PCI with 1st-gen DES (%)	CABG (%)	*p* value
Death, stroke, or MI	7.6	7.7	0.98
Death	4.4	3.5	0.37
Stroke	0.6	2.2	0.003
MI	4.8	3.3	0.11
Repeat revascularization	13.5	5.9	<0.001

ization. At 12-month follow-up, PCI was associated with a statistically significant increase in death, MI, stroke, or repeat revascularization (17.8% versus 12.4%) (Table 13.3). The difference was driven by repeat revascularization (13.5% versus 5.9%), whereas there was no difference in death or MI and there was actually a statistically significant decrease in stroke in the PCI population (Table 13.3). There were similar rates of stent thrombosis and symptomatic graft occlusion. These results are consistent with those of the PTCA and BMS eras. Notably, there was a significant narrowing between PCI and CABG with respect to the rates of repeat revascularization as compared with BARI and RITA II. The left main SYNTAX substudy, the largest set of patients with left main disease randomized to CABG versus PCI to date, showed excellent results with PCI with no difference in death/MI, more repeat procedures, and lower risk of stroke than CABG. Observational registry data have shown that the gap between CABG and PCI for long-term clinical benefit in patients with multivessel disease is further reduced by the use of second-generation DES. PCI still has a higher rate of repeat revascularization and myocardial infarction compared to CABG, but the difference disappears in case of complete revascularization during index PCI. Importantly compared to CABG, PCI was associated with a lower rate of stroke (Fig. 13.2) [25].

The SYNTAX score, a tool for angiographic risk stratification based upon disease burden and complexity, correlated highly with outcomes and may be used to guide a decision for surgical versus percutaneous revascularization. In the final analysis, the physician and patient must balance the surgical risk (including stroke) of CABG versus the risk of repeat revascularization with PCI when making a decision regarding revascularization for multivessel and high-risk CAD.

13.5.3 Diabetic Patients

There has been particular interest in the optimal method of revascularization in diabetic patients. In the BARI trial, which compared CABG to PTCA, CABG was associated with significantly increased survival (58% versus 46% at 10 years) [56]. The survival benefit was most marked in insulin-requiring patients and observed only to those who received an internal mammary graft. The diabetic patients in the study had more severe and diffuse disease than the rest of the study population, a potential confounder especially since the chosen method of percutaneous revascularization was with PTCA. The CARDIA trial randomized diabetic patients with multivessel disease to either PCI (with BMS and later on sirolimus-eluting stents) or CABG. At 1 year the study failed to prove the non-inferiority of PCI compared to CABG.

The BARI-2D trial studied stable diabetic patients with few symptoms or silent ischemia. The investigators concluded the following: (1) an initial medical stabilization therapy with reservation of a revascularization procedure can be undertaken safely and was utilized in about half of the patients studied; (2) as the ischemic risk and coronary heart disease burden increases, complete revascularization may offer significant clinical benefit even in survival; and (3) insulin-sensitizing therapy offers improved metabolic and lipid profiles to an insulin-providing therapy, and this may translate into a clinical benefit in combination with revascularization in the higher-risk patients [57]. This study

included routine coronary angiography in all patients as a method to define risk and did not directly compare stenting with CABG. Furthermore, both bare-metal and drug-eluting stent types were used in PCI procedures. Results indicated (1) no major difference between types of diabetic management, (2) not much difference in death or MI between revascularization and optimal therapy in the low-risk cohort, and (3) advantage with surgery over optimal medical therapy in the higher-risk cohort.

Finally, the FREEDOM trial was specifically designed to discern the optimal means of revascularization for higher-risk (greater than that studied in BARI-2D) diabetic patients with multivessel CAD. FREEDOM has randomized 1901 patients with type I or type II diabetes and multivessel disease with angina or ischemia to CABG versus DES. The primary endpoint was death, MI, or stroke at 3 years [58]. The study concluded that CABG is superior to PCI in that it significantly reduced rates of death and myocardial infarction, at the expense of a higher rate of stroke.

13.6 Ischemic Burden and Revascularization

Multiple lines of investigation in the cardiac imaging literature have correlated the quantitative ischemic burden in CAD patients with adverse cardiac outcomes. Invasive studies using fractional flow reserve (FFR) and intravascular ultrasound have demonstrated that certain cutoffs for hemodynamic flow reserve or lumen cross-sectional area are associated with, and predictive for, future cardiac death and MI. The COURAGE nuclear study, a hypothesis generating subgroup analysis, demonstrated that ischemic burden correlated with the degree of anginal relief following PCI [44]. A mounting body of evidence supports targeting quantitative ischemic burden rather than symptoms with medical therapy and revascularization in an effort to reduce death, MI, and stroke. Among the most recent studies in this series are the FAME trials.

FAME was a multicenter trial that randomized 1005 patients with stable CAD to angiographically versus FFR-guided PCI with DES [10]. The former group underwent revascularization of all angiographically significant lesions. The latter group underwent revascularization of angiographically significant lesions only if the FFR was ≤0.8 (deemed hemodynamically significant). FFR-driven revascularization was associated with a significant reduction in the primary endpoint of death, MI, or repeat revascularization at 1 year. FAME 2 addresses the primary targeting of ischemic burden and outcomes with revascularization and medical therapy.

This trial showed that FFR-guided PCI plus the best available medical therapy decreased the need for urgent revascularization compared to medical therapy alone. Conversely in patient with negative FFR, the clinical outcomes were similar to the medical therapy only patients [11] (Table 13.4).

Table 13.4 Results from the FAME II trial (Kaplan–Meier Curves) [5]

	Positive FFR <0.8		Negative FFR >0.8
Outcome	PCI plus medical therapy, n (%)	Medical therapy alone, n (%)	FAME II registry medical therapy alone, n (%)
Death, MI, or urgent revascularization, *n* (%)	19 (4.3)	56 (12.7)	5 (3.0)
Death, *n* (%)	1 (0.2)	3 (0.7)	0 (0)
MI, *n* (%)	15 (3.4)	14 (3.2)	3 (1.8)
Urgent revascularization, *n* (%)	7 (1.6)	49 (11.1)	4 (2.4)

13.6.1 Recommendations and Guidelines

The latest joint update of the *ACC/AHA guidelines for the management of stable CAD* was published in 2014 [59, 60].

PCI has been deemed appropriate for patients with asymptomatic ischemia and/or CCS class I/II angina who (1) have significant lesion(s) in one to two coronary arteries that subtend a moderate to large area of viable myocardium on noninvasive testing and have a high likelihood of procedural success, (2) restenosis after PCI with a large area of viable myocardium at-risk or high-risk features on noninvasive testing, and (3) left main disease in a patient who is not eligible for CABG.

PCI for stable CAD and unprotected left main disease has a class IIa indication for patients with both a low risk of PCI procedural complications, a high likelihood of good long-term outcome (e.g., a low SYNTAX score of ≤22, ostial or trunk left main CAD), and an increased risk of adverse surgical outcomes (e.g., STS-predicted risk of operative mortality ≥5%) or IIb in case of low to intermediate risk of PCI-related complications. In case of three-vessel disease and/or two-vessel disease, the indication for PCI is class IIb. In patients with single-vessel disease without proximal LAD involvement, the current guidelines give a class III indication for PCI, and medical therapy should be preferred [60].

The focused update in 2014 stresses the importance of a Heart Team approach to revascularization in patients with diabetes mellitus and complex multivessel CAD. CABG is generally recommended in preference to PCI to improve survival in patients with diabetes mellitus and multivessel CAD (3-vessel CAD or complex 2-vessel CAD involving the proximal LAD) [60].

However, PCI in multivessel disease may be considered particularly in patients with multifocal disease and preserved left ventricular ejection fractions, younger patients who may require multiple reoperations during the course of their lives,

and older patients with multiple comorbidities that make the morbidity/mortality of CABG unacceptably high. Finally, all decisions regarding revascularization should take into account the educated opinions of the cardiologist and referring physicians as well as the particular concerns of the individual patient.

Most recently the ACC, AHA, and numerous other professional organizations have published a consensus document regarding the appropriate criteria for percutaneous and/or surgical revascularization of patients in 180 different clinical scenarios [61]. Following this publication, we assisted to a reduction of the non-acute PCI procedures and a reduction of PCIs classified as inappropriate according to current guidelines [62]. A more extensive discussion of these criteria and scenarios is beyond the scope of this chapter.

13.7 Post-Stent Care

Patients who have undergone uncomplicated PCI may be discharged the day after their procedure. The duration of dual antiplatelet therapy varies depending upon the type of stent placed. The current *ACC/AHA guidelines* recommend treatment with aspirin and a thienopyridine for at least 1 month following placement of BMS and at least 1 year following DES [12, 33]. Dual antiplatelet therapy may be extended for patients with complex/high-risk lesions and/or major comorbidities. Result from the recently published DAPT trial showed that prolonged DAPT up to 30 months after DES was associated with a significant reduction in the risk of stent thrombosis and major cardiovascular and cerebrovascular events at the expense of an increased risk of bleeding complications [63]. Similarly the PEGASUS TIMI 54 trial tested the use of DAPT with ticagrelor for 36 months compared to aspirin alone and found a reduction of ischemic events with an excess of bleeding events [64]. Therefore, routine use of prolonged DAPT is not indicated in all patients. However, subgroups of patients with high ischemic risk such as diabetic patients might benefit from this treatment strategy [65]. Regardless of the strategy chosen, a patient's cardiologist should be consulted if there is an indication to suspend dual antiplatelet therapy, for instance, prior to surgery or other circumstances. The importance of the pattern and reason of DAPT cessation has been highlighted by the results of the PARIS observational registry [66]. This study prospectively collected data from an all-comer PCI population in 15 sites in the USA and Europe mostly treated with DES. Antiplatelet therapy was based on aspirin and clopidogrel since data collection preceded the coming of novel P2Y12 inhibitors, prasugrel, and ticagrelor. Patients were followed up for 2 years during which information on compliance to DAPT cessation mode and outcomes were collected. DAPT cessation was classified as follows: physician-recommended discontinuation, brief interruption (for surgery), or disruption due to non-compliance or bleeding events. PARIS revealed that in the real-world setting, cardiovascular adverse events depended on the reason and type of cessation. DAPT disruption seemed associated with the highest risk of clinical outcomes. The risk of events attenuated over time [66].

Prasugrel and ticagrelor have emerged as an alternative to clopidogrel, with higher antiplatelet efficacy (greater inhibition of the P2Y12 receptor), albeit with more bleeding complications. For this reason, prasugrel is contraindicated in patients with low body weight, prior stroke (or transient ischemic attack), or age over 75 years [67]. Prasugrel should not be used in patients where the coronary anatomy is unknown. Ticagrelor is quickly active after administration and has a short half-life. It has been proven to be safe and effective compared to clopidogrel and can be used upstream before coronary angiography. According to recent guidelines, both prasugrel and ticagrelor are indicated as maintenance drug with aspirin for 1 year after stenting and can be particularly useful in patients with clopidogrel hyporesponsiveness due to generic polymorphism [12].

13.7.1 Estimation of Patient's Clinical Risk

Determining the ischemic and bleeding risk of patients after PCI is essential for tailoring the treatment strategy and reducing the rate of DAPT cessation and adverse outcomes. The ACUITY risk score was developed using 2 ACS patient populations from the ACUITY and the HORIZONS-AMI trials [68]. It is based on six baseline measurements (female sex, advanced age, elevated serum creatinine and white blood cell count, anemia, non-ST-segment elevation MI, or ST-segment elevation MI) and one treatment-related variable (use of heparin + glycoprotein IIb/IIIa) (Table 13.5). This score accurately identifies patients at increased risk for non-CABG-related bleeding and subsequent 1-year mortality. The same ACS populations were also used to develop a risk model specific for stent thrombosis (ST). The variables present in this ST score are listed in Table 13.5. Besides baseline clinical characteristics, angiographic characteristics such as the presence of ulcerated lesions and TIMI flow were also taken into account. The rates of ST at 1 year in low-, intermediate-, and high-risk categories were 1.36%, 3.06%, and 9.18%, respectively, in the development cohort and 1.65%, 2.77%, and 6.45% in the validation cohort, proving a very good predictive value of this score [69].

Most recently two new scores have been developed using the contemporary PCI population of the PARIS registry comprising both stable and ACS patients [70]. The PARIS bleeding risk score partially overlaps with the ACUITY score and the PARIS coronary thromboembolic risk score

Table 13.5 Recently published scores for the evaluation of bleeding and thromboembolic risk in patients undergoing PCI (68–70)

PARIS score				DAPT score	
Bleeding risk score		Thromboembolic risk score			
Low 0–3; intermediate 4–7; high ≥8		Low 0–2; intermediate 3–4; high ≥5		Low risk <2; high risk ≥2	
Parameter	Score	Parameter	Score	Parameter	Score
Age, years		Diabetes mellitus		Age ≥ 75	**−2**
<50	**0**	None	**0**	Age 65–75 years	**−1**
50–59	**+1**	Non-insulin-dependent	**+1**	Age < 65 years	**0**
60–69	**+2**	Insulin-dependent	**+3**	Current cigarette smoker	**1**
70–79	**+3**	Acute coronary syndrome		Diabetes mellitus	**1**
≥80	**+4**	No	**0**	MI at presentation	**1**
BMI, kg/m^2		Yes, Tn-negative	**+1**	Prior PCI or prior MI	**1**
<25	**+2**	Yes, Tn-positive	**+2**	Stent diameter < 3 mm	**1**
25–34.9	**0**	Prior PCI	**+2**	Paclitaxel-eluting stent	**1**
≥35	**+2**	Prior CABG	**+2**	CHF or LVEF <30%	**2**
Current smoking	**+2**	Current smoking	**+1**	Saphenous vein graft	**2**
CrCl < 60 ml/min	**+2**	CrCl <60 ml/min	**+2**		
Presence of anemia	**+3**				
Triple therapy on discharge	**+2**				

ACUITY bleeding risk score							
Low risk <15; high risk ≥15							
Parameter	Score						
Gender	Male			Female			
	0			**+8**			
Age (years)	<50	50–59	60–69		70–79	≥80	
	0	**+3**	**+6**		**+9**	**+12**	
Serum creatinine (mg/dl)	<1.0	1.0-	1.2-	1.4-	1.6-	1.8-	≥2.0
	0	**+2**	**+3**	**+5**	**+6**	**+8**	**+10**
White blood cell count (giga/L)	<10	10-	12-	14-	16-	18-	≥20
	0	**+2**	**+3**	**+5**	**+6**	**+8**	**+10**
Anemia	No			Yes			
	0			**+6**			
Presentation	STEMI	NSTEMI – raised biomarkers			NSTEMI – normal biomarkers		
	+6	**+2**			**0**		
Antithrombotic medication	Heparin plus GPI			Bivalirudin monotherapy			
	0			**−5**			

Stent thrombosis risk score			
Low 1–6; intermediate 7–9; high ≥10			
Parameter	Score		
Type of ACS	NSTEMI w/o ST changes: +1	NSTEMI with ST changes: +2	STEMI +4
Current smoking	Yes +1	No +0	
Insulin-treated DM	Yes +2	No +0	
History of PCI	Yes +1	No +0	
Baseline platelet count, K/μL	<250: +0	250–400: +1	>400: +2
Absence pre-PCI heparin	Yes +1	No +0	
Aneurysm or ulceration	Yes +2	No +0	
Baseline TIMI flow grade 0/1	Yes +1	No +0	
Final TIMI flow grade < 3	Yes +1	No +0	
Number of vessels treated	1: +0	2: +1	3: +2

BMI body mass index, *CrCl* creatinine clearance, *Tn* troponin, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass graft, *MI* myocardial infarction, *CHF* cardiac heart failure, *LVEF* left ventricular ejection fraction, *GPI* glycoprotein IIb/IIIa inhibitors

(Table 13.5). Both scores have been tested in the ADAPT DES population and have shown excellent predictive value for 2-year events.

Finally, the DAPT score provides a tool to determine the benefit of prolonging DAPT beyond 1 year after index PCI [71]. The DAPT score takes into consideration variables predictive of both ischemic and bleeding events and combines them in one elegant model (Table 13.5). Similar to the PARIS score, DAPT was developed in a mixed PCI population with 37% stable CAD patients. At 2 years after index PCI, the DAPT score effectively predicts the overall benefit of prolonged DAPT compared to DAPT cessation at 1 year.

13.7.2 Restenosis

Intracoronary stent restenosis has been the Achilles heel of PCI with respect to efficacy. Studies in the 1990s showed that PTCA alone was associated with a 30–40% rate of angiographic restenosis. First-generation stents, such as the Palmaz–Schatz stents, were associated with a 20–30% rate of restenosis. The advent of second-generation bare-metal stent platforms, better post-dilatation techniques, and a standardized antithrombotic regimen dramatically reduced the rates of clinical restenosis to 12–14% at 1 year. After 1 year, restenosis rates dropped precipitously, and recurrent angina and/or ischemia was more likely due to a de novo lesion. The mechanism underlying restenosis appears to be an inflammatory/wound healing response to the stent, smooth muscle cell proliferation and migration, and neointimal growth within the stent.

Drug-eluting stents brought great promise in combating restenosis. Paclitaxel and sirolimus are both drugs that inhibit vascular smooth muscle cell proliferation/migration and, therefore, were expected to reduce neointimal formation within the stent. First-generation DES reduced the rate of clinical restenosis to 6–7% at 1-year follow-up (target lesion revascularization). Second-generation DES, such as those containing everolimus or zotarolimus, have been shown to significantly reduce stent thrombosis compared to first-generation DES [72, 73]. Second-generation DES also reduced the composite endpoint of myocardial infarction, stent thrombosis, and revascularization in both randomized trials and observational studies [74, 75]. Most recently, the bioresorbable scaffolds eluting everolimus might resolve the problem of early, late, and very late stent restenosis: the presence of everolimus reduces inflammation, early/late stent restenosis and favors endothelialization. Since the polymer completely dissolves in 18–24 months, the risk of very late stent restenosis is virtually erased. In addition, the full disappearance of the stent ensures that the vessel wall and endothelium can return to their physiological function and allows for the implantation of a graft in case CABG is required in the future [76].

Restenosis may be focal or diffuse (intrastent, proliferative, occlusive), and the pattern of restenosis correlates with prognosis [77]. Independent procedural predictors include stent length, multiple stents, small vessel size, ostial lesions, prior restenosis at the stent site, post-procedural plaque burden, final minimal lumen diameter <3 mm, stent malapposition, and stent underexpansion. The latter two variables can be optimized by IVUS guidance. Independent clinical predictors include diabetes, renal insufficiency, hypertension, increased BMI, and multivessel disease.

Most cases of clinical restenosis present with new onset angina rather than an acute coronary syndrome or acute MI [78]. Treatment for in-stent restenosis includes DES place-

Table 13.6 Temporal categorization of stent thrombosis [83]

Acute stent thrombosis	0–24 h after stent implantation
Subacute stent thrombosis	>24 h to 30 days after stent implantation
Late stent thrombosis	>30 days to 1 year after stent implantation
Very late stent thrombosis	>1 year after stent implantation

Table 13.7 ARC definitions of stent thrombosis (82)

Definite stent thrombosis
Angiographic confirmation of stent thrombosis
Presence of a thrombus that originates in the stent or in the segment 5 mm proximal or distal to the stent and the presence of at least one of the following criteria within a 48 h time window:
1. Acute onset of ischemic symptoms at rest
2. New ischemic ECG changes that suggest acute ischemia
3. Typical rise and fall in cardiac biomarkers (refer to the definition of spontaneous MI)
4. Nonocclusive thrombus:
Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on three sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream
5. Occlusive thrombus
TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if it originates from the side branch)
Pathological confirmation of stent thrombosis
Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy
Probable stent thrombosis
Any unexplained death within the first 30 days after intracoronary stenting
Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause
Possible stent thrombosis
Any unexplained death >30 days after intracoronary stenting

ment or PTCA alone, often with IVUS guidance. Multiple randomized trials have confirmed the efficacy of treating BMS restenosis with DES [79, 80]. Small observational studies suggest the efficacy of bioresorbable scaffold as well in this setting [81]. CABG is only considered with multiple restenoses or in high-risk clinical cases.

13.7.3 Stent Thrombosis

Stent thrombosis is the Achilles heel of PCI with respect to safety. Stent thrombosis is a rare but often severe complication of PCI that may be fatal. Stent thrombosis often presents as an acute MI. Thrombosis may be classified temporally as acute (≤24 h), subacute (1–30 days), late (1 month–1 year), and very late (>1 year) (Table 13.6) [82]. Each case can be classified according to the consensus ARC definition as definite, probable, or possible (Table 13.7) [83]. Risk factors may be broadly characterized into patient, procedure, stent, or lesion related and are thought to stem from one of the three mechanisms: (1) hypoperfusion, (2) lack of subendothelialization of the stent surface, and (3) increased thrombogenicity. Specific risk factors include impaired LV function, emergent stent placement, increased stent length, stent underexpansion, residual plaque burden, small vessel caliber, residual thrombus or dissection, and medical non-compliance.

Dual antiplatelet therapy with aspirin and a thienopyridine, especially novel potent P2Y12 inhibitors, markedly reduces the incidence of acute, subacute, and late stent thrombosis and may have an impact on very late stent thrombosis [84]. A subanalysis of the PLATO trial has showed that ticagrelor significantly reduces the incidence of stent thrombosis in ACS patients compared with clopidogrel [85]. Some studies have shown that the addition of cilostazol to dual antiplatelet therapy may reduce the incidence of stent thrombosis in selected high-risk clinical scenarios [86].

Most (80%) stent thrombosis after placement of BMS occurs during the first 2 weeks; subacute stent thrombosis is less common, late stent thrombosis is rare, and very late stent thrombosis is almost never described. Notably, sensitivity over this very rare event was not present during BMS trials, and this may have led to underreporting. Meta-analyses of randomized trials have shown DES incurs approximately a 0.6% rate of stent thrombosis at 30 days and 0.75% at 1 year [82]. Very late stent thrombosis may occur at an annual rate of 0.6–0.9% after 1 year. Real-world registries show slightly higher rates of stent thrombosis. Very late stent thrombosis may occur several years following PCI at a very low rate. Ongoing studies are further characterizing the time course of this adverse event.

There is an increased risk of very late stent thrombosis with DES as compared to BMS of approximately 0.5–0.6% per year [87]. However, virtually every pooled analysis shows there is no difference in death or MI during this period of time. Individual risk/benefit analyses should be performed in every case to determine candidacy for BMS versus DES. If a patient has a history of non-compliance with medication, or will be unable to receive DAPT for at least 6 months due to planned surgery of high bleeding risk, strong consideration should be given to placement of a BMS rather than DES. Due to the extremely small incidence of stent thrombosis, any prospective study evaluating this phenomenon would require several thousand patients and long-term follow-up making feasibility extremely difficult.

Newer stent platforms, polymers, and drug formulations seek to maximize stent efficacy by abrogating restenosis while also maximizing safety through better prevention of stent thrombosis.

13.8 Case Studies

13.8.1 Case Study 1

An active 57-year-old male with a history of type 2 diabetes on oral medication, hypertension, and hypercholesterolemia presents to his primary care physician complaining of exertional chest pain after walking ten blocks. He is referred for an exercise stress test with a myocardial perfusion scan. The patient completes 8 min of Bruce protocol, achieving 87% of maximal predicted heart rate. He experiences the same exertional chest pain. There are no EKG changes. The myocardial perfusion scan reveals a moderate-sized area of anterior ischemia (moderate intensity). The patient is referred for cardiac catheterization, which reveals a 70% mid-LAD stenosis. What is the next step in management?

This case represents the plight of a typical patient who would fall within the realm of the COURAGE trial. It is the responsibility of the patient's cardiologist to explain that the LAD stenosis does not present an imminent risk for acute MI or acute coronary syndrome. The main goals of therapy should be symptomatic improvement, secondary prevention, and risk factor reduction. First, the cardiologist must ensure that the patient is receiving optimal medical therapy. PCI would not reduce the patient's risk of death or MI but would reduce the patient's angina and improve quality of life as compared to medical therapy in the short and intermediate terms. The risks of restenosis and stent thrombosis with PCI, as well as the requirement for dual antiplatelet therapy, must be discussed. The decision for adding PCI to optimal medical therapy must be jointly made between the patient, primary care physician, and cardiologist.

13.8.2 Case Study 2

A 66-year-old female with a history of hypertension and hypercholesterolemia presents to her primary care physician complaining of exertional chest pain and dyspnea. The patient has no other medical problems. She is referred to a cardiologist who sends her for an exercise nuclear stress test. The patient performs 7 min of Bruce protocol, achieving 90% of maximal predicted heart rate for her age. She experiences chest pain but no EKG changes. Myocardial perfusion scanning reveals moderate-sized, moderate intensity anterior and inferior defects. Cardiac catheterization reveals a 90% proximal LAD lesion, a 70% lesion of the first obtuse marginal artery, and an 80% mid-RCA lesion. All lesions are focal. Left ventriculography reveals an ejection fraction of 55% with no regional wall motion abnormalities. The patient is reluctant to undergo coronary bypass surgery but is not confident that multiple stents will be the best treatment. She desires the safest and most effective therapy. How should her cardiologist counsel her?

This patient has multivessel coronary disease with a normal ejection fraction. She is otherwise relatively healthy and has focal coronary disease that would be anatomically amenable to both CABG and PCI. A recommendation for this patient should take into account the data from numerous randomized trials in the literature comparing CABG with PCI in multivessel disease. The SYNTAX trial is of particular significance. A conversation with the patient would clarify that the extent and severity of her coronary disease would be amenable to both CABG and PCI. Given that she is relatively healthy, is not diabetic, and has normal LV function, either treatment modality would provide her with symptomatic improvement. With PCI, she would expect an increased likelihood of requiring repeat revascularization. Based on the lesion description, the SYNTAX score would be expected to be low and the repeat procedure rate after PCI not high. She would need to weigh the short-term morbidity of cardiac surgery (including a finite stoke risk) against that associated with subsequent hospitalization(s) for repeat PCI and the requirement of dual antiplatelet therapy for at least 1 year with DES. The patient's treatment plan should be individualized based upon her own thoughts and concerns regarding her health. She should have consultations with both an experienced interventional cardiologist and a cardiac surgeon. The ultimate plan should be a joint decision between the patient, her primary care physician, and clinical cardiologist – the physicians who know her the best. Typically, such conversations might have preceded the catheterization procedure based on noninvasive studies, and if an option of PCI was favored, this could have been performed at the same time as angiography.

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Coronary Artery Bypass Graft

14

Ahmed A. Kolkailah, Fernando Ramirez Del Val, Tsuyoshi Kaneko, and Sary F. Aranki

Abbreviations

ACC	American College of Cardiology
AF	Atrial fibrillation
AHA	American Heart Association
ASA	Aspirin
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CE	Coronary endarterectomy
CEA	Carotid endarterectomy
CPB	Cardiopulmonary bypass
DAPT	Dual antiplatelet therapy
ESRD	End-stage renal disease
HCR	Hybrid coronary revascularization
IMA	Internal mammary artery
LAD	Left anterior descending (coronary)
LIMA	Left internal mammary artery
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
MICS	Minimally invasive cardiac surgery
MIDCAB	Minimally invasive direct coronary artery bypass
OPCAB	Off-pump coronary artery bypass
PCI	Percutaneous intervention
SCAI	Society for Cardiovascular Angiography and Interventions
STS	Society of Thoracic Surgeons
TECAB	Totally endoscopic coronary artery bypass
VT	Ventricular tachycardia

Ahmed A. Kolkailah and Fernando Ramirez Del Val are contributed equally to this work.

A. A. Kolkailah · F. R. Del Val · T. Kaneko · S. F. Aranki (✉)
Division of Cardiac Surgery, Brigham and Women's Hospital, Boston, MA, USA
e-mail: SARANKI@partners.org

14.1 Brief History

Coronary artery bypass grafting (CABG) is the gold standard for myocardial revascularization and is the result of an intricate, challenging, and demanding journey that began more than 100 years ago. In 1899, the first surgical intervention to symptomatically treat angina was proposed by Francois Frank, in the form of the ligation of the sympathetic pain pathways [1]. Although this procedure resulted in considerable symptomatic relief, it was inconsequential in treating the underlying disease process. From 1930 to 1954, a number of abrasive products as well as muscle, omentum, lung, and jejunum pedicles were used in attempts to increase collateral circulation to the myocardium and alter the disease course of coronary ischemia [1–3]. The first descriptions of a coronary endarterectomy were done by Bailey in 1957 [4] and Longmire in 1958 [5], although the first successful endarterectomy was described by Dubost in 1960 [6]. Vineberg, in 1964, described the tunnelization of the left internal mammary artery (LIMA) into the myocardium, near the left anterior descending artery (LAD), to induce the formation of collateral circulation between the two vessels [7]. In 1953, John Gibbon pioneered the first open heart surgery using cardiopulmonary bypass, a groundbreaking advancement not only in the field of cardiac surgery but also in myocardial revascularization [8]. For coronary revascularization, the greatest advancements came from Vasilii Kolesov, who performed the first anastomosis of the LIMA to LAD in 1964; Michael DeBakey, with his experience on saphenous vein conduits; and Rene Favaloro, who through his 1968 publication on 248 bilateral internal mammary graft procedures [9] is responsible for establishing reproducible results with this technique [10–12]. Lastly, in 1969, Dudely Johnson reported on 301 CABG cases, providing evidence of the usefulness and versatility of venous conduits in the "extended treatment of coronary artery disease" [13].

P. P. Toth, C. P. Cannon (eds.), *Comprehensive Cardiovascular Medicine in the Primary Care Setting*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-319-97622-8_14

14.2 Indications for Coronary Artery Revascularization

CABG and percutaneous coronary intervention (PCI) with stenting are the two principal revascularization options in patients with coronary artery disease (CAD). Several considerations are made when deciding on one of the two treatment options as opposed to medical therapy alone. These include acuity of presentation, activity level, and coronary anatomy.

CABG is performed to provide symptomatic relief and/or improve survival. The guidelines note that before a decision is made to proceed with the procedure, patients should clearly understand the main benefit of the procedure – whether to relieve symptoms, improve survival, or both. Improving survival, in general, is given more weight over improving symptoms, when deciding on the best treatment strategy [14].

A "significant" coronary stenosis is defined as ≥50% diameter narrowing in the left main artery or ≥ 70% in other coronary arteries. Coronary stenosis with fractional flow reserve ≤0.80 is also considered "significant" [15, 16]. The SYNTAX score, developed during the SYNTAX trial [17], classifies patients according to the severity of their CAD and is additionally used as a surrogate for the extent and complexity of CAD. It utilizes the results of coronary angiography and considers characteristics of lesion complexity, location, and number. It is classified as low (≤22), intermediate (23–32), and high (≥33) [17–20].

With the emergence of PCI as a less invasive therapeutic intervention for CAD, it was essential to have a more robust tool for risk stratification, ultimately aiding in selection of most appropriate management for these patients. Since the SYNTAX score does not include any clinical variables, an attempt was made to improve its predictive value score by utilizing patients' baseline characteristics in the SYNTAX trial and formulating the SYNTAX II score or the clinical SYNTAX score (CSS) [21]. It factors patients' clinical characteristics such as age, ejection fraction, and creatinine clearance to enhance the prognostic value of the SYNTAX score. CSS is a promising new tool and has shown superior results in predicting mortality and major adverse cardiac events in patients with complex CAD [22]. It has also been recently validated in patients with ST-elevation myocardial infarction (STEMI) undergoing PCI and was found superior to SYNTAX score in predicting long-term prognosis [23].

Overall, patients with lower SYNTAX scores were found to have better outcomes than those with higher scores at 12 months of follow-up. In addition, patients with an intermediate to high score did better with CABG than with PCI [17].

14.2.1 Clinical Scoring Systems

Two of the most commonly used clinical scoring systems for predicting morbidity and mortality after CABG are the Society of Thoracic Surgeons (STS) score and European System for Cardiac Operative Risk Evaluation (EuroSCORE).

STS Score The STS risk models underwent several revisions ever since their introduction in 1999 and are now the most commonly used models in the United States [24]. The most recent, 2008, STS risk score is based on a large registry of 774,881 patients spanning from 2002 till 2006 [25]. Not only does it predict operative mortality in patients undergoing CABG, it also estimates the risk of other complications, such as prolonged ventilation and renal or neurological complications [26]. A user-friendly, online STS score calculator is available at www.sts.org/quality-research-patient-safety/quality/risk-calculator-and-models/risk-calculator.

EuroSCORE First developed based on data from 1995, EuroSCORE was used as a predictor for immediate mortality after cardiac surgery and widely believed to be the gold standard [24, 27]. It had a simple, additive predictive model and a more complex logistic model [28]. The first sometimes underestimates the risk of mortality, while the latter tends to overestimate it [24]. In 2011, they have been replaced by the EuroSCORE II model, which was based on 22,381 patients undergoing cardiac surgery in 43 countries from May to July 2010 [29]. This provided a more calibrated model with a better predictive value. However, it still lacks the ability to estimate other complication, unlike the STS score [24]. A user-friendly, online EuroSCORE II calculator is available at www.euroscore.org.

Evidence-based indications for CABG are incorporated in the ACC/AHA and ESC guidelines' recommendations [14, 18]. These guidelines can be broadly classified into either symptom improvement or survival improvement (*see Appendix*).

14.3 Coronary Artery Revascularization with Cardiopulmonary Bypass

Despite the increasing risk profile of patients undergoing CABG procedures, short- and long-term clinical outcomes are excellent [30]. Coronary revascularization with cardiopulmonary bypass (CPB) remains the most common surgical treatment for CAD, constituting 80% of all CABG procedures, and a "gold standard" for coronary revascularization [31].

14.3.1 Preoperative Assessment

Preoperative management of patients undergoing CABG requires thorough evaluation of their medical history and a complete physical examination. Baseline comorbidities such as diabetes, chronic pulmonary disease, chronic kidney disease, and previous surgeries have important implications in selecting the optimal revascularization strategy and a substantial influence on the operative outcomes. A detailed history of sternal wound infections and wound dehiscence as well as any interventions used to treat such complications in patients with a previous sternotomy will help plan entry to the chest cavity. Of particular importance is the patient's history with regard to conduit availability. Prior radiation or end-stage renal disease with arteriovenous fistula may compromise the use of internal mammary artery graft. The Allen test to assess the patency of the radial and ulnar arteries and inspection of the lower extremity for varicose veins or prior venous procedures will influence the surgeon's choice of graft conduit.

Preoperative workup includes baseline electrocardiogram (ECG), chest radiograph, echocardiogram (ECHO), and selective coronary angiography. Meticulous assessment of the patient's angiographic studies is required to develop a tailored surgical plan. As a general rule, all angiographic lesions with a cross-sectional area of 70% or more are considered to be significant stenosis and amenable for revascularization, in order to minimize competitive flow [32] (see previous section on *indications for CABG*).

The use of computerized tomography (CT) scans in the overall preoperative planning of cardiac surgery has been well documented [33]. Chest CT with intravenous contrast is particularly useful in reoperative cases, especially those who underwent a previous CABG, as it helps plan the reentry incision to the chest cavity by identifying the anatomic location of previous bypass conduits in relation to the sternum as well as the previous use of soft tissue flaps (omental or muscle) to treat previous wound complications. Additionally, chest CT without contrast can identify the presence of porcelain aorta in sagittal, axial, and volume-rendered images.

14.3.2 Operative Technique

The operative field is delineated to include the patient's neck, chest, abdomen, and both lower extremities. A midline sternotomy, from the angle of Louis to the xiphoid process, offers excellent exposure. Systemic anticoagulation is achieved by administering a minimum of two units per milliliter of estimated blood volume (as calculated by point-of-care coagulation monitoring tests) of unfractionated heparin before cannulating. Prior to initiating CPB, a target activated clotting time greater than 350 seconds and a minimum heparin concentration of two units per milliliter of estimated blood volume should be achieved. Successful anticoagulation is maintained by repeating both the ACT and heparin concentration P.O.C. tests at 30-minute intervals. Strict systolic blood pressure control to less than 100 mmHg, before arterial cannulation, reduces the risk for aortic dissection. A two- or three-stage venous cannula is inserted through the right atrial appendage, with the tip of the cannula positioned in the inferior vena cava. The use of both antegrade and retrograde cold blood cardioplegia is used to achieve asystolic cardiac arrest in diastole.

As a general rule, more severe coronary lesions should be revascularized with higher-quality conduits. Whenever possible, the LAD coronary artery should be bypassed using the LIMA [32]. Complete arterial revascularization may be considered for patients 60 years of age or younger for whom a greater long-term survival effect is likely, with severe (70%) left-sided stenosis and critical right-sided stenosis (90%) [18]. However, the choice of conduit is a matter of ongoing clinical research (see section on *multiple arterial grafts*).

Discontinuation of CPB requires surgical hemostasis, correction of all acid-base and electrolyte abnormalities, and normothermia defined as a minimum core temperature of 35.5°C typically measured in the bladder. Reversal of heparin is achieved with 1.10 milligrams of protamine for every milligram (100 units) of circulating heparin as calculated by point-of-care heparin/protamine titration and estimated blood volume.

14.3.2.1 Multiple Arterial Grafts

CABG with multiple arterial grafts is regarded as a more complex procedure, compared to the traditional CABG (LIMA to LAD with additional saphenous vein grafts), which is yet to achieve consensus on its superiority. The results of two retrospective studies suggested improved 10-year survival and an increased risk of wound infections with bilateral IMA as graft conduits [34, 35]. In 2014, a meta-analysis of nine studies compared the use of bilateral to unilateral IMA grafts and reported an overall significant survival advantage with the use of multiple arterial conduits [36]. It is important to note that most of the unmatched studies (3/4) failed to show a difference in survival, while all five propensity-matched studies favored the use of arterial grafts.

The short-term benefits of multiple arterial grafts were shown in a prospective trial of 200 patients randomly assigned to receive total arterial revascularization or traditional CABG [37]. Total arterial revascularization resulted in lower recurrence of angina (2% vs. 13%), lower postoperative PCI requirements, and higher freedom from cardiac events (96% vs. 67%) at 12-month follow-up. The most recently performed randomized control trial of 3102 patients

who underwent bilateral or unilateral IMA grafts showed no difference in death rate at 5-year follow-up [38]. An increased incidence of sternal wound infection and sternal wound reconstruction, however, was observed among bilateral graft recipients. Because substantial survival differences are unlikely to be present before such short-term follow-up, the 10-year follow-up results of this trial are expected to further clarify the association between the use of multiple arterial conduits and long-term survival after CABG surgery. Considering the current available evidence, the patients expected survival, favoring younger patient populations, and underlying comorbidities should be thoroughly considered while selecting the type of conduits.

14.4 CABG in Special Circumstances

14.4.1 CABG in Patients with Left Ventricular Dysfunction

The role CABG plays in management of heart failure has not been well established. In the STICH trial of 1212 patients with ejection fraction <35% and CAD requiring CABG, the 10-year follow-up data showed a significant decrease in the rates of all-cause mortality, cardiac death, and hospitalization for cardiovascular causes among patients who were receiving medical therapy and undergoing CABG than among those who were receiving medical therapy alone [39].

14.4.2 CABG in Patients with Diabetes Mellitus

Despite the improvements in surgical management of CAD, including diabetic populations, these patients consistently experience worse outcomes than nondiabetics [40]. However, when compared to PCI, CABG performed better in this specific population. In the FREEDOM trial, a large, prospective randomized trial of 1900 diabetic patients, CABG was found to be superior to PCI in terms of death and myocardial infarction outcomes, but these patients had a higher stroke rate.

Based on results from the BARI, FREEDOM, and SYNTAX trials, there is a general agreement in preference of CABG over PCI for diabetic patients with multivessel disease [41]. This is supported by the guidelines from major guideline bodies [42–44]. *See Appendix* for a case study.

14.4.3 CABG in Patients with End-Stage Renal Disease (ESRD)

The overall mortality and complication rates after CABG are increased in patients with ESRD compared to patients without ESRD [45–48]. Limited data exists on the optimal method of coronary revascularization in patients with ESRD [49]. The few retrospective studies that have looked into this suggest that drug-eluting stents are associated with lower early mortality than CABG in the first 3 months but higher risks for repeat revascularization and mortality after this period. Cumulative evidence suggests that long-term risk of cardiac events and/or death in patients with ESRD is generally higher following PCI than after CABG [45, 48, 50, 51]. Therefore, CABG is generally preferred over PCI for coronary revascularization in patients with ESRD [52].

14.4.4 Coronary Endarterectomy (CE)

Bailey et al. were the first to report on successful CE in 1957 [4]. The procedure has not gained popularity, owing to its associated increase in morbidity and mortality [53–55]. Nonetheless, some studies have demonstrated good survival and graft patency with surgical expertise and appropriate postoperative medical therapy [56, 57].

The rationale of the procedure is based on thorough removal of the plaque for completeness of myocardial revascularization – an essential component of a successful CABG [58]. Therefore, in patients with total or subtotal large coronary artery occlusions that preclude graft placement in an area of viable ischemic myocardium, the benefits of an endarterectomy may overweigh its risks [59–61].

After the coronary arteriotomy is performed, an endarterectomy spatula is used to identify the plane of dissection for mobilization of the plaque proximally and distally. A 1 mm probe is then advanced gently through the plane of dissection to break adhesions. Gentle traction and countertraction on the plaque and the adventitia, respectively, are used in combination to extract the plaque. If proper distal tapering of the plaque is not achieved, the arteriotomy is distally extended for complete extraction of the plaque. After complete extraction, retrograde cardioplegia is given to flush out any debris that may have embolized distally. Successful endarterectomy is thought to be achieved on visible retrograde flow of cardioplegic solution into the septal and diagonal branches of the LAD [56].

The clinical scenario can sometimes be an intraoperative finding of coronary arteries that cannot be revascularized with CABG after making an arteriotomy, usually inconsistent with preoperative angiographic findings. In such cases, endarterectomy is the only option to salvage the revascularization procedure. CE should not be performed for nonviable myocardium, which can be detected on viability studies in the preoperative workup [56].

MI has been shown to be more frequent in patients after CE than in patients after CABG alone. It is speculated though that such observation is mainly because of the advanced coronary artery disease burden in these patients as well as the longer ischemic time [62].

Although several studies report low associated operative morbidity and mortality [57, 63–65], it is worth noting that this procedure should only be utilized as an adjunct to CABG in specific patients where it would facilitate complete revascularization in otherwise inoperable patients. As previously mentioned, benefits of complete revascularization should outweigh potential risks associated with CE in these patients [59].

14.4.5 CABG and Carotid Endarterectomy (CEA)

The incidence of coexisting coronary and carotid artery disease varies between 2% and 14%, which may pose an increased risk for stroke, as carotid artery stenosis greater than 75% was found to be an independent predictor of stroke risk during cardiac operations [66, 67].

The three strategies for CEA in patients undergoing CABG are:

- Concomitant, where CEA is performed prior to CABG, in the same setting
- Staged, where CEA is performed prior to CABG, in a different setting
- Reverse staged, where CABG is performed first and CEA is scheduled at a later time

Concomitant or staged CEA and CABG may reduce stroke risk compared to CEA after CABG in patients with symptomatic CAD and severe asymptomatic carotid artery stenosis. In a randomized trial including patients undergoing CABG, who had unilateral asymptomatic carotid stenosis >70%, 185 patients were randomized to CABG with prior or concomitant CEA vs. CEA 1 to 3 months after CABG. Operative mortality was not different among both groups. However, ipsilateral ischemic stroke (0% vs. 7.7%, $p = 0.008$) and combined 90-day death and stroke rate (1% vs. 9%, $p = 0.02$) were significantly lower for patients undergoing CABG with prior or concomitant CEA [68].

Advocates of concomitant CEA and CABG believe that it provides more efficient use of resources (operating room facilities and surgical personnel), resulting in shorter hospital length of stay and lower cost, compared with staged procedures [69], in addition to the increased risk of MI in staged procedures and increased risk of stroke in reversed-staged procedures [68, 70]. On the other hand, operative morbidity and mortality may be higher with concomitant CEA and CABG than with each procedure alone [71–73].

Having mentioned that, a systematic review suggested that at least 50% of perioperative strokes are not preventable by carotid intervention [74]. It is also worth noting that optimal medical treatment for stroke risk factors has evolved over the past two decades, particularly with the widespread use of statin therapy for hypercholesterolemia, more aggressive lipid and blood pressure targets, and novel antiplatelet drugs [75]. In reports published since the mid-2000s, rates of stroke in patients with significant carotid stenosis who are only medically managed have declined when compared to those who underwent surgery. This goes in line with the idea that optimal medical therapy alone may be the most suitable treatment for patients with asymptomatic carotid disease. Moreover, the trials that reported a benefit of CEA excluded patients who had a recent (within 6 months) history of MI or unstable angina. Hence, these results may not be readily applicable to all patients undergoing CABG [76, 77].

Consequently, multi-societal guidelines remain conservative about the value of concomitant CEA and CABG. The safety and efficacy of carotid revascularization, even for severe carotid stenosis, before or concurrent with myocardial revascularization have not been well established. Nonetheless, concomitant CEA and CABG are thought to be reasonable approaches in patients with greater than 80% carotid stenosis who have experienced ipsilateral retinal or cerebral ischemic symptoms within 6 months (Class IIa, Level of Evidence: C) [78].

Despite the lack of randomized controlled trials and lack of consensus on the optimal management strategy, major guideline bodies [14, 18, 78] agree that CEA for patients undergoing CABG is reasonable in the following conditions:

- A recently *symptomatic* carotid stenosis (50% to 99% stenosis in men or 70% to 99% stenosis in women)
- Bilateral *asymptomatic* 80% to 99% carotid stenoses
- Unilateral asymptomatic stenosis of 70% to 99% and contralateral carotid occlusion

However, CEA is *not* recommended for patients with isolated unilateral asymptomatic 50% to 99% carotid artery stenosis.

14.4.6 Reoperative CABG

Advances in percutaneous treatment of coronary vessels and coronary grafts, along with improvements and routine use of LIMA to graft the LAD, have influenced the frequency of reoperative CABG. As the proportion of reoperative CABG decreased from 7.2% in the 1990s to 2.2% in the early 2000s, the number of PCI before redo CABG increased from 14.5% to 26.6% during the same time periods [79]. Due to the protective effect of the internal mammary artery (IMA) against atherosclerosis, most reoperative CABG focuses on the saphenous conduits.

Currently, reoperative CABG is recommended for patients with a greater than 50% stenosis in a vein graft perfusing the LAD [80]. For patients with an IMA to LAD graft and persistent angina despite medical therapy, reoperative CABG is reasonable to treat ischemic lesions in the distribution of the right and circumflex coronary artery that are not amenable to PCI [18], with no additional survival benefit [81].

A thorough evaluation on the increased risk of reoperative CABG must be weighed against its benefits as a number of studies have shown increased operative mortality and decreased survival in these patients [82, 83]. These outcomes are influenced by both increased technical difficulties and higher disease burdens [84, 85]. However, due to advancements in surgical technique over the past 30 years, most of the increased risk in these patients is determined by the latter [84]. Patient characteristics associated with worse outcomes are advanced age, nonelective surgery, decreased LVEF, renal disease, peripheral arterial disease, hypertension, elevated cholesterol, and diabetes mellitus [86]. Overall, reoperative mortality has declined from 6.1% in 2000 to 4.6% in 2009, and long-term survival at 10-year follow-up varied between 55% and 78% [82, 87, 88].

Preoperative imaging with CT is useful in identifying the presence of complex anatomical features, often present in reoperative cases. A thorough preoperative assessment of the anatomical structures, including the relationship between the great vessels or previous bypass grafts to the sternum, is crucial in planning a successful reentry into the chest cavity to minimize complications during sternotomy [89–91].

14.4.7 Off-Pump CABG

Off-pump coronary artery bypass (OPCAB) allowed surgeons to perform a surgical coronary revascularization procedure without the drawbacks of cardiopulmonary bypass. OPCAB follows the main principles of traditional CABG, but without the need for CPB by performing the anastomosis on the beating heart. This is accomplished through the use of deep pericardial retraction sutures to expose the various walls of the myocardium, transitory proximal occlusion of the target vessels, and coronary stabilizer to diminish the movement of the target coronary as the heart contracts. In the United States, the frequency of OPCAB, among all CABG procedures, increased from 10% in the late 1990s to 22% in the early 2000s [92–95]. However, contemporary results from large prospective databases show that currently 15% to 17% of all CABG are performed without CPB [96].

Superiority of OPCAB is mainly claimed in the form of large retrospective series [93, 97]. However, the opponents suggest that the marked differences in baseline characteristics between patients who underwent off-pump and on-pump revascularization may be responsible for the observed differences in early retrospective publications.

A 2004 retrospective review of 812 propensity-matched patients (OPCAB vs. CABG with CPB) showed no difference in operative mortality, death, stroke, MI, cumulative survival, or freedom from coronary re-intervention [98]. The authors did find a lower incidence of sternal wound complications, dialysis requirement, and red blood cell transfusions in patients who underwent OPCAB. Two recent RCTs, the CORONARY trial in 2009 and the GOPCABE trial in 2013, had similar results, with no difference in the incidence of the composite outcome (death, nonfatal stroke, nonfatal MI, or new onset renal failure) between OPCAB and CABG with CPB [99–101]. In these studies, OPCAB was associated with lower transfusion requirements, reoperation for bleeding, acute kidney injury, and respiratory complications. OPCAB was also associated with an increased risk in early repeat revascularization, although that difference was no longer present at 1-year follow-up [100]. Contemporary results using large data suggest a lower morbidity and similar mortality with OPCAB compared to CABG with CPB [102]. Individuals who are likely to obtain the greatest benefit from the use of OPCAB appear to be those with low ejection fraction, prior cardiac surgeries, calcified aorta, and a high burden of comorbidities and who are elderly [103–105].

14.5 Minimally Invasive CABG

Although PCI has emerged as a viable alternative to CABG for acute ischemic presentations and localized CAD [106], its long-term durability is suboptimal when compared to surgical revascularization [107–110]. Nonetheless, CABG is associated with major morbidity in almost 15% of patients, including, but not limited to, infection, stroke, reoperation for bleeding, and acute renal failure [111, 112]. Furthermore, atrial fibrillation is seen in up to 50% of patients after CABG [113, 114], and up to 30% of CABG patients still report pain 1 year after operation [115, 116].

The invasiveness of CABG has not been changed since its introduction over 40 years ago. Sternotomy remains a key component for all revascularization techniques, and attempts to decrease the invasiveness of CABG while preserving complete revascularization have not had much success over the years, with the exception of a few specialized centers [117].

Minimally invasive cardiac surgery CABG (MICS CABG) allows the surgeon to perform a revascularization equivalent to that of a regular CABG, while maintaining the patient's anterior thorax closed. It is usually performed via lateral mini-thoracotomy, by a 4–6 cm incision at the level of the fourth or fifth rib, extending laterally from the midclavicular line, thereby keeping the procedure minimally invasive (i.e., without a sternotomy) and in many cases using

OPCAB [118]. The main challenge is the ability to harvest a good mammary artery. MICS CABG has been shown to decrease length of hospital stay and costs [119]. However, given the approach is relatively recent, adequately powered randomized, controlled trials are still necessary to compare MICS CABG with conventional CABG in terms of survival, long-term patency, and physical functioning [117]. It is therefore suggested that MICS CABG would only be performed with proper surgeon and center experience, where minimally invasive procedures are performed on a regular basis [120].

Minimally invasive direct coronary artery bypass (MIDCAB) is another operation, where the incision is usually larger but more medial in position. This creates more pain at costochondral sites from rib spreading and is restricted to the performance of a single LIMA-LAD graft [121, 122]. One the other hand, MICS CABG is utilized for triple-vessel or diffuse CAD, allowing for complete revascularization. In addition, all coronary arteries can be visualized and identified because the pericardium is opened widely. Proximal anastomoses can also be routinely performed onto the ascending aorta with MICS CABG [117].

14.6 Robotic Totally Endoscopic Coronary Artery Bypass (TECAB)

The summit of minimally invasive surgical revascularization is robotic totally endoscopic coronary artery bypass (TECAB). The adoption of robotic TECAB has been sparse. The first large series of robotic TECAB came from Germany [123] and was strained by high conversion rates for on-pump (18%) and off-pump (75%) surgeries. The first feasibility trial in 2006 [124] and the first triple-vessel robotic TECAB in 2010 [125] were instrumental in confirming its viability and furthering its acceptance. A systematic review of 14 original manuscripts showed comparable results to standard CABG, 0.04% all-cause mortality and 15% conversion with CPB and 1.2% all-cause mortality and 5.6% conversion without CPB [126]. The largest single-institution series of successful robotic TECAB was published in 2012, reporting 0% conversion rate and a 99.5% patency [127]. Although these improvements in robotic TECAB are encouraging, its steep learning curve and elevated cost have limited its widespread adoption. Ongoing research will help elucidate the future role of robotic TECAB in the management of CAD.

14.7 Hybrid Coronary Revascularization

Hybrid coronary artery revascularization (HCR) refers to using the combination of single-vessel CABG (LIMA-LAD) and PCI of other significant coronary lesions [128]. MIDCAB has gained momentum as part of a hybrid strategy for multivessel coronary artery disease and has shown promising outcomes [129]. However, compared to OPCAB, HCR has been associated with a higher need for repeat revascularization (12.2% compared to 3.7%) [130]. Despite gaining some popularity, HCR only accounts for 0.5% of CABG volume performed in the United States, according to a 2014 Society of Thoracic Surgeons' (STS) database report. It was noted that most interventions in HCR adopted a minimally invasive approach, but the technique has not been well evaluated in randomized trials comparing it with CABG or PCI [131]. As with MICS CABG, and until high-quality evidence exists on its use, it may be a reasonable approach only with experienced surgeons and centers.

14.8 CABG Outcomes

14.8.1 Operative Mortality

Operative mortality for CABG, using data registries in the United States, ranges from 0.4% to 5% and is mostly influenced by patient comorbidities and hospital volume [30, 132–134]. The most important predictors of operative mortality are renal function, age, LVEF, prior cardiac surgery, and nonelective status [18, 135–138]. In addition to hospital volume, each surgeon's procedural volume has been significantly associated with operative mortality in an inverse fashion [132, 139].

Several risk-predicting models have been developed to stratify patients into single risk scores, depending on their baseline characteristics. The two most commonly used are the one developed by the STS [140] and the EuroSCORE [27], both with comparable performance [141].

14.8.2 Long-Term Survival

Continuing improvements in the perioperative management of CAD have produced important advancements in long-term survival after CABG [142]. Data from the STS Adult Cardiac Surgery Database showed a 3.2% operative mortality and 76% survival at 3-year follow-up in 348,341 isolated CABGs [143].

While operative characteristics, nonelective status, and previous cardiac interventions are associated with worse early survival, long-term survival appears to be influenced by chronic processes such as chronic kidney disease, diabetes, smoking, and lung disease [143]. Using data from the New York State Cardiac Surgery Reporting System, Shahian and colleagues developed a predictive model for cumulative survival, which underscores the importance of chronic diseases in these patients' long-term outcomes [144]. In their

study, cumulative survival at 7 years of follow-up was 75.6%. The use of arterial conduits, mainly the IMA, to graft the LAD coronary, compared to the saphenous vein, is significantly associated with superior survival and symptomatic relief [145, 146]. The use of multiple arterial conduits is a subject of ongoing debate.

14.8.3 Vein Graft Patency

Loss of venous patency may be attributed to thrombosis, intimal hyperplasia, and accelerated atherosclerosis, leading to graft failure in the acute, subacute, and late postoperative periods, respectively [147]. Early venous graft failures, at 18-month follow-up, can be as high as 25% and are thought to be a consequence of damage to the venous conduit during the procedure [148]. Overall, venous grafts have a significantly lower 16-year patency (64–83% vs. 88%) and 15-year cumulative survival (55–56% vs. 63–68%), compared to arterial conduits [145, 149, 150]. However, the occurrence of vein graft failure during angiographic follow-up has been associated with increased need for a re-revascularization, but not with increased mortality [151].

The most important predictors of graft patency at medium-term follow-up are vein preservation solution temperature, serum cholesterol, number of proximal anastomosis, and recipient coronary artery diameter [152]. A post-study analysis of the post-CABG trial done in 1248 patients revealed 12 predictive factors associated with worse venous patency including graft stenosis at baseline angiography, time after CABG, the use of moderate low-density lipoprotein lowering strategy, high low-density lipoprotein, previous myocardial infarction, elevated triglycerides, small minimum graft diameter, low high-density lipoprotein, low left ventricular ejection fraction, high mean arterial pressure, male gender, and current smoking [153].

14.9 Complications

As any major surgery, CABG carries the risk of complications, including deep vein thrombosis, anesthetic complications such as malignant hyperthermia, and death.

14.10 Cardiac Complications

14.10.1 Myocardial Infarction (MI)

The diagnosis of MI after CABG may be difficult, since cardiac enzyme elevations routinely occur as a result of the surgical manipulation and electrocardiographic changes may be associated with postoperative pericardial inflammation [154]. It is therefore suggested to use the Joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Health Federation Task Force definition for MI (type V) after CABG, which is defined as "an increase in biomarkers greater than five times the 99th percentile of the upper reference limit plus either new pathologic Q waves or new left bundle branch block, angiographic documentation of a new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium" [155].

In PREVENT IV study [156], a phase III, multicenter, randomized, double-blind, placebo-controlled trial on 3014 patients undergoing isolated CABG, MI was defined as "creatinine kinase-MB increase ≥10 times the upper limit of normal or ≥5 times the upper limit of normal with new 30-ms Q waves within 24 hours of surgery." In this study, 10% of patients had perioperative MI. This was associated with an increased risk of death, MI, or revascularization at 2 years.

14.10.2 Early Graft Occlusion

Early graft occlusion (i.e., within 30 days after surgery) occurs in 5–10% of saphenous vein grafts. It is usually thrombotic and is generally related to technical problems with the anastomosis or injury related to manipulation during graft harvesting [157]. Aspirin therapy, typically restarted within 6 h after surgery, may reduce the risk of such complication.

The American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions (ACC/AHA/SCAI) focused guideline update in 2011 recommends the use of PCI for treatment for saphenous vein graft occlusion, with the use of a distal embolic protection device, if feasible [158].

14.10.3 Low Cardiac Output

This is not an uncommon complication of CABG, which is primarily due to left ventricular dysfunction. In a prospective observational study of over 8600 patients undergoing CABG, the incidence of low output syndrome varied from 6% with a left ventricular ejection fraction (LVEF) >40% to 12% with an LVEF between 20% and 40% to 23% with an LVEF <20% [137]. A number of factors are possibly implicated, including arrhythmias, perioperative MI, hypertension leading to excessive afterload [159, 160], and/or decreased preload postoperatively (possibly due to blood loss or increased capillary permeability). Low cardiac output after CABG is often transient though, responding to fluid resuscitation and inotropic and/or mechanical support such as an intra-aortic balloon pump (IABP).

14.10.4 Vasoplegic Shock

This is thought to be an effect of CPB, characterized by a marked reduction in systemic vascular resistance with a well-preserved or increased cardiac output [161, 162]. Preoperative use of angiotensin-converting-enzyme (ACE) inhibitors has also been implicated as a risk factor [161, 163]. Treatment primarily consists of intravenous norepinephrine (NE). In those who are NE resistant, intravenous vasopressin may be effective [164]. Increased nitric oxide (NO) production has also been implicated in the pathogenesis, rendering methylene blue, which inhibits NO synthesis, a possible therapeutic intervention in severe cases not responding to other measures [165].

14.10.5 Atrial Fibrillation

Atrial fibrillation (AF) is one of the most frequent complications following CABG operations, with an incidence reaching up to 40% [166]. Age has been shown to be the most consistent independent predictor for postoperative AF [166, 167], and studies have tried to identify other predictors, in an attempt to provide prophylactic interventions [168, 169]. Beta blockers, sotalol, and amiodarone have been shown to reduce the frequency of postoperative AF by 52% to 65% in patients undergoing cardiac surgery [170]. The beta blocker should be given before and right after the surgery [171, 172].

14.10.6 Ventricular Tachyarrhythmias/ Bradyarrhythmias

Nonsustained VT is thought to be reperfusion-induced and occurs in over 17% of patients. It is usually benign, although it may impose a future risk of life-threatening arrhythmias [173–175]. Sustained monomorphic or polymorphic VT or ventricular fibrillation occurs in approximately 1–3% of patients, typically within the first week after surgery [173, 175–179]. In a meta-analysis of ten trials including 1195 patients, magnesium supplementation was found to reduce the incidence of postoperative ventricular arrhythmias [180]. *Bradyarrhythmias* are less common than ventricular tachyarrhythmias, and those requiring permanent pacemaker implantation occur in 0.8–4% of patients [181–183].

14.10.7 Pericarditis, Pericardial Effusion, and Tamponade

Also known as postpericardiotomy syndrome (PPS) and usually mimics post-MI syndrome. The most frequent complaint is chest pain, occurring a few days to several weeks after surgery. Steroids, nonsteroidal anti-inflammatory drugs, and colchicine have been used in attempts to prevent and/or treat PPS [184–186]. Based on serial echocardiographic findings, it was found that postoperative pericardial effusion is more common than clinically apparent, occurring in as many as 85% of patients [187]. The effusion is usually small and clinically insignificant. However, if the effusion is large, it may result in tamponade and hemodynamic instability, requiring urgent intervention with pericardiocentesis or reoperation. Postoperative anticoagulation may increase the risk of tamponade in patients who develop an effusion [188, 189].

14.11 Non-cardiac Complications

14.11.1 Neurological Complications/ Cognitive Dysfunction

In a review of the STS database of patients from 2002 to 2006, 774,881 patients underwent isolated CABG with a *stroke* incidence of 1.4% [25]. In an observational study of 2711 patients who underwent CABG, 2.7% had postoperative strokes, defined as focal neurologic deficit lasting more than 24 hours and/or localized by imaging [190]. Post-CABG strokes are usually secondary to aortic manipulation and embolism [191]. In the aforementioned study, more patients (6.9%) had postoperative *encephalopathy*, which was defined as abnormal level of consciousness manifested as confusion, delirium, or altered thinking [190]. The risk for these complications increases with age and is associated with increased mortality and longer length of hospital stay compared to those without neurologic sequelae [192]. Another neurological complication many patients experience is *cognitive decline* post-CABG, which often improves within 6 months [193]. Late cognitive decline has been reported for patients who undergo CABG, but this was not found to be different than that observed in patients of similar age with coronary artery disease who have not undergone CABG. Hence, this particular complication is not believed to be CABG/CPB specific [194].

14.11.2 Bleeding

Patients requiring a blood transfusion after CABG reach up to 30% [195], and rates of reoperation range from 4% to 6% [196]. Risk factors include prior bleeding, low preoperative hemoglobin, old age, female gender, and liver cirrhosis [195, 197]. Use of antiplatelet or antithrombotic drugs, coagulation abnormalities, and emergency operations have also been implicated as possible risk factors for bleeding [198].

14.11.3 Acute Renal Dysfunction

This is a very common complication after cardiac surgery. Its incidence is estimated at 30%, with almost 1–5% requiring dialysis, carrying a heavy burden of morbidity and mortality as well as prolonged hospital length of stay [199–201]. In a retrospective study on 13,847 patients, 40 patients (0.3%) developed acute kidney injury. Of those who survived, 64% required permanent dialysis [202]. Several scores have been recently developed to estimate the risk for developing post-CABG acute renal failure. Those are Cleveland Clinic score, Mehta score, and Simplified Renal Index score, with Cleveland Clinic score being the most predictive [203]. Acute kidney injury can arise from a variety of causes, including intraoperative hypotension, hemolysis, preoperative exposure to contrast media, low cardiac output, and cardiogenic shock [199, 204].

14.11.3.1 Nonunion of the Sternum, Deep Sternal Wound Infection, and Mediastinitis

These are particularly pronounced if the LIMA was harvested and more so if bilateral IMA were used, since it devascularizes the sternum, thereby increasing the risk [205]. However, there is evidence that a skeletonized harvest of the IMA decreases the incidence of deep sternal wound infection [206, 207]. Mediastinitis after CABG occurs in 0.9–1.3% of patients, usually presenting within the first 2 weeks [208–211]. Symptoms include fever, tachycardia, chest pain or sternal instability, local signs of sternal wound infection, and/or purulent discharge from the mediastinal area. Other risk factors include obesity [209, 211, 212], diabetes [208, 213], and prolonged duration of surgery [211].

14.12 Postoperative Management of Antiplatelet Therapy

Aspirin (ASA) has been shown to improve 1-year vein graft patency after CABG [214]. Its role is prominent when initiated prior to CABG and then restarted 6 h after surgery [215]. Medium doses of ASA (300–325 mg daily) were found no more effective than low doses (75–160 mg daily) in preventing graft occlusion, although an indirect meta-analysis showed weak evidence that medium doses might be more effective [216].

Several factors have been implicated in impaired inhibition of platelet function by ASA after CABG, such as drug interactions, decreased absorption, and increased platelet turnover. Such factors may increase the risk of early graft occlusion [217, 218]. Nevertheless, this phenomenon is usually transient and may be resolved by early intravenous or rectal administration of the drug, followed by oral once-daily administration in the early postoperative period [219].

14.12.1 Preoperative Versus Postoperative Administration of Aspirin

In a prospective, randomized, double-blind, placebo-controlled trial, Goldman et al. compared the safety and effectiveness of 325 mg of aspirin therapy initiated either the night before CABG as opposed to 6 h post-CABG [220]. Saphenous vein graft occlusion rate was 7.4% vs. 7.8% ($p = 0.87$) for pre- vs. postoperative aspirin administration, respectively. Preoperative aspirin was associated with a greater amount of blood volume transfused (900 vs. 725 cc, $p = 0.006$), greater chest tube drainage at 6 h (500 vs. 448 cc, $p = 0.011$), and a higher rate of reoperation for bleeding (6.3% vs. 2.4%, $p = 0.036$). On the other hand, some surgeons recommend the continuation of ASA therapy throughout the perioperative period, as it has been shown to reduce in-hospital mortality without a significant increase in risk of bleeding [221–224]. Furthermore, stopping aspirin before CABG was found to be associated with an increased in-hospital mortality [225]. It has therefore been suggested that ASA would be continued perioperatively in patients already being treated, with the possible exception of those at high risk for bleeding.

14.12.2 Dual Antiplatelet Therapy (DAPT) After CABG

The safety of early postoperative clopidogrel use following CABG has been demonstrated by several observational studies [224, 226, 227]. An RCT evaluating the efficacy of DAPT vs. ASA monotherapy, in terms of short-term venous graft patency, showed a significantly higher graft patency rates in the DAPT group [228]. In addition, two meta-analyses demonstrated that the use of DAPT reduced early vein graft occlusion [229, 230]. Deo and colleagues' meta-analysis also showed that the DAPT group had lower operative mortality than the ASA monotherapy group (0.8 vs. 1.9%, $p < 0.0001$). There is weak evidence (level C) that a loading dose of clopidogrel 300 mg post-CABG, followed by lifelong 75 mg/day, is a good alternative in case of ASA contraindication or intolerance [231]. However, there is a trend toward an increased risk of major bleeding with the combined use of ASA and clopidogrel [229, 230].

The ACC/AHA [232] and ESC [231] have produced guidelines and recommendations for the duration of

DAPT (see Appendix). However, owing to the paucity of data, the optimal bleeding-thrombotic risk balance before and after surgery remains unclear. More studies are required for an informed best practice antiplatelet strategy after CABG [231].

14.13 Case Study (Diabetic Patient with Multivessel Coronary Artery Disease)

History of Present Illness A 77-year-old female patient presented to the clinic with a chief complaint of severe, recurrent chest pain that starts on exertion and is relieved by rest. The pain is associated with shortness of breath, nausea, and vomiting and radiates to her left arm. The patient denies any palpitations or loss of consciousness.

Past Medical History *Diabetes mellitus type 2* (*non-insulin-dependent*), hypertension, hyperlipidemia, peripheral vascular disease, and congestive heart failure

Past Surgical History Carotid endarterectomy 5 years ago, right femoral-popliteal bypass 7 years ago, and tubal ligation 10 years ago

Family History Sister has coronary artery disease (CAD) with multiple stent procedures.

Social History Former smoker of one pack per day, 25 pack-years; quit 30 years ago. Drinks one glass of wine per night and denies illicit drug use

Medications Metformin, aspirin, carvedilol, clopidogrel, furosemide, and rosuvastatin

Allergies No known drug allergies

Review of Systems As per history of present illness. No other pertinent items

Focused Physical Examination

Head and neck: Bilateral carotid bruits. Right neck scar from the endarterectomy procedure

Cardiovascular: S1 and S2, regular rate and rhythm. No murmurs or gallops appreciated

Pulmonary: Vesicular breath sounds. Lungs clear to auscultation bilaterally

Abdomen: Soft, non-tender, and non-distended. Normal bowel sounds and no organomegaly

Neurological: Patient alert and oriented to time, place, and person, with no focal deficits

Extremities: Normal strength and pulsations 2+ bilaterally. No cyanosis, clubbing, or edema

Investigations

Electrocardiogram was done, showing normal sinus rhythm, with signs of anterolateral ischemia. *Echocardiography* demonstrated moderate left ventricular dysfunction, 35% ejection fraction, and no valvular pathology. Patient had an elevated glucose level (160 mg/dl), but all *labs* were otherwise normal. *Coronary angiography* was performed, showing severe, multivessel CAD (Fig. 14.1), with an estimated SYNTAX score of 35.

Assessment and Plan

The assessment and plan were discussed with the patient at length. She inquired whether she was a good candidate for percutaneous coronary intervention (PCI) like her sister. In an evidence-based approach, it was explained that given her history of *diabetes mellitus* and *multivessel CAD*, current evidence supports coronary artery bypass grafting (CABG) rather than PCI in her condition. A thorough literature review summary was presented to the patient, emphasizing the studies on long-term comparative outcomes of these two procedures (CABG and PCI) and that they all arrived at the same conclusion; *CABG is superior to PCI in diabetic patients with multivessel CAD*. The following landmark trials were highlighted:

1. *BARI trial*: This involved 1829 patients with symptomatic, multivessel CAD, randomized to PCI or CABG. At 10 years of follow-up, PCI patients with a markedly higher need for repeat revascularization and patients with treated diabetes had lower survival than CABG patients [44].

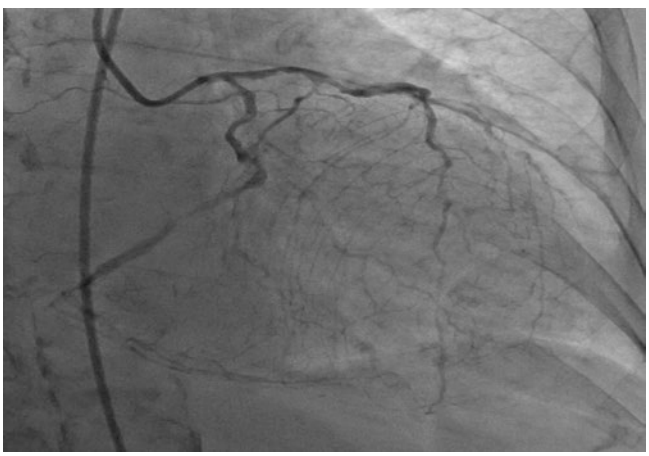

Fig. 14.1 Preoperative coronary angiogram showing severe, multivessel involvement

2. *FREEDOM trial*: This involved 1900 patients with diabetes mellitus and multivessel CAD, randomized to PCI or CABG. At 5 years of follow-up, stroke rate was higher among the CABG group, but MI and all-cause death were higher among the PCI group [41].
3. *SYNTAX trial*: This involved 1800 patients with left main and/or multivessel CAD, randomized to PCI or CABG. At 5 years of follow-up, PCI patients with diabetes mellitus had a higher frequency of the composite outcome (all-cause death, cerebrovascular accident, MI, and repeat revascularization) than CABG patients. Additionally, patients with higher SYNTAX scores had better outcomes with CABG than with PCI, and diabetic patients had more diffuse coronary lesions, as well as a higher EuroSCORE [246].

It was also considered that the patient would require endarterectomy based on the coronary angiogram findings. Because of this, the patient made a well-informed decision to undergo CABG, and a quintuple bypass was performed. Saphenous venous grafts (SVGs) were used for the posterior descending artery (PDA) and first diagonal artery (D1). Sequential SVGs were then used for the first and second obtuse marginal arteries. A left internal mammary to left anterior descending (LAD) artery graft was also used. The large size of the plaques required three adjunct coronary endarterectomies to the PDA, D1, and LAD arteries. The LAD endarterectomy was done through a long arteriotomy, which required major reconstruction with a venous patch. The complex plaque anatomy further supports the unfeasibility of PCI in her case (Fig. 14.2).

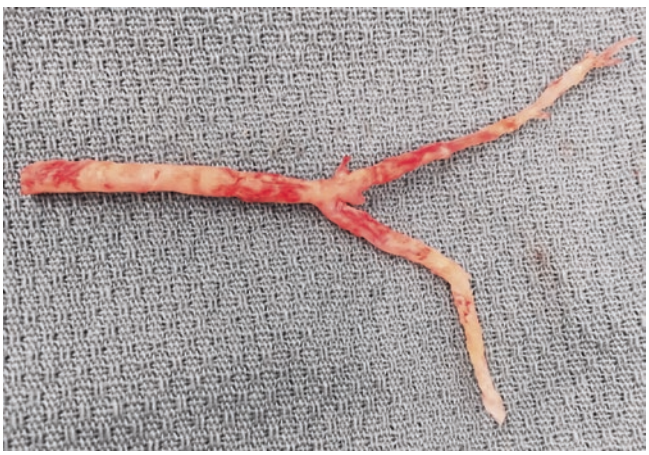

Fig. 14.2 Large coronary plaque specimen retrieved by coronary endarterectomy. *N.B.* This anatomy would have not been amenable to percutaneous treatment

Appendix

Table 14.1 Some indications where CABG is mainly utilized to *improve symptoms* [14, 18]

Indication	Class	LOE
One or more significant (≥70% diameter) coronary artery stenosis and intolerable angina, despite adequate medical treatment	I	A
One or more significant coronary artery stenosis and intolerable angina, if medical treatment is not feasible because of contraindications, adverse effects, or patient preferences	IIa	C
Complex triple-vessel CAD, with or without involvement of the proximal LAD artery, if patient is a good surgical candidate	IIa	B
Guidelines classification of recommendations are explained below, as follows: Class I: There is evidence and/or consensus that the procedure is useful and effective (i.e., *SHOULD* be performed) Class II: There is conflicting evidence and/or no consensus about the usefulness or efficacy of a procedure		
This is further subclassified into: Class IIa: Weight of evidence or opinion is in favor of usefulness or efficacy (*REASONABLE* to perform) Class IIb: Usefulness or efficacy is less well established by evidence or opinion (*MAY BE* considered) Class III: There is evidence and/or general agreement that the procedure/treatment is not useful or effective and, in some cases, may be harmful (should *NOT* be performed)		
Levels of evidence are also explained below, as follows: Level A: Data obtained from multiple randomized clinical trials or meta-analyses Level B: Data obtained from a single randomized trial or non-randomized studies Level C: Expert opinion, case studies, or standard of care		

Class classification of recommendation, *LOE* level of evidence

Table 14.2 Summary of the 2011 ACC/AHA guidelines [18] to *improve survival*

Indication	Class	LOE
Left main stenosis >50%	I	B
Triple-vessel disease with or without proximal LAD stenosis	I	B
Double-vessel disease with proximal LAD stenosis	I	B
Double-vessel disease without proximal LAD stenosis	IIa (with extensive ischemia)	B
Single-vessel disease with proximal LAD stenosis	IIa (with LIMA for long-term benefit)	B
Single-vessel disease without proximal LAD stenosis	III (i.e., harmful)	B
Survivors of sudden cardiac death with presumed ischemia-mediated VT	I	B

LAD left anterior descending, *VT* ventricular tachycardia, *LIMA* left internal mammary artery

Some Special Considerations and Clinical Subsets [18]

CABG in Patients with Acute Myocardial Infarction (MI)

Emergency CABG is recommended in cases of primary PCI failure in patients with acute MI, or if a significant area of myocardium is persistently ischemic at rest, despite adequate nonsurgical therapy (Class I, Level of Evidence: B) [233, 234].

Emergency CABG is recommended with surgical repair of postinfarction sequelae of MI, including mitral valve insufficiency, ventricular septal rupture, or free wall rupture (Class I, Level of Evidence: B) [235, 236].

Emergency CABG is recommended in cases of cardiogenic shock, if patient is a good candidate for CABG, regardless of the time interval between onset of MI and shock or the time interval between onset of MI and CABG (Class I, Level of Evidence: B) [237, 238].

Emergency CABG is also recommended in patients with life-threatening ventricular arrhythmias (if ischemia is thought to be the underlying cause), in the presence of triple-vessel disease and/or ≥50% left main stenosis (Class I, Level of Evidence: C) [238]

CABG in Patients with Life-Threatening Ventricular Arrhythmias

CABG is recommended in patients with resuscitated sudden cardiac death or sustained ventricular tachycardia (VT), if significant CAD, with resultant myocardial ischemia, is thought to be the underlying cause (Class I, Level of Evidence: B) [239–241].

Emergency CABG After Failed PCI

Emergency CABG is recommended after failed PCI if ischemia persists or if there is substantial myocardium at risk from a threatened occlusion (Class I: Level of Evidence: B) [242, 243].

Emergency CABG is recommended after failed PCI, due to hemodynamic compromise, in patients with no history of previous sternotomy or coagulopathy (Class I, Level of Evidence: B) [242, 244, 245].

CABG in Association with Other Cardiac Procedures

CABG is recommended with other cardiac procedures (i.e., non-coronary cardiac surgery) in patients with ≥50% left main stenosis or ≥70% stenosis of other major coronary arteries (Class I, Level of Evidence: C) [18].

Table 14.3 The 2016 ACC/AHA focused guideline update for recommendations on the optimal duration of DAPT in patients undergoing CABG [232]

	Class	LOE
In patients who undergo CABG and have stable ischemic heart disease, it is reasonable to continue clopidogrel plus ASA for 12 months postoperatively, to improve venous graft patency	II	B
In patients who undergo CABG and have a recent history of ACS, resumption of $P2Y_{12}$ inhibitor is recommended postoperatively to complete a total of 12 months of DAPT after ACS	I	C
In patients who undergo CABG and have recently undergone PCI, resumption of $P2Y_{12}$ inhibitor is recommended postoperatively to complete the recommended duration of DAPT after PCI (4 weeks to over 12 months)[a]	I	C
ASA dose of 81 mg (75–100 mg) is recommended in all DAPT regimens	I	B

[a]According to bleeding risk and clinical setting

Table 14.4 The 2014 ESC guidelines for resuming antiplatelet therapy after coronary artery bypass grafting surgery [231]

	Class	LOE
ASA 75–160 mg/day should be restarted within the first 24 h after CABG (preferably within 6 h) and maintained lifelong	I	B
Loading dose of clopidogrel 300 mg, as soon as bleeding is controlled, followed by 75 mg/day is recommended lifelong, in case of aspirin contraindication or intolerance	I	C
DAPT with clopidogrel may be restarted after CABG in patients with stable CAD, as soon as considered safe	IIb	C
Resumption of $P2Y_{12}$ inhibitor should be considered, as soon as bleeding is controlled, in patients who undergo CABG within 1 year of ACS	IIa	B

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Cardiac Rehabilitation: New Emphasis on Metabolic Disease

15

Robert W. McGarrah and William E. Kraus

Key Points

- Changes in Medicare reimbursement guidelines, updating of program guidelines, expansion of the role of cardiac rehabilitation to all aspects of cardiac prevention, incorporation of the principles of exercise testing, and behavior change into clinic encounters have made cardiac rehabilitation more powerful and effective.
- Although much is known about how patients respond to and benefit from regular exercise and therapeutic lifestyle changes, more work is needed relative to improving long-term compliance to known beneficial lifestyle and medical therapies, improving referral rates of eligible patients to secondary prevention programs, and improving retention of patients who are referred to and begin participation in cardiac rehabilitation.
- Despite cardiac rehabilitation representing a Class 1A guideline therapy for most patients with cardiovascular disease, gender, age, and race discrepancies persist in terms of program access and utilization.
- Like other therapies available to patients with cardiovascular disease, cardiac rehabilitation has a bright future as a cost-effective strategy that improves mood, restores functional capacity, lessens or alleviates symptoms, and lowers the risk for and occurrence of subsequent clinical cardiovascular events, with all of the attendant social, economic, and medical benefits that ensue from its successes. The primary care physician who understands these principles can be an invaluable ally in this process.

R. W. McGarrah · W. E. Kraus (✉)
Division of Cardiology, Department of Internal Medicine, Duke University School of Medicine, Durham, NC, USA
e-mail: william.kraus@duke.edu

15.1 Introduction

Cardiac rehabilitation was developed in the mid-1970s as a mechanism by which to instruct and deliver exercise therapy to those having survived a recent acute coronary syndrome. Although the field of cardiac rehabilitation has a relatively short (40 years) history as evidence-based care for patients with cardiovascular disease, it continues to evolve. Changes in program scope have shifted the emphasis away from cardiac rehabilitation as a limited short-term intervention to one of a comprehensive secondary preventive strategy targeting the multiple medical, exercise, nutritional, and behavioral factors that place a patient at increased risk for a subsequent cardiac event. Consistent with this change in program scope, third-party payers such as Medicare now recognize the importance of a comprehensive secondary preventive approach to the cardiac patient. In fact, the national coverage policy from Medicare specifies that rehabilitation should not be solely an exercise program but rather a multidisciplinary one aimed at reducing subsequent cardiovascular disease risk through intensive risk factor management and institution of therapeutic lifestyle changes.

For the physician and allied health professional interested in the secondary prevention of cardiovascular disease, a good summary of the secondary prevention goals and treatment guidelines can be found in an American Heart Association/American College of Cardiology (AHA/ACC) statement on this topic [1] and other associated statements from the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) [2–5]. Table 15.1 provides a summary of these goals. In addition, the AACVPR also has been a long-standing proponent of a multidisciplinary program for cardiac rehabilitation, such that programs address the broad scope of cardiovascular disease and its related risk-related morbidities (diabetes, hypertension, dyslipidemias, metabolic syndrome, psychosocial stress, and smoking behavior) through both medical and multicomponent lifestyle interventions [6, 7]. In fact, both the ACC and the AACVPR, along

P. P. Toth, C. P. Cannon (eds.), *Comprehensive Cardiovascular Medicine in the Primary Care Setting*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-319-97622-8_15

Table 15.1 Summary of the American Heart Association/American College of Cardiology goals for secondary prevention in patients with coronary and other atherosclerotic vascular disease [1]

Risk factor or therapy	Goal
Smoking	Complete cessation. No exposure to environmental tobacco smoke
Blood pressure[a]	<140/90
Lipid management[a]	LDL cholesterol <100 mg/dL; if triglycerides are ≥200 mg/dL, then non-HDL cholesterol should be <130 mg/dL
Physical activity	30 min, 7 days/week (minimum 5 days/week)
Weight management	Body mass index: 18.5–24.9 kg/m^2 Waist circumference: men <40 in. and women <35 in.
Diabetes management	HemoglobinA_{1c} < 7% may be considered
Antiplatelet agents/ anticoagulants	See full paper for treatment recommendations [1]
Renin–angiotensin–aldosterone system blockers	See full paper for treatment recommendations [1]
Beta-adrenergic blockers	See full paper for treatment recommendations [1]
Influenza vaccination	Patients with cardiovascular disease should be vaccinated

[a]These guidelines (2011) have not incorporated the most recent hypertension [10] and lipid [11] guideline recommendations

with the American College of Sports Medicine, the American Hospital Association, and other organizations and individuals, were instrumental in providing the scientific evidence and opinion that led to the most recent changes in Medicare's national coverage policy [8, 9]. A summary of these changes is outlined in Table 15.2. As is evident, Medicare now expects rehabilitation programs to extend service beyond exercise only, by using an interdisciplinary team approach to promoting recovery from an acute cardiac event and reducing the risk of subsequent events.

In this chapter, we will provide information of use to practicing physicians who are considering referral to and interacting with a cardiac rehabilitation program. First, we will explore the utility and interpretation of the graded exercise tolerance test in the cardiac and noncardiac patients undergoing evaluation. Second, we will review the emerging role of cardiac rehabilitation in metabolic disorders. Third, we explore the structure of a cardiac prevention strategy, whether it be conducted within a clinic setting, in cardiac rehabilitation, or in a combination of the two, where the cardiac rehabilitation program communicates with the referring physician to address the needs and progress of the cardiac rehabilitation participant. Finally, we will provide some patient individual cases to illustrate these concepts.

Table 15.2 Summary of important changes in Medicare national coverage decision policy, 1982 to March 2006 and March 2006 to present [8, 9]

	1982 to March 2006	March 26, 2006 to present
Program components	Stipulated exercise only	Medical evaluation, risk factor modification, exercise, and education
Program duration	36 visits in 12 weeks	36 visits in 18 weeks (following review, up to 72 visits in 36 weeks)
ECG rhythm strips	Required	Clinician determined the need for ECG monitoring
Level of physician supervision	Proximal to exercise area	Hospital premises (within 250 yd for separate buildings on campus). Off-hospital campus then present and immediately available
"Incident to" physician	Unclear	Can vary based on the setting of the services provided; however, ordering physician, primary care physician, or program medical director should all suffice as long as there is documentation in the medical record of interactions between the physician and rehabilitation staff concerning patient status
Indications	STEMI, NSTEMI, CABG, stable angina	NTEMI, STEMI, CABG, angina, PTCA, coronary stenting, heart valve surgery, cardiac transplant, stable chronic systolic HF with LVEF ≤35% with NYHA class II-III symptoms, and optimal HF therapy for ≥6 wk

STEMI ST-segment elevation myocardial infarction, *NSTEMI* non-ST-segment elevation myocardial infarction, *CABG* coronary artery bypass graft surgery, *PTCA* percutaneous transluminal coronary angioplasty, *HF* heart failure, *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association

15.2 The Graded Exercise Test

In the primary care setting or in cardiac rehabilitation, a graded exercise test (GXT) might be obtained for risk stratification and prognostication, for diagnostic reasons (e.g., to test for residual ischemia in the setting of recurrent symptoms following an invasive therapeutic cardiovascular procedure), for therapeutic reasons (to develop an exercise prescription), or to quantify functional capacity—at baseline or in response to exercise training. It is important that the primary care provider be able to understand the reason for testing and the potential results obtained, so as to be able to adequately address the needs and status of the cardiac patient.

Reasons for obtaining a GXT in cardiac rehabilitation:

1. Diagnosis—evaluation of ischemia and symptoms following event or procedure
2. Prognosis—following a cardiac event

3. Exercise prescription—when entering a CR program
4. Evaluation of functional capacity—following exercise training for reinforcement

15.2.1 The GXT for Diagnostic Purposes

In most settings, the primary reason for obtaining a graded exercise test (GXT), sometimes referred to as an exercise tolerance test (ETT), is to confirm or refute the diagnosis of functionally significant occlusive coronary artery disease when patients have symptoms suspicious for stable angina pectoris. The consensus guidelines and literature supporting this indication are thoroughly addressed in the periodically updated official guidelines of the American Heart Association and American College of Cardiology [12]. However, in the cardiac rehabilitation setting, only rarely is graded exercise testing performed for a de novo diagnosis of occlusive coronary artery disease. Rather, following an invasive procedure (percutaneous coronary intervention or coronary artery bypass grafting) for correction of occlusive disease, the cardiac patient might experience recurrent symptoms reminiscent or suggestive of angina. In such settings, it is reasonable to consider performing a graded exercise test with ECG monitoring in order to screen for exercise-induced ischemia. This may occur early in the setting of post-event rehabilitation and discharge, during a cardiac rehabilitation program (e.g., indicative of incomplete revascularization), or later in the patient's course after cardiac rehabilitation (e.g., restenosis following angioplasty or stenting). If ischemia is documented, the patient is most often referred for more extensive studies and perhaps a repeat revascularization procedure.

15.2.1.1 The Positive Exercise ECG Tracing

The diagnosis of functionally occlusive coronary artery disease is made on the basis of the exercise ECG. The following criteria are used to read the test as "positive" for such a condition. The criteria are designed to optimize the balance between sensitivity and specificity in a population with a relatively high prevalence of cardiovascular risk factors. The ST segments have to be depressed 0.1 mV compared with the PR interval for the same beat, with a configuration that is downsloping or flat at a point in the complex that is 0.08 ms from the conclusion of the QRS complex in a lead tracing with no baseline ST depression. Additionally, this configuration has to be consistent and evident in at least three successive complexes to avoid findings due to motion artifacts. The finding must be in at least one of the ten standard ECG leads other than III and aV_R. A lone finding in lead III is not considered to be valid; rather, it has to be accompanied by a similar finding in leads II or aV_F. In lead tracings with baseline ST depression, the tracing has to meet "double criteria" in order to be considered positive: the ST tracing has to be depressed further than baseline by an additional 0.2 mV. That is, if the tracing is already 0.05 mV below the resting PR interval, then to meet double criteria, the tracing has to be 0.25 mV below the PR interval (baseline) at 0.08 ms from the conclusion of the QRS complex.

There are several additional caveats. In order to reduce the prevalence of false-positive tests, the exercise ECG is "uninterpretable" if there are baseline ST changes due to left ventricular hypertrophy or left bundle branch block or if the subject is taking digitalis and related medications. A test is considered interpretable in the lateral precordial leads (V_4–V_6) and in the limb leads in the presence of a right bundle branch block.

Note that there is a high prevalence of false-positive tests in patients using exogenous estrogens. This is likely due to the fact that the chemical structure of estrogens resembles that of digitalis. Higher levels of endogenous estrogens are also likely the cause of the higher rate of false-positive testing in middle-aged women, although this has never been conclusively proven. Instead of obtaining a simple GXT, it might be prudent to proceed directly to a functional imaging study for diagnosis or exclusion of occlusive coronary artery disease in women on exogenous estrogen therapy, given the relatively higher rate of false-positive tests in this demographic, and since progression to functional imaging studies might be required anyway. Many of these considerations are summarized in an excellent text by Ellestad on the subject dealing with the interpretation of the exercise electrocardiogram [13].

Interpretations of the exercise ECG:

1. Criteria for positive test:
   (a) ST segments depressed 0.1 mV in the absence of baseline changes
      - Three successive beats
      - Flat or downsloping 0.08 ms from the completion of the QRS complex
      - Any one or more of the ten leads, excluding III and aV_R
   (b) Meets "double criteria" in the presence of baseline ST depression
2. Uninterpretable in the presence of:
   (a) LBBB, LVH with strain, and digitalis
3. High prevalence of false positives (i.e., use caution) in the presence of:
   (a) Exogenous estrogen used
   (b) LVH without strain
   (c) Middle-aged women

15.2.2 The GXT for Prognostic Purposes

15.2.2.1 Cardiorespiratory Fitness

Cardiorespiratory fitness, as measured by a graded exercise tolerance test, provides strong and independent prognostic information about overall—and especially cardiovascular—morbidity and mortality. Cardiorespiratory fitness is a valid prognostic indicator in apparently healthy individuals; in at-risk individuals with diabetes mellitus, metabolic syndrome, and hypertension; and in patients with cardiovascular disease, such as those presenting to cardiac rehabilitation programs [14–20]. However, despite the profoundly important prognostic information provided by simple clinical assessments of fitness, they are, unfortunately, rarely used in the clinic setting and often ignored in the exercise testing laboratory. There appears to be an undue emphasis—both on the part of the cardiac specialist and primary care physician—on the exercise ECG for the diagnostic interpretation just discussed. Tables 15.3 and 15.4 indicate, for women and men, the expected fitness level in METS; 1 MET is the "metabolic equivalent" or energy utilized by a person at rest (approximated by 3.5 mL O_2/kg/min or 1 kcal/kg/min). Due to its increasingly recognized value, testing laboratories should report the fitness classification on clinical GXT reports. This can be used as a valuable marker to follow longitudinally the changes in risk stratification in individuals in cardiac rehabilitation programs.

15.2.2.2 The Exercise ECG for Prognostic Purposes

There is a rich literature from the 1980s regarding the use of the exercise ECG—specifically, the time during the GXT at which it becomes abnormal—and the prognostic implications of this in clinical decision-making. In one set of investigations, it was observed that, after myocardial infarction, a sub-maximal test can be used to determine medium- and long-term risk of recurrent ischemic events and cardiovascular death. Additionally, GXT information can be used to determine the likelihood of left main and three-vessel coronary artery disease (sometimes referred to as "surgical disease").

In a publication during this period, the Duke Treadmill Score was developed and subsequently reached broad popularity for prognostic purposes [18]. It was observed that a limited GXT performed within the first several weeks following a myocardial infarction could assist in determining whether follow-up testing was indicated in order to identify patients who would benefit most from coronary artery bypass grafting (CABG). If the exercise ECG of a GXT was positive or symptoms developed before a HR of 120 beats per minute (bpm) was achieved, this indicated a 22% likelihood of the patient having three-vessel occlusive coronary disease or 8% of having left main coronary artery disease [22]. This would prompt further studies in the coronary catheterization laboratory with the anticipation that the patient will require CABG. Soon, these criteria were found to be relevant for all individuals suspected of having occlusive coronary artery disease [23]. Unfortunately, with the ready availability of invasive diagnostic and therapeutic catheterization laboratories at many institutions, this practice has fallen out of favor, and the GXT is rarely used today as a prognostic test when developing a therapeutic plan.

Table 15.3 Cardiorespiratory fitness classifications for women (METS) [21]

Age (year)	Low	Below average	Average	Above average	High
20–29	≤8.0	8.0–9.9	10.0–12.4	12.5–13.9	≥14.0
30–39	≤7.7	7.8–9.6	9.7–11.9	12.0–13.6	≥13.7
40–49	≤7.1	7.2–9.0	9.1–11.6	11.7–13.0	≥13.1
50–65	≤6.0	6.2–8.2	8.3–10.5	10.6–11.9	≥12.0

Table 15.4 Cardiorespiratory fitness classifications for men (METS) [21]

Age (year)	Low	Below average	Average	Above average	High
20–29	≤10.9	11.0–12.5	12.6–14.8	14.9–16.2	≥16.3
30–39	≤9.7	9.8–11.3	11.4–13.6	13.7–14.8	≥14.9
40–49	≤8.6	8.7–10.2	10.3–12.5	12.6–13.6	≥13.7
50–59	≤7.1	7.2–9.0	9.1–11.3	11.4–12.5	≥12.6
60–69	≤6.0	6.1–7.6	7.7–10.2	10.3–11.3	≥11.4

15.2.3 The Use of the GXT for Therapeutic Purposes: Modifying the Exercise Prescription

The GXT can also be used to follow a patient's progress and to adjust exercise training intensity. It is for this purpose that the Center for Medicare and Medicaid Services (CMS) recognizes the need to reimburse for a GXT both prior to and following an approved period (36 sessions) of cardiac rehabilitation. The principles underlying this practice in the coronary patient are summarized in Fig. 15.1.

It is a basic principle of exercise physiology that there is a linear relation between heart rate and workload from rest to the ventilatory threshold when the oxygen demands precipitated by the exercise workload exceeds the oxygen supply to working muscles. After a period of exercise training, there occur three observable physiologic responses characterizing the "training effect." These three responses are illustrated in Fig. 15.1: (1) resting bradycardia, where the resting heart rate is lower following exercise training; (2) a training bradycardia, a relative bradycardia at each successive workload to HR maximum; (3) an increase in maximum workload (measured as time to exhaustion in a given exercise protocol or as peak

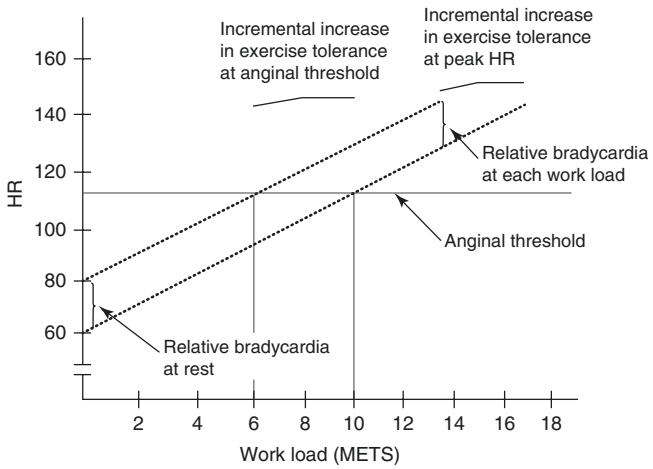

Fig. 15.1 The principles underlying graded exercise testing in the cardiac patient. For a full discussion of the principles, please see the text. The graphic depicts the linear response of heart rate (HR) to increasing workloads in metabolic equivalents (METs, multiples of resting energy expenditure) before and following an exercise training program (shown by the *dotted lines* where the pre-program line is higher and to the left of the post-program line). The three components of an exercise "training effect" are evident: decrease in resting heart rate (training bradycardia), a relative bradycardia at each workload, and an increase in maximum work tolerance. When angina from a fixed lesion reproducibly occurs at a heart rate of 115 bpm, there is a similar increase in workload (from 6 to 8 METs) before the onset of angina, resulting in an effective increase in asymptomatic work tolerance with exercise training for the cardiac patient having stable exercise-induced angina

VO_2 with indirect calorimetry using a metabolic cart). This physiology is particularly pertinent for individuals with occlusive coronary artery disease and angina pectoris. With a fixed lesion, the angina threshold (HR at which angina occurs) is reproducible and corresponds to a given level of work (workload). In the figure, before and following exercise training, the angina threshold is approximately 115 bpm. The maximum workload at the angina threshold is 6 METS prior to training, but 10 METs following; this represents a 66% increase in exercise tolerance following exercise training.

It should be noted that these responses are specific to the muscles undergoing exercise training, and, therefore, careful attention should be given to the exercise prescription and the muscle groups that will be commonly used in the activities of daily living when the angina threshold is likely to be exceeded. For example, if a patient works in a job that requires primarily upper body work, then consideration should be given to exercise training primarily the upper body during the cardiac rehabilitation period in order to provide the greatest increase in exercise tolerance in the work setting.

Thus, graded exercise testing is a useful clinical tool with prognostic, diagnostic, and therapeutic uses. Careful attention to the use of this tool in the cardiac rehabilitation program can increase the utility of program components to modify risk for subsequent events.

15.3 Cardiac Rehabilitation: Expanding Applications to Metabolic Disease

The increasing prevalence of overweight and obesity has contributed to a diabetes epidemic in the USA. In response to this growing health concern, the AHA issued a scientific statement regarding the role of exercise training in type 2 diabetes to reduce cardiovascular risk [24]. Because diabetes is a strong risk factor for initial and subsequent cardiovascular events, exercise training should be employed in both the primary and secondary prevention settings. In individuals with diabetes, exercise training improves glycemic control, reduces body fat and body mass index, reduces hypoglycemic medication requirement, and improves exercise capacity. Moreover, exercise has favorable effects on other cardiovascular risk factors in diabetic individuals, including hypertension and hyperlipidemia [25, 26].

The growing obesity epidemic has also increased the prevalence of the metabolic syndrome. The metabolic syndrome, characterized by systemic insulin resistance, is generally defined as the presence of any three of the following traits [27]: (1) abdominal obesity, defined as a waist circumference in men ≥102 cm (40 in) and in women ≥88 cm (35 in); (2) serum triglycerides ≥150 mg/dL or drug treatment for elevated triglycerides; (3) serum high-density lipoprotein (HDL) cholesterol <40 mg/dL in men and <50 mg/dL in women or drug treatment for low HDL cholesterol; (4) blood pressure ≥130/85 mmHg or drug treatment for elevated blood pressure; and (5) fasting plasma glucose (FPG) ≥100 mg/dL or drug treatment for elevated blood glucose. A recent study estimated that nearly 35% of all US adults and 50% of those 60 years or older have the metabolic syndrome [28]. Importantly, the metabolic syndrome significantly increases risk for cardiovascular events and death [29], so interventions targeting this condition will have major impact on population health. Because numerous studies demonstrate the beneficial effects of exercise training on the individual components of the metabolic syndrome [30], exercise prescriptions should be considered in every individual who presents with the metabolic syndrome.

The ability of individuals with diabetes or metabolic syndrome to participate in formal exercise programs may be limited due to access to facilities or lack of insurance coverage. However, evidence demonstrates a benefit of home-based exercise programs in combination with ongoing physical activity counseling by health-care providers [31], underscoring the importance of continued exercise-related discussions at each patient visit. Cardiac rehabilitation for those with cardiac disease and metabolic syndrome or diabetes mellitus is even more imperative than in those without these comorbid conditions.

15.4 Cardiac Care in the Outpatient Setting: Behavioral and Therapeutic Strategies

The assessment of global cardiovascular risk at baseline and in response to therapy is an important issue to assess during cardiac rehabilitation. Many cardiac rehabilitation programs assess the patient before and after a period of cardiac rehabilitation using established modifiable markers of cardiovascular risk, including each component of the lipid profile, blood pressure, metabolic syndrome, diabetes mellitus, central adiposity, cigarette smoking, depression, social support, and others. The goal is to modify the risk in order to prevent downstream cardiovascular morbidity and mortality. Although much is accomplished in the setting of the cardiac rehabilitation program itself, much can also be accomplished in the clinic-based visits with physicians and mid-level providers to reinforce messages from the cardiac rehabilitation program, to titrate and optimize medical therapy, and to further refine risk modification strategies when cardiac rehabilitation is completed. For lifestyle modification to be successful in the clinic setting, the provider must base the approach upon a behavioral construct that to the clinician makes sense and is one that can readily be employed. Many consider the standard stages of change behavioral change construct [32] to be the most useful. This is discussed below.

15.4.1 Assessment of Risk in the Cardiac Rehabilitation Setting

It is critical to assess modifiable cardiovascular risk factors prior to, and following, a course of cardiac rehabilitation. First, such an assessment can focus the attention of the patient and the CR staff on targeted areas of particular interest during the rehabilitation period. Follow-up assessments can demonstrate significant improvement when patients are compliant with prescribed therapeutic and lifestyle modifications. Second, such information can be shared as objective evidence of success to referring providers, thus becoming a reinforcing strategy for participant recruitment. Two case examples demonstrating these principles are presented later. Third, the CR staff can use these data to assess the effectiveness of the program, and, in general, ineffective strategies can be modified and adapted to be more efficacious or abandoned if found to have no utility.

We have used the format illustrated in the case examples to collect relevant data on individual participants. Such data are shared with the referring health-care provider and can become part of the medical record of the individual. In addition, data are collected in a longitudinal database for subsequent program-wide assessments, as previously discussed.

15.4.2 Assessment and Modification of Risk in the Clinic Setting

As noted, a clinic visit, with either a member of the CR team or the referring physician, is an important ancillary component of cardiac rehabilitation. It is important to incorporate smoking, inactivity, and poor eating habits into a behavior change strategy. There are at least four steps to a successful intervention when trying to achieve behavioral change: (1) bringing attention to the behavior, (2) discussion of the behavior with the individual, (3) developing an effective strategy with the patient for changing behavior, and (4) following up with the progress of the strategy at the next encounter. It is clear, however, that such approaches take time and the pressures of current medical practice require that strategies to address behavior change in the outpatient setting be both effective and time-efficient.

Steps in successful clinic-based behavior change strategies:

1. Bring attention to the behavior—surveying
2. Discussion of importance of changing the behavior
3. Agreeing on plan and contracting
4. Follow-up

15.4.2.1 Bringing Attention to the Behavior

There are several methods to bring a particular behavior to the attention of a patient. When this comes from the physician, the individual becomes aware that the physician believes in its importance. For example, measuring a weight or waist circumference or asking about eating and physical activity behaviors are important components of drawing the patient's attention to the issue; it also stresses that the health-care provider believes the issue is important enough to seek and record this information. Short surveys administered about eating and physical activity behaviors, administered in the waiting room while the individual is waiting to see the caregiver, also provide an effective strategy for collecting this information. It is essential, however, in order for this strategy to be effective, that the information subsequently be addressed and referenced during the clinic encounter with the physician. Such data should also become part of the medical record, preferably in the clinic visit note.

15.4.2.2 Discussion of the Behavior in the Clinic with the Patient

It is important, once the data are collected on a given behavior, to discuss the behavior with patients during the clinic encounter. That being said, it is clear, that not all behaviors of interest can be effectively addressed in each

clinic visit. That is, it may be particularly ineffective to mention as a parting comment during a clinic encounter that the individual "should lose weight, eat better, and get more regular exercise." Although better than not acknowledging the problem at all, the absence of a detailed, if brief, discussion of important behavioral issues will rarely lead to significant or long-term behavior change. Rather, the provider must spend some time explaining the importance of the behavior at issue. Addressing *one* of the potentially four important cardiovascular behaviors in *each* visit is an efficient and effective means to promoting behavior change. In the prevention setting, the important behaviors that should be addressed are smoking, poor nutrition choices, lack of sufficient physical activity, and type A behavior (high mental stress levels due to excessive external demands as perceived by the individual). How does one choose which behavior to address in a given clinic visit?

Choosing Which Risk Factor to Address: The Transtheoretical Model of Behavioral Change

The transtheoretical model of behavior change (pre-contemplation, to contemplation, to planning, to action, to maintenance and reinforcement) is a common approach to instituting behavior change in the clinic setting. It can also be used to decide which behavior of several that could best be chosen should be addressed in any given encounter. For example, should an individual be a smoker, have a poor diet, excessive job-related stress, and be physically inactive, one might ask which behavior might be best to address first. One approach might be to assess in which stage of pre-contemplation, contemplation, or planning the individual is in, by prompting with questions such as "Have you considered stopping smoking?" or "Have you made plans to stop smoking within the next several months?" Depending upon this survey of prospective behaviors, it might make sense first to address those behaviors to which the individual is willing or even eager to direct their attention. For example, in a patient that responds to such queries with "I enjoy smoking and do not wish to consider stopping at the present, but I do want to consider changing my diet and getting more exercise," it does not make sense to address first the smoking issue ahead of diet and exercise issues.

15.4.2.3 A Series of Clinic Visits Become a Program for Behavior Change

Given time constraints and limitations on the amount of information any one individual can absorb in one visit, it makes sense to address only one behavior in each visit and attempt to move the behavior change along the transtheoretical model spectrum in each clinic encounter. This typically may take from 5 to 15 min. Thus, in reality, *a series of clinic visits becomes a program of behavior change*, and, for example, it may take up to 16 sequential clinic visits to address and promote effective behavior change in each of 4 distinct behaviors.

Developing a Behavior Change Plan

As noted, developing a behavior change plan is an essential step in the process of promoting lifestyle changes in the clinic setting. This may take as little as 5 min and as much as 15 min. Addressing the need to increase physical activity, for example, the clinician might probe the individual's lifestyle and suggest where within the normal routine of a day a patient may dedicate time for physical activity and exercise. As it does not require large changes in physical activity to make a significant difference in health parameters and modest changes in physical activity are relatively easy to institute, formulating a plan with an individual in the clinic setting is important. Often, for example, in order to promote daily, moderate levels of activity of about 30 min duration, we often suggest that patients walk the dog daily—whether he/she has one or not! Once a plan is made, it is important to document it in the clinic record for later reference.

15.4.2.4 Follow-Up at the Next Encounter: The Importance of Contracting

The final essential step in a clinic-based process promoting behavior change is follow-up and reinforcement. By recording the plan in the clinic note, the clinician is prepared to query progress at the next visit. Contracting also is a useful approach. For example, if weight loss is a goal, one might agree on a target for a given amount of weight loss in the interim until the next visit (e.g., agreeing on a 10 lb weight loss in 5 months). One might reinforce the understanding by contracting on the behavior (looking the patient in the eyes, shaking hands on the agreement, and recording it in the chart). This can be particularly effective in helping the individual recall the contract. The contract and progress in achieving the agreement are then reviewed at the next encounter and a new contract formed. When it is important to reinforce behavior when change is actively taking place, more as opposed to less frequent clinic visits might be arranged.

15.5 Summary and Outstanding Questions

Assessing global cardiovascular risk is important in both the cardiac rehabilitation setting and in the cardiovascular disease prevention or primary care clinic working in parallel. Assessing risk permits one to assess the effectiveness and make necessary adaptation of procedures and tactics for promoting lifestyle changes in these settings. In the clinic set-

ting, promotion of lifestyle change is a progressive process, often based upon behavioral change strategies, such as the transtheoretical model, where a series of stepwise counseling can be considered a program. Although many of the suggestions presented in this summary are seemingly rational and self-evident, many questions are in need of scientific testing for efficacy in randomized trials. For example, an important question might be, when multiple behaviors need to be addressed, whether it is better to address a behavior that the individual is open to change (i.e., contemplative) or one that potentially presents the greatest risk (e.g., smoking). Scientific studies addressing such questions will greatly assist those that promote lifestyle change strategies in the clinic setting.

15.6 Summary

These are exciting times for professionals working in the field of cardiac rehabilitation and secondary prevention. Although much is known about how patients respond to and benefit from regular exercise and therapeutic lifestyle changes, more work is needed relative to improving long-term compliance to known beneficial lifestyle and medical therapies, improving referral rates of eligible patients to secondary prevention programs, and improving the retention of patients who are referred to and begin participation in cardiac rehabilitation. Despite cardiac rehabilitation representing a Class 1A guideline therapy for most patients with cardiovascular disease, gender, age, and racial discrepancies persist in terms of program access and utilization. Like other therapies available to patients with cardiovascular disease, cardiac rehabilitation is a cost-effective strategy that improves mood, restores functional capacity, lessens or alleviates symptoms, and lowers the risk for and occurrence of subsequent clinical cardiovascular events, with all of the attendant social, economic, and medical benefits that ensue from its successes. It is imperative that primary care physicians ally themselves with the multidisciplinary team approach which cardiac rehabilitation offers to patients who have sustained acute coronary syndromes, have undergone coronary revascularization, have had cardiac surgery, or who have chronic systolic heart failure.

15.7 Patient Examples

15.7.1 Patient Example 1

The patient is a 58-year-old gentleman referred to cardiac rehabilitation with a diagnosis of recurrent angina pectoris and status post-angioplasty. He has a history of coronary artery disease dating back 4 years when he presented with classical angina pectoris and underwent percutaneous coronary intervention with a stent to the right coronary artery (RCA). Now 4 years later, he presented with an abnormal stress ECG and underwent coronary catheterization and stent placement for an in-stent restenosis in the RCA and to a 90% new lesion in the large optional marginal coronary artery. A 40% lesion in the proximal left anterior descending coronary artery was not stented. The patient carries cardiac comorbidities and risk conditions including diabetes mellitus, dyslipidemia, hypertension, and depression. His medical regimen includes aspirin, simvastatin/ezetimibe-40/10, valsartan, clopidogrel, triamterene/HCTZ, metformin, rosiglitazone, glipizide, and Wellbutrin XL (Fig. 15.2).

15.7.2 Patient Example 2

The patient is a 60-year-old woman referred to cardiac rehabilitation after bypass surgery for a single-vessel coronary artery lesion. She had no significant past medical history before she presented to her primary doctor complaining of a history of chest discomfort and palpitations for several months that had been increasing in frequency. The chest discomfort was described as a pressure sensation without radiation, diaphoresis, or shortness of breath, originally only associated with exertion but now also occurs at rest and upon awakening in the morning. Risk factor evaluation revealed a lipid panel of total cholesterol 251 mg/dL, LDL cholesterol of 154 mg/dL, triglycerides of 50 mg/dL, and HDL cholesterol of 78 mg/dL. A stress echocardiogram revealed evidence of stress-induced anteroseptal and apical wall motion abnormalities with a normal left ventricular ejection fraction. Cardiac catheterization revealed a 95% proximal left anterior descending (LAD) coronary artery lesion that was not approachable by percutaneous angioplasty; therefore, the patient underwent single-vessel coronary artery bypass grafting to the LAD. She was discharged home on aspirin, clopidogrel, metoprolol, atorvastatin, omega-3 fatty acids, and sublingual nitroglycerin as needed and referred to cardiac rehabilitation.

The patient's cardiac rehabilitation course is described in Fig. 15.3. She experienced improvement in serum lipids, Framingham risk factor score, exercise fitness level, 6-min walk, waist circumference, and education level regarding cardiac risk. She had also adopted a regular exercise habit, better nutrition habits, and a plan for managing job-related stress. A recommended discharge treatment plan is provided.

DUKE CARDIAC REHABILITATION

PATIENT'S NAME: Mr. XXXXX
MD: XXXXX HISTORY NUMBER: XY0000

EXIT SUMMARY

Program dates: 10.29.07 to 3.12.08 Number of sessions: 32/36

	Initial	Exit	%Change	Comments
Metabolic Syndrome	Yes	No		Diabetic; HTN
Smoking	No	No		
Hypertension				Average of first and last 3 BP readings
systolic	132	117	11%	
diastolic	74	67	9%	
Hyperlipidemia				
Total	138	113	18%	
LDL	57	32	44%	Goal for LDL is <70mg/dL
HDL	35	45	29%	Goal : >40mg/dL men, >50 mg/dL women
Triglycerides	228	179	21%	Goal for TG is <150 mg/dL
Diabetes				
HBA1C	6.7	6.2	7%	
Fasting glucose	183	110	40%	Average of first and last 3 fasting glucoses
Framingham 10 yr. CHD Risk	9%	6%	33%	
Exercise METS	3.6	9.5	164%	
6 Minute Walk (meters)	510.3	774.4	52%	
Waist Circumference (cm)	106.5	96	10%	Goal for men < 102 cm
Educational score	15	18	20%	20 total questions

MEDICATIONS AT DISCHARGE: Aspirin, 81 mg daily; Diovan, 160 mg daily; Plavix, 75 mg daily; Metformin, 500 mg twice daily; Avandia, 4 mg daily; Vytorin, 10/40 mg daily; Wellbutrin XL, 150 mg daily; Triamterene/HCTZ, 32.5/25 mg ½ daily

PROGRESSION TOWARD GOALS: Mr. XXXXX's goals coming into rehab were to lose 20 pounds and to run a 5k race in under 35 minutes. His weight at the beginning of rehab was 196.4 and on the last session of rehab his weight was 176. He recently competed in a race in Raleigh and finished the 3.2 miles in 31:40.

BEHAVIOR MODIFICATION: Mr. XXXXX saw great improvements in his lipids, blood glucose, exercise METS and waist measurement. He made significant lifestyle changes and seemed to do so in a way that he will be able to maintain. Throughout his participation in rehab, he appeared to handle his stress well and did not cite any anxiety or depressive symptoms.

NUTRITION COMPONENT: Mr. XXXXX attended the November classes and found he was eating more starches than needed and less vegetables than suggested. His weight loss is evidence of adopting positive eating habits.

OTHER SERVICES ATTENDED: Regular lecture attendance ☐ Stress Management series ☐ Relaxation/Meditation class ☐
Strength training ☐ Flexibility program ☐ Consistent exercise outside of cardiac rehab ☐

RECOMMENDED EXERCISE PLAN

	AEROBIC EXERCISE	STRENGTH	FLEXIBILITY
FREQUENCY	3 -4 times/week	2 – 3 times/week	After each exercise session
INTENSITY	120 – 144 bpm	Somewhat hard	Light
TYPE	Jogging; walking	Free weights	Stretches
TIME	30 – 50 minutes	20 -30 minutes	10 minutes
ENERGY EXPENDITURE	1200 calories/week		

EXERCISE PHYSIOLOGIST

MEDICAL DIRECTOR

If you have any concerns, please call our team at 660-6724.

Cardiac Rehab Plan

- ☐ Join the Fred Cobb Healing HEARTS program
- ☐ Join the Duke Health and Fitness Center
- ☒ Home exercise program
- ☐ Discharge to exercise facility of choice

Fig. 15.2 Patient example 1. The cardiac rehabilitation program report to his primary care doctor is presented here. One can see from the report that the patient was able to develop rigorous exercise habits, better nutrition habits, and lose 9 kg (20 lb) in the process so that he was able to participate in a 5 k race. As a consequence, there were significant improvements in serum lipids, blood glucose control, fitness, and waist circumference. A recommended discharge treatment plan is provided

DUKE CARDIAC REHABILITATION

PATIENT'S NAME: Ms. YYYYY
MD: YYYYY
HISTORY NUMBER: XY11111

EXIT SUMMARY

Program dates: 7-9 to 12-19-07 Number of sessions: 36

	Initial	Exit	% Change	Comments
Metabolic Syndrome	no	no		
Smoking	no	no		
Hypertension	no	no		Average of first and last 3 BP readings
systolic	96	106	-10%	
diastolic	62	68	-10%	
Hyperlipidemia	yes	yes		
Total	205	134	35%	
LDL	112	52	54%	Goal for LDL is <70mg/dL
HDL	77	73	-5%	Goal : >40mg/dL men, >50 mg/dL women
Triglycerides	79	45	43%	Goal for TG is <150 mg/dL
Diabetes	no	no		
HBA1C	5.8	n/a		
Fasting glucose	n/a	n/a		Average of first and last 3 fasting glucoses
Framingham 10 yr. CHD Risk	6%	4%	33%	
Exercise METS	4.0	5.8	45%	
6 Minute Walk (meters)	574.9	680.8	18%	
Waist Circumference (cm)	77	70.5	8%	Goal for women: <88cm
Educational score	13	17	31%	20 total questions

MEDICATIONS AT DISCHARGE: Plavix 75 mg daily, Axid 150 mg daily, Lipitor 20 mg daily, ASA 81 mg daily, Iron 325 mg daily, Vitamin C 250 mg tid, Lopressor 12.5 mg bid

PROGRESSION TOWARD GOALS: Ms. YYYYY's goals included exercising 3-5 days per week, learn meditation skills and to get to a goal weight of 130. She achieved all of her stated goals and plans on maintaining her current exercise program.

BEHAVIOR MODIFICATION: She is regularly meditating at home and is working on her primary stressor, which is her job.

NUTRITION COMPONENT: She attended the 4 hour nutrition class in December.

OTHER SERVICES ATTENDED: Regular lecture attendance ☒ Stress Management series ☐ Relaxation/Meditation class ☒
Strength training ☒ Flexibility program ☒ Consistent exercise outside of cardiac rehab ☒

RECOMMENDED EXERCISE PLAN

	AEROBIC EXERCISE	STRENGTH	FLEXIBILITY
FREQUENCY	3-5 days per week	2-3 days per week	After each exercise session
INTENSITY	TR: 96-123	1-3 sets; 10-15 reps	
TYPE	TM, EFX, biking		
TIME	30-60 minutes		
ENERGY EXPENDITURE	1000-1200 calories/week		

EXERCISE PHYSIOLOGIST

MEDICAL DIRECTOR

If you have any concerns, please call our team at 660-6724.

Cardiac Rehab Plan

- ☐ Join the Fred Cobb Healing HEARTS program
- ☒ Join the Duke Health and Fitness Center
- ☐ Home exercise program
- ☐ Discharge to exercise facility of choice

Fig. 15.3 Patient example 2. The report provided to the referring physician about the course during participation in cardiac rehabilitation is shown here. Note the improvement in serum lipids, Framingham risk factor score, exercise fitness level, 6-min walk, waist circumference, education level regarding cardiac risk, adoption of a regular exercise habit, better nutrition habits, and a plan for managing job-related stress. A recommended discharge treatment plan is provided

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Part III

Peripheral Forms of Venous and Arterial Disease

Carotid Artery Disease

16

Andreas Kastrup

Key Points

- In patients with carotid artery stenosis, risk factors such as hypertension, diabetes mellitus, hyperlipidemia, and smoking should be evaluated and treated aggressively.
- The use of prophylactic aspirin is recommended in all patients with carotid artery stenosis.
- Patients with an asymptomatic carotid stenosis should be educated about possible symptoms of transient ischemic attacks and should immediately contact a physician in case a transient ischemic attack occurs.
- In patients with an asymptomatic carotid stenosis, prophylactic carotid endarterectomy (CEA) can be recommended only in highly selected patients with high-grade stenosis (>70%) performed by surgeons with established perioperative morbidity and mortality rates of <3%. With regard to carotid angioplasty and stenting (CAS), there is currently a lack of data comparing this treatment modality with contemporary best medical therapy alone. If considered, CAS should be performed only by operators with established perioperative morbidity and mortality rates of <3%.
- Carotid endarterectomy should be considered in patients with recent TIA or ischemic stroke within the last 6 months and ipsilateral severe (>70%) carotid artery stenosis. CAS is an indicated alternative to CEA in younger patients with a symptomatic severe (>70%) carotid artery stenosis, whereas patients older than approximately 70 years of age should preferentially be treated with CEA. Both procedures should be performed only by surgeons or interventionalists with established perioperative/peri-interventional morbidity and mortality rates of <6%.
- In patients with a recently symptomatic carotid artery stenosis, surgery or interventional treatment should ideally be performed within 2 weeks.

16.1 Introduction

Stroke is one of the leading causes of morbidity and mortality in North America, affecting over half a million patients at a cost of over $30 billion a year. Depending on the population studied, extracranial internal carotid artery stenosis accounts for approximately 10–15% of ischemic strokes. Aside from these symptomatic cases, large population-based studies indicate that the prevalence of asymptomatic carotid artery stenosis is approximately 0.5% in the sixth decade and increases up to 10% in persons over 80 years of age [1].

Carotid stenoses may result in brain ischemia either through direct hemodynamic impairment of the cerebral blood circulation or, more commonly, as a source of thromboembolic material arising from symptomatic carotid plaques. These mainly develop in regions of low vessel-wall shear stress such as the carotid bulb and are characterized by increased cellular proliferation, lipid accumulation, calcification, ulceration, hemorrhage, and thrombosis. Symptomatic carotid artery disease is commonly manifested by transient contralateral symptoms or ipsilateral monocular blindness and then detected during further diagnostic workup, whereas patients with an asymptomatic carotid stenosis are most commonly found by physical examination of a carotid bruit.

The main approaches for treating patients with carotid artery disease include the stabilization of the carotid plaque

A. Kastrup
Departments of Neurology, Klinikum Bremen-Ost and Klinikum Bremen-Mitte, Bremen, Germany

P. P. Toth, C. P. Cannon (eds.), *Comprehensive Cardiovascular Medicine in the Primary Care Setting*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-319-97622-8_16

through risk factor modification and medication as well as the removal of the stenosis through carotid endarterectomy (CEA) or carotid angioplasty and stenting (CAS).

16.2 Diagnostic Testing

Obtaining a history and performing general medical (including auscultation of the neck for carotid bruits and transmitted murmurs) and neurological (to correlate neurological symptoms with an ischemic territory) examinations are crucial steps in selecting proper treatment for patients with carotid artery disease. The approach of any patient with carotid artery disease should also involve recognition of this disease as a specific manifestation of a generalized arteriopathy. Therefore, a thorough search should be made for other evidence of atherosclerosis, including cardiac and peripheral vascular disease. A clear separation between symptomatic and asymptomatic carotid artery stenosis is critical. Symptoms of a carotid artery stenosis typically include contralateral weakness or numbness, dysphasia, ipsilateral monocular blindness (amaurosis fugax), and, in rare instances, syncope, confusion, or seizures. Specific signs of left hemisphere ischemia include aphasia, while right hemisphere ischemia may be manifest by apraxia or visuospatial neglect. All of these symptoms may be transient, representing TIAs, or permanent, resulting in cerebral infarction. Non-specific symptoms such as a blurred vision or a subjective generalized weakness should not be considered as a symptomatic event. Laboratory testing should be performed to determine the presence of cardiovascular risk factors (e.g., unknown diabetes mellitus and hyperlipidemia). It is also useful in ruling out metabolic and hematologic causes of neurological symptoms such as hypoglycemia, hyponatremia, and thrombocytosis.

Patients with an asymptomatic carotid stenosis are most commonly found by physical examination of a carotid bruit. Although carotid bruits only have a limited value for the diagnosis of carotid artery disease, carotid auscultation should be part of the routine physical examination of patients with cardiovascular risk factors. While carotid auscultation is a sufficient screening test for asymptomatic patients, all patients with a TIA or stroke must be evaluated with duplex ultrasonography either alone or supplemented with digital subtraction angiography (DSA), computed tomographic angiography (CTA), magnetic resonance angiography (MRA), or contrast-enhanced MRA. *Duplex ultrasonography is the imaging tool of choice to screen for carotid artery stenosis*.

To date, conventional or digital subtraction cerebral angiography is still considered to be the gold standard for imaging the carotid arteries. In the large clinical trials, cerebral angiography was used to evaluate the entire carotid system, including the intracranial collateral circulation, and served as standard for defining the degree of carotid stenosis and for defining morphological features of the offending plaque. Usually, the degree of a carotid artery stenosis is determined with the North American method (NASCET method), which measures the minimal residual lumen at the level of the more distal internal carotid artery. It is based on the formula: stenosis = $(1 - N/D) \times 100\%$, where N is the diameter at the point of maximum stenosis and D is the diameter of the arterial segment distal to the stenosis where the arterial walls fist become parallel. Using this method a hemodynamically significant carotid stenosis would correspond to a 60% diameter stenosis.

Digital subtraction angiography, however, is invasive and expensive and is associated with a risk of serious neurological complications or death of approximately 0.5–1%. Therefore, it has largely been replaced by CTA or MRA. Nowadays, the latter techniques are mainly used as confirmatory tests after results of an ultrasound examination are suggestive of the presence of a carotid stenosis in most centers. Carotid duplex ultrasound is a noninvasive, safe, and inexpensive technique that has a high sensitivity and specificity in detecting a significant stenosis of the ICA. On the other hand, the accuracy of carotid ultrasound relies heavily upon the experience and expertise of the examiner and may be limited by features such as calcified, tortuous arteries, or far distal stenoses. In these cases, CTA may be particularly useful. With this technique, three-dimensional reconstruction allows relatively accurate measurements of the residual lumen diameter. MRA images are either based on two- or three-dimensional time-of-flight (TOF) or gadolinium-enhanced sequences. The contrast-enhanced techniques produce higher quality images that are less prone to artifacts. While MRA is less operator dependent than ultrasound, it is more expensive and time-consuming and may not be performed if the patient has claustrophobia, a pacemaker, or ferromagnetic implants.

16.3 Medical Treatment

The estimated annual risk of stroke in patients with an asymptomatic stenosis is approximately 1–2% [2] and 4–6% in patients with a symptomatic carotid stenosis [3], respectively. Aside from considering a surgical removal or an interventional therapy for a carotid stenosis, primary and secondary medical therapies are clearly indicated, all the more considering that 20% of patients undergoing CEA for symptomatic carotid artery stenosis and 45% of patients undergoing CEA for asymptomatic carotid artery stenosis subsequently have strokes related to other etiologies [4]. While the concept of "best medical therapy" for patients with asymptomatic or symptomatic carotid artery disease

mainly consisted of "stop smoking" and "take aspirin" in the large trials comparing CEA with medical therapy, major advances have been made in the past two decades regarding statin, antiplatelet, and antihypertensive therapies. Although several cardiovascular risk factor modifications and medical therapies have not been specifically evaluated in patients with severe carotid artery stenosis, they are generally recommended to limit progression of atherosclerosis and decrease clinical events, irrespective of carotid revascularization.

In patients with an asymptomatic carotid stenosis, antiplatelet therapy with aspirin is indicated for primary prevention mainly of cardiovascular events [5]. In patients with symptomatic carotid stenosis current recommendations are based on the results of large stroke prevention studies with mixed patient populations and include the use of aspirin, clopidogrel, or a fixed combination of aspirin with extended-release dipyridamole [6, 7]. There is no data to support the use of aspirin in doses greater than 325 mg day. Clopidogrel might be a more potent antiplatelet agent than aspirin, but due consideration must also be given to the risk of excess bleeding should the patient require surgery.

Although not specifically tested for in patients with carotid artery disease, there is a general consensus that a stringent control of blood pressure is the cornerstone of therapy to modify atherogenic risk factors, and the benefits of antihypertensive therapy extend to all patient subgroups, especially diabetic patients. For primary stroke prevention, a large meta-analysis found that regardless of the agent used, a 10 mmHg reduction in systolic blood pressure produced a 31% relative risk reduction for stroke [8]. For secondary stroke prevention, proven agents include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and the combination of a thiazide diuretic with an angiotensin-converting enzyme inhibitor [6, 7]. Although there is emerging evidence that some antihypertensive medications may exert their beneficial effect in ways other than by reducing blood pressure, the primary goal of blood pressure therapy should be to achieve values of <140/90 mmHg for nondiabetic patients and < 130/80 mmHg for patients with diabetes. The selection of drugs should therefore primarily be influenced by the presence of comorbid conditions such as diabetes mellitus, renal failure, or left ventricular dysfunction. Many patients will require multiple medications to achieve optimal blood pressure values.

Statins have assumed a prominent role in cerebrovascular and cardiovascular risk modification [9, 10]. The SPARCL trial, which randomized 4732 patients with recent stroke or TIA to atorvastatin 80 mg/day or placebo, reported a 16% relative risk reduction (RRR) in future stroke [10]. In a subgroup analysis of 1007 patients with documented carotid stenosis patients taking atorvastatin 80 mg daily, the RRR for future stroke was 33%, 42% for major coronary events, and 56% for the need of carotid revascularization [11]. In a review of 180 patients undergoing CAS, a significantly higher 30-day rate of stroke, MI, or death was identified among patients who were not taking preprocedural statin therapy [12]. A similar result was obtained for symptomatic patients undergoing CEA [13]. In a further study of patients receiving medical treatment for severe carotid artery disease, statin use was associated with significantly lower rates of stroke, MI, or death [14].

Smoking, physical inactivity, and eating habits are also important modifiable risk factors for the development and progression of carotid artery disease. While preventive medications are easy to prescribe, lifestyle modification should be considered as equally important. A combination of nicotine replacement therapy, social support, and skills training, for instance, has been shown to be effective in treating tobacco dependence.

In patients with carotid artery stenosis, risk factors such as hypertension, diabetes mellitus, hyperlipidemia, and smoking should be evaluated and treated aggressively.

16.4 Carotid Endarterectomy in Patients with Symptomatic Carotid Stenosis

The superiority of CEA over medical treatment in the management of symptomatic high-grade (>70% angiographic stenosis) atherosclerotic carotid artery stenosis has been established in two, large randomized trials: the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [3] and the European Carotid Surgery Trial (ECST) [15]. A third trial was stopped prematurely when the results of NASCET were announced [16].

In NASCET and ECST, all surgeons were screened for an acceptable operative record. Entry criteria for these trials included carotid artery stenosis (>30% reduction in the luminal diameter on conventional angiogram) and ipsilateral TIA, non-disabling stroke, or retinal infarction within 4–6 months. The main exclusion criteria included a probable cardiac source of embolism, serious disease likely to cause death within 5 years, or intracranial disease that was more significant than the carotid lesion. Both trials used different methods to measure carotid stenosis. While NASCET used the residual lumen diameter at the most stenotic portion of the vessel and compared this to the lumen diameter in a normal portion of the internal carotid artery distal to the stenosis to determine the degree of stenosis (see above), ECST used the lumen diameter at the most stenotic portion of the vessel and compared this to the estimated probable original diameter at the most stenotic portion of the vessel. In the meantime, equivalent measurements for the two methods have been determined: a 50% stenosis with the NASCET method is equivalent to a 75% for ECST, and a 70% stenosis with the NASCET method is equivalent to an 85% stenosis for ECST.

In NASCET and for patients with symptomatic carotid stenosis of 70–99% (measured by the NASCET method), CEA reduced the 2-year risk of ipsilateral stroke from 26% in the medical group ($n = 331$) to 9% in the surgical group ($n = 328$), yielding an absolute risk reduction of 17% ($p < 0.001$). The number needed to treat (NNT) to prevent one stroke was 6 (NNT = 12 at 1 year). A 5.8% incidence of perioperative stroke or death was reported for patients in the surgical arm. In patients with moderate degrees of stenosis (50–69%), the 5-year ipsilateral stroke risk was 22.2% in the medical arm and 15.7% in the surgical arm ($p < 0.045$). The NNT to prevent one stroke was 15 (NNT = 77 at 1 year). Benefit in the 50–60% stenosis group was best achieved in patients presenting with hemispheric, not retinal symptoms, with stroke rather than TIA, male sex, and intracranial carotid artery stenosis. In this group of patients, subgroup analysis did not demonstrate a benefit of CEA in women (NNT = 125 to prevent one major ipsilateral stroke in 5 years). Patients with <50% stenosis did not benefit from surgery.

The ECST reported a similar efficacy of CEA in the secondary prevention of stroke for patients with a high-grade carotid stenosis. In this trial, the frequency of a major stroke or death at 3 years was 26.5% in the control group ($n = 220$) versus 14.9% in the surgical group ($n = 356$), so that surgery was associated with an absolute benefit of 11.6% ($p < 0.001$). The NNT to prevent one stroke annually was 21. A 7.4% incidence of perioperative stroke or death was reported for patients in the surgical arm. The risk of these complications was not related to the severity of the stenosis.

Although NASCET and ECST have clearly demonstrated the superiority of CEA combined with medical therapy over medical management alone for symptomatic patients with carotid artery stenosis of >70% (NASCET) [3] or >80% (ECST) [15], several post hoc analyses have been performed to identify subsets of patients who are most likely to benefit from surgery. In fact, the decision to treat individual patients with carotid artery disease surgically should not be exclusively based on the stenosis severity, but should also take into account age, gender, neurological symptoms, and other determining factors for subsequent stroke or surgical risk. In addition, patients who have severe comorbidities, patients with persistent disabling neurological deficits, and those with a total occlusion of the carotid artery are unlikely to benefit from CEA and should thus be treated with medical therapy.

The benefit of CEA increases steadily from 50% to 99% (NASCET method) as a consequence of an enhanced risk of ipsilateral stroke, proportional to the severity of the stenosis, while surgery-related morbidity does not vary substantially with the degree of stenosis [17]. A patient with a 90–99% symptomatic stenosis derives twice the benefit from CEA than one with a 70–79% stenosis.

Other factors that can be used to estimate the absolute risk of ipsilateral stroke for individual patients with symptomatic carotid stenosis who are candidates for CEA include patient age, gender, type of presenting event, plaque morphology, and time since last event [18].

In a subgroup analysis of NASCET, the benefit of CEA for patients with a symptomatic carotid stenosis aged 75 years or older was compared with that for those aged 65–74 years and less than 65 years [19]. Among medically treated patients with 70–99% carotid stenosis, the risk of ipsilateral ischemic stroke at 2 years was highest (36.5%) in patients aged 75 years or older. The rates of perioperative stroke and death were 7.9, 5.5, and 5.2% in patients younger than 65 years, 65–74 years, and >75 years, respectively. Because patients aged 75 years or older had the highest risk with medical treatment, the absolute risk reduction by CEA was greatest in this subgroup (28.9%). Only three patients had to undergo surgery to prevent one ipsilateral ischemic stroke at 2 years. Thus, elderly patients profited more from CEA than younger patients in this trial. Likewise, the ECST data has indicated that increasing age is associated with a greater benefit from CEA for symptomatic carotid stenosis [20].

Men gain more benefit from CEA than women. The stroke risk reduction with CEA is highest in patients presenting with hemispherical TIAs or minor strokes compared to retinal symptoms. Plaque ulceration also confers an increased stroke risk on medically treated patients. Patients with recently symptomatic stenoses are at the highest risk of subsequent stroke and thus derive a substantial benefit from surgery. *Patients with a recently symptomatic carotid artery stenosis have a high early risk for subsequent stroke, so that expedited evaluation and surgery are of utmost importance to maximize benefit of treatment.*

In a combined 5-year analysis of the NASCET and ECST patients with a symptomatic carotid stenosis (≥50%, NASCET method), the NNT to prevent one stroke was 9 for men and 36 for women, 5 for age ≥75 years and 18 for <65 years, and 5 if randomized within 2 weeks of the last TIA and 125 if randomized >12 weeks after the last TIA [21].

According to current guidelines, CEA should be considered in patients with recent TIA or ischemic stroke within the last 6 months and ipsilateral severe (>70%, NASCET method) carotid artery stenosis [6, 7]. In patients with recent symptomatic moderate (50–69%, NASCET) carotid stenosis, CEA should be considered in men, in patients older than 74 years of age, and in patients with hemispheric symptoms rather than transient monocular blindness (Fig. 16.1). Since the medical management has greatly improved in the past few years, current guidelines advise proceeding with CEA only if the perioperative morbidity and mortality risk is estimated to be <6% [6].

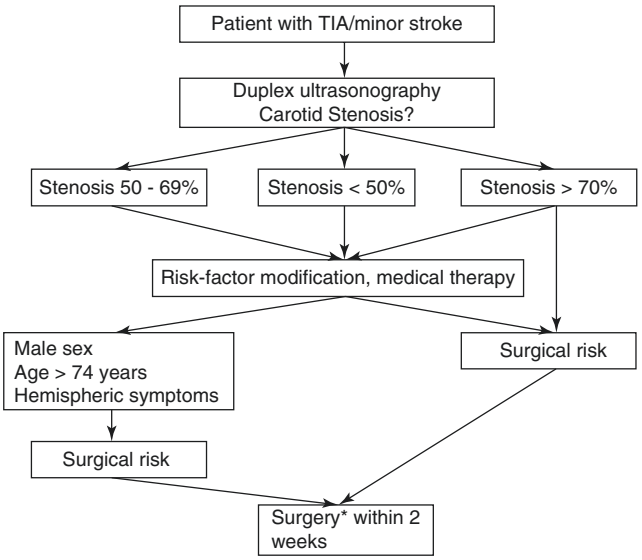

Fig. 16.1 Algorithm for CEA considerations

16.5 Carotid Endarterectomy in Patients with Asymptomatic Carotid Stenosis

Altogether, there have been five randomized trials comparing endarterectomy with medical treatment in patients with asymptomatic extracranial carotid artery stenosis.

The Carotid Artery Surgery Asymptomatic Narrowing Operation Versus Aspirin (CASANOVA) trial included 410 patients with an asymptomatic internal carotid artery stenosis of 50–90%, based on cerebral angiography [22]. Patients with more than 90% stenosis were excluded from this trial. All patients were treated with 330 mg aspirin daily and 75 mg dipyridamole three times daily. After a minimum of 3 years of follow-up for each patient, statistical analysis found no significant difference in the number of neurological deficits and deaths between both groups.

The Veterans Affairs Asymptomatic Carotid Endarterectomy Trial compared the outcomes of 211 surgically versus 233 medically treated patients with an asymptomatic angiographically proven carotid stenosis of 50–99% [23]. While the combined outcome of stroke and death was not significantly different between both treatment groups, the study showed a reduction in the relative risk of ipsilateral neurological events with surgery when TIA and stroke were included as composite endpoints.

The Mayo Asymptomatic Carotid Endarterectomy (MACE) trial was terminated early due to a significantly higher number of TIAs and myocardial infarctions in the surgical group compared with the medical group, likely reflecting the avoidance of aspirin in the surgical group [24].

The Asymptomatic Carotid Atherosclerosis Study (ACAS) evaluated the efficacy of endarterectomy in patients with a >60% diameter reduction (determined either by angiography or by Doppler ultrasound scanning) in asymptomatic carotid stenosis [25]. Patients were aged 40–79 years and had a life expectancy of at least 5 years. Approximately 30% of patients had other cerebrovascular symptoms. The event rate in surgically treated patients for the primary endpoint (ipsilateral stroke, perioperative stroke, or death) was 5.1% over 5 years. This included a 1.2% risk of angiography-related complications among the 424 patients undergoing postrandomization angiograms and an exceedingly low 1.1% surgical risk (2.3% aggregate perioperative stroke risk). The corresponding rate in medically treated patients was 11% (5.9% absolute risk reduction; NNT = 17; $p = 0.004$). The NNT to prevent one event was 83 at 1 year. The risk of major ipsilateral stroke or any perioperative stroke or death was not significantly different between both treatment groups (6.5% in the medical group versus 3.4% in the surgical group, $p = 0.12$). The benefits of CEA were greater for men than women (relative risk reduction in men 66% versus 17% in women, respectively), and perioperative complications were higher among women than men (3.6% versus 1.7%).

The Asymptomatic Carotid Surgery Trial (ACST) confirmed the marginal benefit of CEA in patients with asymptomatic severe stenoses [26]. In this study, 3120 asymptomatic patients with >60% carotid stenosis identified during ultrasonography were assigned to immediate CEA or deferral of surgery and were followed for a mean period of 3.4 years. The risk of stroke or death within 30 days of CEA was 3.1% in the CEA group and 0.8% in the deferral group, whereas 5-year risks of non-preoperative stroke were 3.1 and 11% ($p < 0.0001$). When the preoperative and non-perioperative stroke risk were combined, a significant 5.4% absolute risk reduction occurred, very similar to the ACAS results. The benefits were similar in males and females and were not substantially different with varying degrees of carotid stenosis. However, patients 75 years of age and older did not benefit. Despite the relatively low perioperative complication rate in ACST, the net benefit of CEA was delayed for about 2 years after surgery, so that CEA in asymptomatic patients should be considered a long-term investment.

In both the ACAS and the ACST, an extremely low perioperative stroke rate was achieved, without which there would be no benefit from surgical management of asymptomatic carotid artery stenoses. A combined analysis of ACAS and ACST suggests that CEA in asymptomatic patients with >60% carotid stenosis leads to a small but significant overall benefit if the surgery can be performed with low preoperative morbidity and mortality rates [26]. Especially in patients with an asymptomatic carotid stenosis, the benefit of CEA is highly dependent on a low risk of procedural neurological complications and is eliminated when

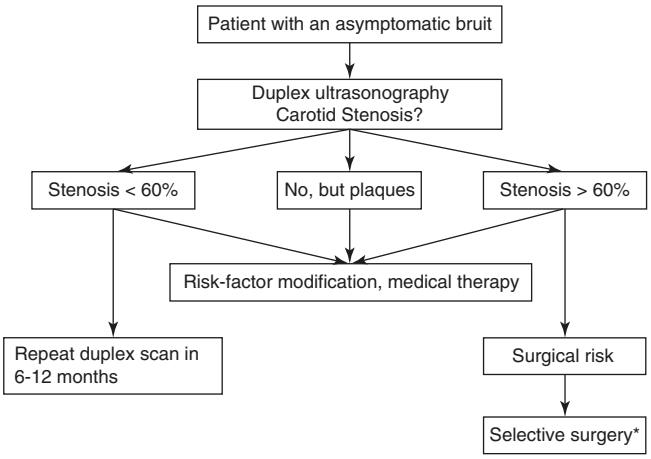

Fig. 16.2 Algorithm for the management of patients with an asymptomatic carotid stenosis

the combined 30-day stroke and death rates exceed approximately 3% [27, 28]. It should also be considered that the benefits of CEA in asymptomatic patients may generally be overestimated. In a subgroup analysis of NASCET, the causes of stroke on the asymptomatic side of 1800 patients were determined during follow-up. Nearly 50% of the strokes were lacunar or cardioembolic in origin and were thus not preventable by CEA [2].

According to current guidelines, all patients with an asymptomatic carotid stenosis should receive low-dose aspirin and a statin [5]. Prophylactic CEA can be recommended in highly selected patients with high-grade asymptomatic carotid stenosis performed by surgeons with <3% morbidity and mortality rates. Patient selection should be guided by an assessment of comorbid conditions and especially life expectancy and should include a thorough discussion of the risks and benefits of the procedure with an understanding of patient preferences (Fig. 16.2).

16.6 Carotid Angioplasty and Stenting

While CEA is currently the accepted standard for the treatment of patients with high-grade symptomatic and for the treatment of selected patients with an asymptomatic internal carotid artery stenosis, carotid angioplasty and stenting (CAS) has emerged as a treatment alternative to CEA for the primary and secondary prevention of stroke related to carotid stenosis. Potential advantages over surgery include avoiding a surgical incision and its complications, including cranial nerve palsies and wound hematoma. Unlike CEA, which is limited to the cervical carotid artery, CAS can be performed in patients with distal or even intracranial lesions. It has also been argued that CAS does not require general anesthesia and may be associated with shorter hospitalization and thus lower costs. On the other hand, CAS has the major disadvantage of producing more emboli to the brain than CEA [29].

In the past few years, several large randomized single or multicenter trials comparing CAS with CEA and large stent registries have been published. In the large stent registries encompassing many thousands of patients, the 30-day stroke, myocardial infarction, and death rates have varied from approximately 2 to 8% in mixed populations of asymptomatic and symptomatic patients [30, 31]. The very first, prospective, randomized trial comparing CAS with CEA was performed at a single university teaching hospital in Leicester and was stopped early by the Steering Committee after inclusion of only 17 patients with a symptomatic carotid stenosis (≥70%) due to an excessive complication rate in the CAS arm trial (5 out of 7 CAS patients developed a stroke) [32].

The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) was the first completed, prospective multicenter trial comparing endovascular ($n = 251$, mainly angioplasty alone) versus surgical treatment ($n = 253$) of patients with symptomatic (96.4%) and asymptomatic carotid stenosis [33]. Periprocedural stroke (symptoms >7 days) and death rates were similar for endovascular treatment and surgery (10.0% versus 9.9%). After 3 years the rate of any stroke or death after 3 years was 14.3 in the endovascular group versus 14.2% in the surgical group indicating that the long-term results are also comparable between both procedures [33].

The Wallstent study was a multicenter randomized trial comparing CAS ($n = 107$) with CEA ($n = 112$) in patients with a symptomatic carotid stenosis of at least 60% [34]. The cumulative incidence of ipsilateral stroke and procedure related or vascular death within 1 year was 12.1% for the stent group versus 3.6% for the endarterectomy group ($p < 0.05$). The incidence of any stroke or death within 30 days was significantly higher after CAS than CEA (12.2% versus 4.5%, $p < 0.05$).

Two prospective, single-center, randomized trials performed in a community hospital with either patients with a symptomatic carotid stenosis (CEA $n = 51$ versus CAS $n = 53$) or with an asymptomatic carotid stenosis (85 patients randomly assigned to CAS or CEA) have been published [35, 36]. In the trial dealing with symptomatic patients, the composite outcome of any stroke or death within 30 days was 2% in patients treated with CEA and 0% in those treated with CAS, whereas no strokes or deaths occurred in both treatment arms of the asymptomatic trial.

The multicenter Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) study compared CEA with protected CAS in patients with a moderate to severe carotid stenosis (exceeding 80% in asymptomatic patients or 50% in symptomatic patients who also had comorbid conditions that might increase the risk of

surgery (e.g., recent myocardial infarction, congestive heart failure, severe pulmonary disease, advanced age, and contralateral carotid occlusion) [37]. Excluded patients (n = 404) were entered into a registry and not randomized. The trial was terminated early after randomization of 334 patients because of an abrupt slowing in the pace of patient enrollment. The primary endpoint (composite of stroke, myocardial infarction, or death within 30 days or ipsilateral stroke between 31 days and 1 year) occurred in 20 CAS patients versus 32 CEA patients (12.2% versus 20.1%, p = 0.004 for non-inferiority and p = 0.053 for superiority). With respect to the subgroup of symptomatic patients, the primary endpoint was similar between CAS and CEA (16.8% versus 16.5%).

The Endarterectomy Versus Stenting in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) study compared CAS (n = 261) with CEA (n = 259) in patients with a symptomatic (amaurosis fugax, hemispherical transient ischemic attack, or minor stroke in the previous 120 days) carotid stenosis of 60–99% according to NASCET criteria [38]. The trial was stopped prematurely after the inclusion of 527 patients due to increased complication rates in the CAS group. The 30-day incidence of any stroke or death was 3.9% in surgical patients versus 9.6% in patients treated with CAS ($p < 0.05$). Thirty-day mortality was similar in both groups. The 30-day incidence of disabling stroke or death was 1.5% after CEA compared with 3.4% after CAS. The main prespecified secondary outcome (any periprocedural stroke or death and any ipsilateral stroke occurring in up to 4 years of follow-up) was also significantly higher with CAS than with CEA (11.1% versus 6.2%, $p < 0.05$). This difference was largely driven by the higher periprocedural complications rates associated with CAS, demonstrating a low risk of ipsilateral stroke after the periprocedural period, which was similar in both treatment groups.

The Stent-Protected Angioplasty Versus Carotid Endarterectomy in Symptomatic Patients (SPACE) study compared CAS (n = 605) with CEA (n = 595) in symptomatic patients with a carotid stenosis of at least 70% (according to ECST criteria, corresponding to a stenosis of ≥50% according to NASCET) [39]. High-risk patients with uncontrolled hypertension or severe concomitant disease and a poor prognosis were excluded from this trial. The use of embolic protection devices was optional (eventually 26.6% of the patients were treated with embolic protection devices during CAS). The primary endpoint was ipsilateral stroke (ischemic stroke or intracerebral hemorrhage or both, with symptoms lasting longer than 24 h) or death of any cause between randomization and 30 days after treatment. Using a predefined non-inferiority margin of 2.5% or more, this trial aimed to show that CAS is not worse than CEA. The primary endpoint occurred in 41 CAS patients versus 37 CEA patients (6.84% versus 6.34%, p = 0.09 for non-inferiority). Therefore, SPACE failed to prove the non-inferiority of CAS compared with CEA, expressed as the rate of ipsilateral stroke or death within 30 days. The rate of any stroke or death within 30 days was 7.68% in CAS patients compared to 6.51% in CEA patients. In a subgroup analysis, older age in the CAS group was significantly associated with an increased risk for ipsilateral stroke [40]. At 2 years follow-up, there was no statistically significant difference between CAS and CEA with respect to the composite endpoint of any periprocedural stroke or death and ipsilateral ischemic stroke (9.4% versus 7.8% using a per protocol analysis). However, recurrent carotid stenoses were significantly more frequent in the CAS group.

The International Carotid Stenting Study (ICSS) compared CEA (n = 858) with CAS (n = 855) in patients with a recently symptomatic carotid artery stenosis ≥50% [41, 42]. *The primary outcome measure of this trial was the 3-year rate of fatal or disabling stroke in any territory. In the first 120 days after randomization, the CAS group had significantly greater incidences of stroke, death, or MI (8.5%* vs. *5.2%; hazard ratio: 169, 116–2.45), any stroke (65* vs. *35 events; HR 1.92, 1.27–2.89), and all-cause death (19* vs. *7 events; HR 2.76; 1.16–6.56) compared to the CEA group* [41]. *After a median follow-up period of 4.2 years, the number of fatal or disabling strokes (52* vs. *49), as well as the cumulative 5-year risk, did not differ significantly between the CAS and CEA groups (6.4%* vs. *6.5%; p = 0.77)* [42]. *In the CAS group the 5-year cumulative risk for any stroke was significantly higher than in the CEA group (15.2%* vs. *9.5%, p < 0.001), but these were mainly non-disabling strokes* [42]. A preplanned meta-analysis of individual patient data of EVA-3S, SPACE, and ICSS showed that the rates of any stroke or death within 120 days after randomization were significantly higher after CAS (8.9%) than after CEA (5.9%) ($p < 0.001$) [43].While there was no significant difference in the outcome between CEA and CAS in patients <70 years of age, the rates of stroke and death at 120 days among patients aged ≥70 years were significantly higher after CAS (12%) than after CEA (5.9%) ($p < 0.01$) in these trials.

The Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST), performed in the United States and Canada, compared CAS with CEA in 2502 patients with a symptomatic carotid stenosis >50% (by angiography) or with an asymptomatic carotid stenosis >60% [44]. Nearly half of the patients had been treated for an asymptomatic stenosis in this trial. With respect to the primary composite endpoint (perioperative stroke, death, myocardial infarction, and ipsilateral stroke within 4 years of randomization), there were no significant differences between the CAS and CEA groups (7.2% vs. 6.8%, p = 0.5) proving the non-inferiority of CAS compared to CEA. However, when only the perioperative endpoints were compared, the incidences of stroke where higher in the CAS group than in the CEA group (4.1% vs. 2.3%, p = 0.01), whereas surgery was associated with higher rates of MI than stenting (2.3% vs. 1.1%, p = 0.03).

Prespecified analyses did not show a modification of the treatment effect by symptomatic status. In asymptomatic patients, the 4-year rate of the primary composite endpoint was 5.6% with CAS and 4.9% with CEA ($p = 0.056$). In symptomatic patients, the rates were 8.6% with CAS versus 8.4% with CEA ($p = 0.69$). In contrast, there was a significant interaction between age and treatment efficacy. Comparable with the results of the large European trials (EVA-3S, SPACE, and ICSS [43]), CEA showed a greater efficacy than CAS in patients older than approximately 70 years of age. In CREST there was no difference in the incidence of restenosis between CEA and CAS at 2 years as measured with a standardized ultrasound protocol [45].

In an updated review of the Cochrane Stroke Group comprising 16 trials and a total of 7572 patients, the risk of any stroke or death within 30 days in symptomatic patients was significantly higher after CAS than after CEA (OR 1.72; 95% CI 1.29–2.31), whereas the subsequent risk of ipsilateral stroke during long-term follow-up was comparable between both treatment groups [46].

Based on the results of the randomized trials summarized above, current guidelines have incorporated CAS as a *treatment alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the internal carotid artery is reduced by >70% by noninvasive imaging or >50% by catheter-based imaging and the anticipated rate of periprocedural stroke or death is <6%* [6]. In addition it has been recommended to consider patient age in choosing between CAS and CEA in the sense that patients older than approximately 70 years of age should preferentially be treated with CEA [6].

With the exception of CREST and until the recent publication of the Asymptomatic Carotid Trial (ACT) in 2016, there was paucity of data comparing CEA with CAS in patients with an asymptomatic carotid stenosis. ACT randomized 1453 patients younger than 79 years of age and with a ≥70% carotid stenosis who were asymptomatic (i.e., no stroke, TIA, or amaurosis fugax within the last 180 days) [47]. The primary endpoint was a composite of stroke, death, or MI within 30 days postprocedure or ipsilateral stroke within 1 year postprocedure. CAS was non-inferior to CEA with similar event rates (3.8% vs. 3.4%). The rate of stroke and death within 30 days was 2.9% in the stenting group and 1.7% in the surgical group ($P = 0.33$). From 30 days to 5 years after treatment, the rate of freedom from ipsilateral stroke was 97.8% in the stenting group and 97.3% in the endarterectomy group ($P = 0.51$).

While ACT has provided evidence that CAS is non-inferior to CEA in patients with a high-grade asymptomatic carotid stenosis, there was a lack of a treatment group that received contemporary medical treatment only. With modern medical therapy, observational studies have indicated that the annual risk of a stroke is likely less than 1% per year in patients with an asymptomatic carotid stenosis [48], questioning the benefit of any revascularization procedure.

16.7 Summary

The approach to any patient with carotid artery disease should always involve recognition of this disease as a specific manifestation of a generalized arteriopathy.

In patients with a carotid artery disease, best medical management should be given scrupulous attention including control of blood pressure, reduction of atherogenic lipoproteins, glycemic control, smoking cessation, and control of heart disease if it develops. All patients should receive antithrombotic medication in the form of aspirin.

From an evidence-based point of view, CEA currently remains the treatment of choice for patients with a symptomatic carotid stenosis and selected patients with an asymptomatic carotid stenosis. Especially in patients younger than 70 years of age, CAS is an alternative to CEA. However, the overall benefits of both procedures strongly depend on the surgical or interventional risks. Therefore, appropriate patient selection remains a key issue for any physician to consider. Acceptable guidelines for operative/interventional risk are 3% for asymptomatic patients and 6% for those patients with a TIA or stroke due to a carotid stenosis. Current guideline recommendations and the positive data of the large surgical trials should not be used to justify performing CEA or CAS without a clear medical indication or in centers with little experience and poor outcome data. Against the background of a continuously improving "best medical treatment" and the lack of trial data comparing CAS or CEA with contemporary medical therapies in asymptomatic patients, the potential advantages of revascularization in these patients still needs to be determined in further randomized trials.

16.8 Case Study

A 54-year-old man presented with two transient episodes of right-sided hemiparesis mainly involving the upper extremity combined with some slurring of his speech as well as difficulty finding appropriate words. Both episodes had occurred in the last 2 days and had lasted less than 10 min each. There were no further episodes of transient or permanent focal neurological deficits. The patient was taking no medications. He had a history of smoking (45 pack years). Except for a bruit in the left side of the neck, the neurological examination was normal on admission.

A computed tomography scan showed no signs of ischemia, whereas a diffusion-weighted MRI scan revealed

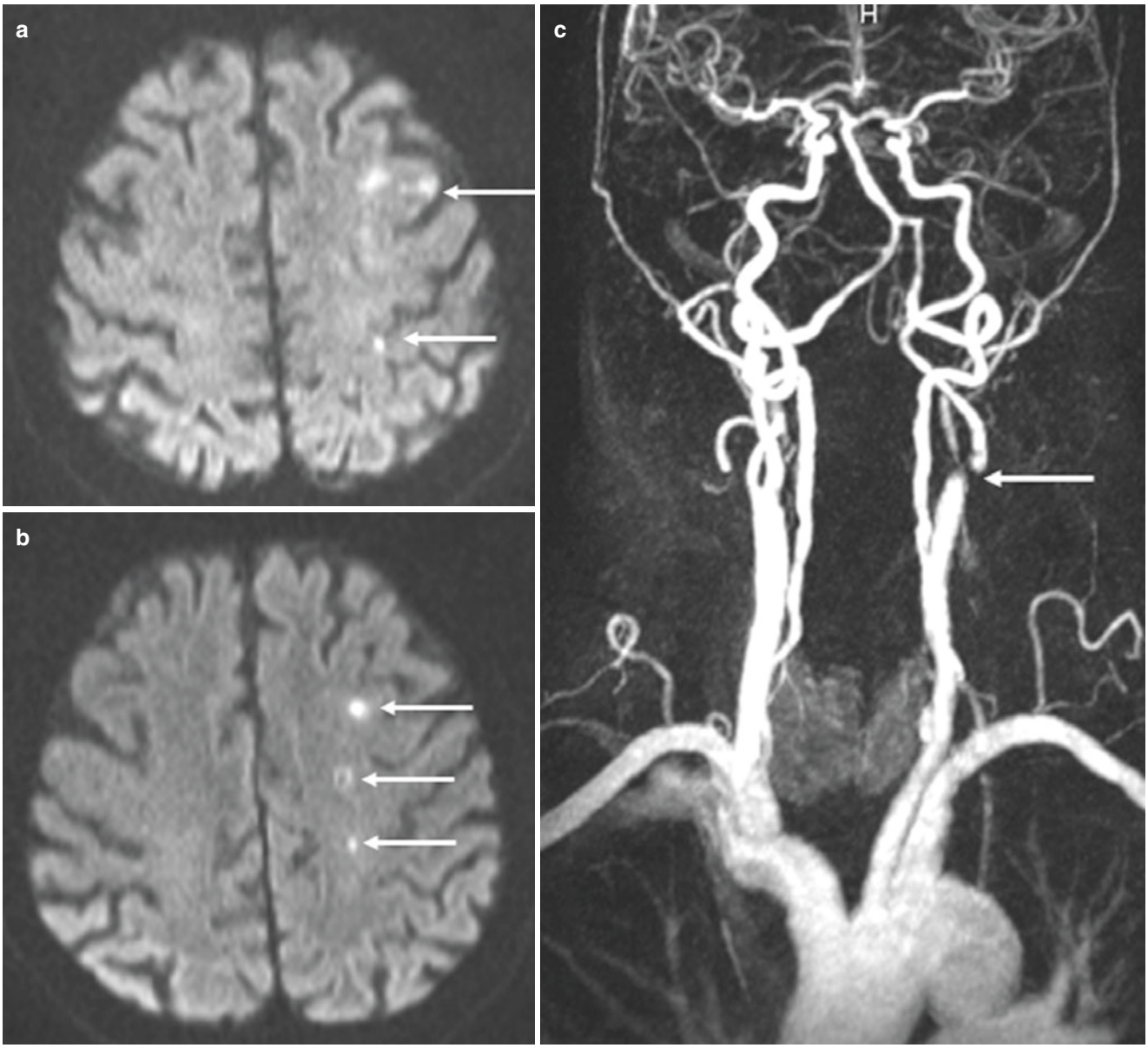

Fig. 16.3 Diffusion-weighted MR images (**a**–**c**) showing multiple embolic lesions throughout the left hemisphere (arrows), partially involving hemodynamic border zones. Contrast-enhanced magnetic resonance angiogram revealing a high-grade stenosis at the origin of the left internal carotid artery

multiple cortical signal abnormalities throughout the left hemisphere, as well as internal border zone regions consistent with multiple ischemic lesions of embolic and possibly also hemodynamic origin (Fig. 16.3). An extracranial Doppler and duplex sonography showed a severely ulcerated high-grade stenosis at the origin of the left internal carotid artery (ICA) (approximately 90%), which was confirmed by a contrast-enhanced magnetic resonance angiography. A post-stenotic flow pattern was seen in the left main segment of the middle cerebral artery with transcranial duplex sonography, all other detectable intracranial vessels revealed normal and symmetric flow signals. A cardiac source of embolism was ruled out by performing a 24-h electrocardiogram and transthoracic echocardiography. Diabetes mellitus and hyperlipidemia were ruled out.

Based on the clinical presentation and the results of the workup, the diagnosis of a symptomatic high-grade stenosis of the left ICA with a lumen reduction of about 80–90% was made. The current American Heart Association guidelines for the care of patients with a TIA or minor stroke due to a high-grade carotid stenosis recommend risk factor modification, the use of antithrombotic medications, and endarterectomy. The risks and potential benefits of surgical removal of the ICA stenosis were discussed extensively with the patient

and his family. Three days after admission, the patient underwent uneventful carotid endarterectomy and was given aspirin indefinitely. In addition, he was encouraged to change his lifestyle (smoking cessation, regular exercise, and avoidance of excessive alcohol consumption).

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Peripheral Arterial Disease

17

Taisei Kobayashi, Jay Giri, and Emile R. Mohler III

Abbreviations

ABI	Ankle-brachial index
ACC	American College of Cardiology
ACE	Angiotensin-converting enzyme
AHA	American Heart Association
CLI	Critical limb ischemia
CTA	Computed tomographic angiography
Hgb A1c	Hemoglobin A1c
LDL	Low-density lipoprotein
MRA	Magnetic resonance angiography
PAD	Peripheral arterial disease
TASC-II	Trans-Atlantic Intersociety Consensus Working Group
TBI	Toe-brachial index

Key Points

- Peripheral arterial disease (PAD) is common and highly underdiagnosed.
- Patients with PAD have a higher rate of cardiovascular events than the highest risk groups predicted by the Framingham risk score, up to 20% over 5 years.
- Over half of PAD patients have concomitant coronary artery disease.
- The American Heart Association (AHA), the American College of Cardiology (ACC) view PAD as a coronary heart disease (CHD) risk equivalent, which defines these patients as being at high risk for CHD-related events, such as myocardial infarction and death.
- Only one-third of patients with PAD have typical calf symptoms of claudication.
- All patients at risk of PAD should be screened with the simple, noninvasive, inexpensive ankle-brachial index (ABI). The ABI is 95% sensitive and 99% specific for the diagnosis of PAD.
- Management of PAD involves two paths: aggressive treatment of cardiovascular risk factors to decrease cardiovascular events and mortality as well as treatment of lower extremity symptoms.
- Lower extremity revascularization is never indicated in the asymptomatic patient. However, aggressive risk factor modification should be undertaken in all PAD patients.
- Consensus guidelines for PAD are produced by two major societies, the ACC/AHA and the Trans-Atlantic Intersociety Consensus Working Group (TASC-II). Recommendations from the two societies are largely concordant.

17.1 Introduction

For the purposes of this chapter, peripheral arterial disease (PAD) refers to the development and progression of atherosclerotic disease in the arteries of the lower extremities. A broader definition of peripheral arterial disease would encompass the aorta and all its major visceral branches (carotid arteries, mesenteric arteries, renal arteries, and extremity arteries). This chapter will not cover therapeutic considerations related to disease in each of these arterial beds.

T. Kobayashi · J. Giri
Cardiovascular Division, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

E. R. Mohler III (✉)
Department of Vascular Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA, USA
e-mail: mohlere@uphs.upenn.edu

P. P. Toth, C. P. Cannon (eds.), *Comprehensive Cardiovascular Medicine in the Primary Care Setting*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-319-97622-8_17

17.1.1 Pathophysiology

While there are several uncommon causes of lower extremity arterial disease, the predominant pathophysiologic process in the majority of PAD cases is atherosclerosis. The uptake and oxidation of low-density lipoprotein (LDL) in the vessel wall is a key-triggering event for atherosclerosis [1–4]. The oxidation of LDL leads to a cascade of inflammatory and proatherogenic events that result in increased LDL uptake by macrophages with foam cell formation, smooth muscle proliferation and migration, arterial stenosis, and, when an atheromatous plaque ruptures, in situ thrombosis [5–15]. While these principles provide a framework for a general understanding of atherosclerosis, factors specific to the peripheral arteries have not been well studied. It is unusual for patients to suddenly develop claudication symptoms; rather, claudication is typically an insidious process. It is unclear if plaque rupture and thrombosis results in claudication symptoms. For this reason, PAD is currently best thought of as progressive arterial stenosis of the lower extremity arteries due to atherosclerotic plaque formation, with subsequent development of exertional skeletal muscle and other tissue ischemia.

17.1.2 Prevalence

PAD affects 8.5 million people over the age of 40 and the prevalence continues to grow [16]. In selected populations of elderly patients or those with major risk factors for cardiovascular disease, the prevalence of PAD ranges from one in three to one in eight patients. In the PAD Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) study, a large observational study of patients over 70 years old or aged 50–69 with a history of diabetes mellitus or smoking, the prevalence of PAD, as defined by an ankle-brachial index (ABI) of less than 0.9, was 29% [17]. An analysis of data from the National Health and Nutrition Examination Survey (NHANES) revealed that, in patients over the age of 40, the prevalence of PAD was 4.3%. However in patients over age 70, the prevalence increased to 14.5% [18]. The prevalence of PAD dramatically increases with age and is common in both men and women [19, 20]. Epidemiologic studies have suggested that African-Americans and women may have the highest prevalence of PAD [16, 21].

17.1.3 Risk Factors

Risk factors for PAD are familiar, as they are those that underlie atherosclerosis more generally. These include age, smoking, diabetes mellitus, hypertension, hypercholesterolemia, and chronic renal insufficiency. Based on epidemiologic studies of patients with PAD, various risk groups have been identified. An American College of Cardiology/American Heart Association (ACC/AHA) consensus working group has identified an at-risk population for PAD [22]. This population is defined as having any one of the following characteristics:

1. Known atherosclerotic coronary, carotid, or renal arterial disease
2. Age >70
3. Age >50 with risk factors of diabetes mellitus or smoking
4. Age <50 with diabetes mellitus and an additional cardiovascular risk factor (smoking, hypertension, hyperlipidemia)
5. Abnormal lower extremity pulse examination
6. Exertional leg symptoms

The value of aggressively screening for PAD became apparent in a primary care practice-based screening study. In the PARTNERS study, patients over the age of 70 or those over 50 with a history of diabetes mellitus or smoking were screened for PAD with an ABI measurement. Twenty-nine percent of those screened had PAD. Importantly, greater than half of those patients found to have PAD had evidence of concomitant coronary artery disease [17].

In order to confirm the diagnosis of PAD, patients who meet any of the above criteria should be studied with the simple, noninvasive ankle-brachial index (ABI). The ABI is an office-based measurement that is 95% sensitive and 99% specific for the presence of PAD (see below) [22].

17.2 Prognosis

17.2.1 Limb Outcomes

In patients diagnosed with PAD, regardless of their initial symptoms (or lack thereof), will all become symptomatic over 5 years. Roughly 70–80% will develop stable claudication symptoms, 10–20% will develop accelerating claudication symptoms, and less than 2% will progress to critical limb ischemia (CLI) [22]. The intermediate-term outcomes for patients who develop critical limb ischemia, defined as ischemic rest pain, gangrene, or non-healing ulcers, are dismal. An analysis of patients with CLI treated medically showed a 6-month amputation rate of 35% and, even more worrisome, a 6-month mortality rate of 20% [23].

17.2.2 Cardiovascular Events

PAD patients are at significantly higher risk of myocardial infarction than those in the highest risk category predicted by

the Framingham risk score. Specifically, epidemiological studies have shown that the risk of myocardial infarction in patients with ABI <0.7 is nearly 20% at 5 years. For those in the mild PAD risk category, with ABI of 0.7–0.9, the risk is 10% at 5 years [24]. For comparison, high-risk Framingham patients have 10-year event rates of 20%. Additionally, a recent meta-analysis demonstrated a doubling of Framingham-predicted cardiovascular risk in patients with ABI <0.9 [25]. Importantly, regardless of the clinical presentation, cardiovascular events occur more frequently in PAD patients than ischemic limb events.

17.2.3 Death

Overall, intermediate- and long-term mortality risk in PAD is high accounting for over 13,000 deaths yearly [16, 26]. In patients with PAD, yearly mortality rates range from 3% to 6%. All-cause mortality reliably increases with ABI less than 1.00 or greater than 1.30 as evidenced by a threefold relative risk of death with an ABI <0.9 [16, 27]. Patients with diabetes and coexistent PAD fare particularly poorly. In one cohort of men with a mean age of 68 followed longitudinally, 2-year mortality rates in this subset of patients approached 40% [28]. More recent data show that woman have a higher mortality than men and represent a population at high risk for death [16].

17.3 Diagnosis

17.3.1 History and Physical

Evaluation of patients for PAD should begin with a careful history and physical examination. A comprehensive vascular examination includes palpation of the carotid, radial, femoral, popliteal, posterior tibialis, and dorsalis pedis pulses (Table 17.1). The measurement of bilateral arm blood pressures, examination for aortic aneurysm, careful inspection of the feet, and auscultation over the various arteries for bruits are also part of the complete vascular examination. By history, the classic presentation of lower extremity peripheral artery disease is one of intermittent claudication, the onset of calf pain with walking that is relieved by rest. Examination findings in the patient with PAD include diminished or absent lower extremity pulses. Arterial bruits, brittle lower extremity nails, prolonged (greater than 10 s) pallor after leg elevation for 1 min, and dependent rubor also point to the diagnosis. While it is important to identify these characteristics if they exist, their sensitivity for PAD detection is poor. Population studies have shown that only 15–30% of patients present with typical symptoms of claudication. A large percentage of patients, as many as 50%, have more atypical presentation of leg pain that is not so closely tied to exertion. Many have no symptoms at all, perhaps due to collateralization of arteries in the lower extremities. A small minority of patients (~1%) present with CLI. And, unlike in the coronary or cerebrovascular circulations where acute coronary syndrome and strokes are common initial manifestations of the underlying disease, acute limb ischemia is a relatively rare presentation of PAD, accounting for less than 2% of initial diagnoses. However a provider should be especially vigilant for the symptoms of acute limb ischemia (ALI). These include the six Ps: pain, pallor, paresthesia, paralysis, pulselessness, and poikilothermia. All represent a true vascular and limb threatening emergency and should be referred to the emergency room with prompt vascular medicine consultation as this entity has been associated with high risk of mortality and limb loss [29, 30]. Thus, it is important to conduct a careful vascular review of symptoms in patients at risk for PAD. This should include specific questioning regarding the presence of any discomfort in the lower extremity, from the buttocks to the foot. Limitation of activity due to the discomfort and its relationship to exertion must be assessed. Patients may describe the discomfort associated with PAD in various terms including pain, achiness, numbness, tingling, or fatigue [22].

As for the examination findings, a diminished or absent pedal pulse has been shown to have relatively poor sensitivity and positive predictive value for the diagnosis of PAD [31, 32]. Thus, in patients in the risk groups described above, it is important that the ABI is used as the screening test for PAD (Fig. 17.1).

Table 17.1 Physical examination findings of lower extremity arterial disease

Diminished or absent pulses
Brittle nails
Pallor with leg elevation
Dependent rubor
Non-healing, punched-out ulcers
Gangrene

17.3.2 Performing an ABI Test

The ABI examination should be performed with the patient in the supine position. Appropriately sized blood pressure cuffs must be used on the upper arm and ankle. An ultrasound probe should be used to identify the strongest arterial signal over the brachial arteries bilaterally. Bilateral systolic brachial artery blood pressures should be obtained. Next, the probe should be used to identify the strongest posterior tibial and dorsalis pedis pulses bilaterally. The systolic blood pressure should be obtained using the probe in all four extremities. The higher of the posterior tibial or dorsalis pedis

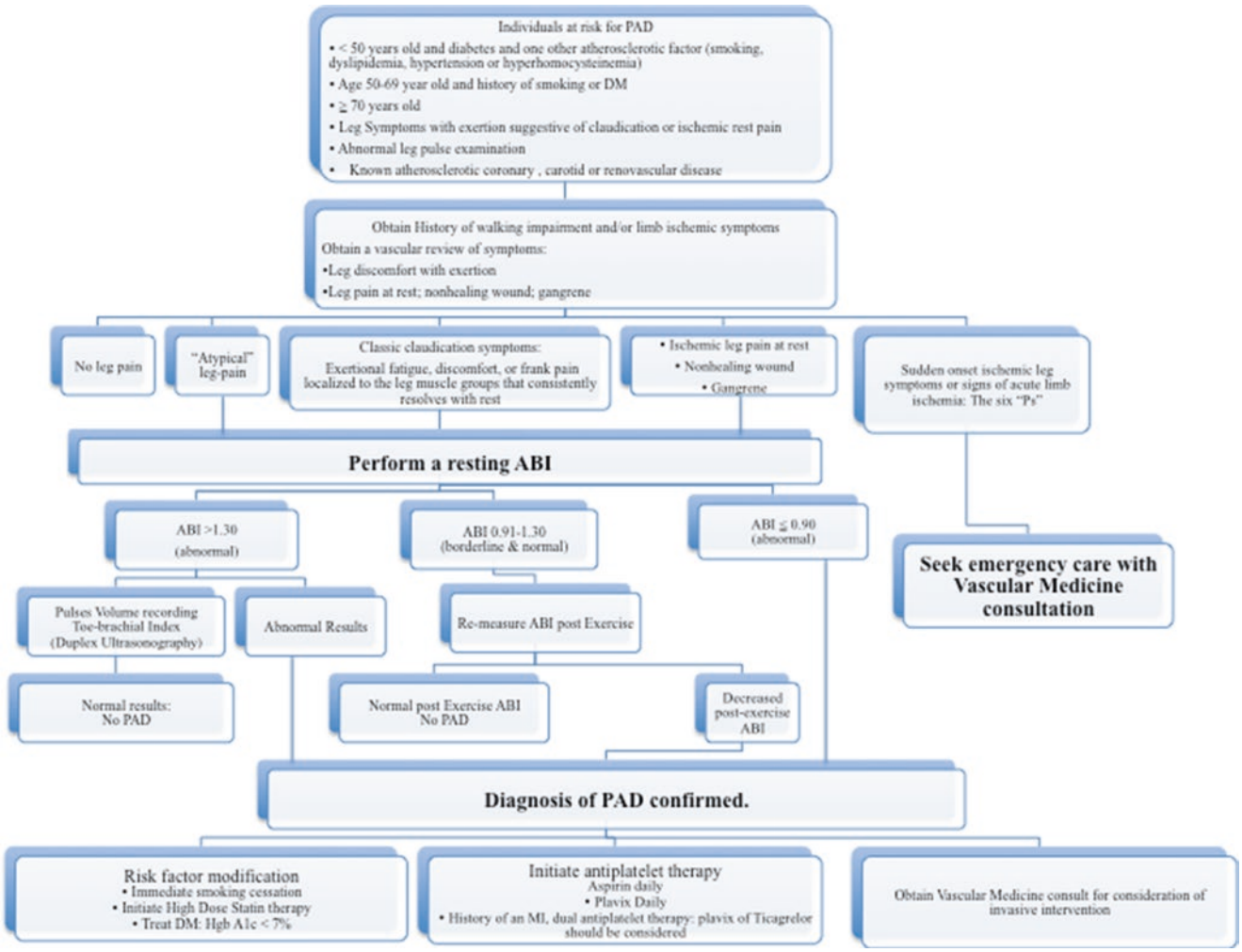

Fig. 17.1 Suggested approach toward the initial diagnosis and management of PAD. PAD peripheral arterial disease, DM diabetes mellitus, Hgb A1c hemoglobin A1c, ABI ankle-brachial index, MI myocardial infarction. Diagnostic algorithm for PAD. (Adapted from [22])

Table 17.2 Interpretation of ABI measurements

>1.30 uninterpretable
1.00–1.29 normal
0.91–0.99 borderline
0.71–0.90 mild PAD
0.41–0.70 moderate PAD
<0.40 severe PAD

pressures in a given leg is used as the ankle systolic blood pressure for that leg. For example, in order to calculate the left-leg ABI, divide the left ankle systolic pressure by the highest brachial systolic pressure. The same calculation can be used to obtain the right-leg ABI, again using the highest brachial systolic pressure (Table 17.2).

$$\text{ABI} = \frac{\text{ankle systolic blood pressure}\left(\text{higher of DP / PT}\right)}{\text{higher brachial artery systolic pressure}}$$

There are some circumstances in which the ABI is limited in its ability to properly diagnose PAD. The most common case is in the patient with an ABI >1.3. These patients have poorly compressible arteries due to medial artery calcification. This finding is not uncommon in patients with diabetes mellitus, renal failure, or advanced age. An ABI over 1.3 should not be considered normal, but rather uninterpretable. A retrospective study of 112 symptomatic patients referred to the Massachusetts General Hospital vascular laboratory with supranormal ABI revealed only 5% to be free of peripheral artery disease [33]. A toe-brachial index (TBI) can sometimes be effective in evaluating for the presence of PAD in those with a supranormal ABI. A specially designed cuff is placed around the great toe to obtain the systolic arterial pressure there. This is divided by the highest brachial arterial systolic pressure to derive a TBI. Values of <0.7 have been found to be sensitive for the diagnosis of PAD [22].

In some cases, patients may have a normal resting ABI but develop an abnormal ABI with exercise. Thus, performing an ABI after a treadmill exercise test or calf raise exercises can quickly help to clarify functional status as well as confirm the diagnosis of PAD in patients in whom a high suspicion for disease exists despite a normal resting ABI. Important additional information regarding a patient's PAD can be provided with segmental pressures and pulse volume recordings. These are noninvasive tests performed in vascular laboratories that allow for evaluation of the level of disease in lower extremities. Segmental pressures are typically performed by placing four blood pressure cuffs sequentially down each leg, two at the thigh, as well as the calf and ankle, and measuring systolic blood pressures at each leg segment. Pulse volume recordings are noninvasive recordings of the arterial wave forms representing blood flow at the same levels where pressures are obtained. A metatarsal or toe pressure cuff may also be applied for evaluation of pedal vessels. Abnormally low pressures or abnormally shaped pulse volume waveforms in a given portion of the leg allow interpreters to localize lower extremity arterial stenoses. One drawback to segmental pressures and pulse volume recordings is that the techniques do not allow for precise localization of the exact area of stenosis.

Some laboratories do an initial ABI and, if abnormal, do an extensive ultrasound evaluation of the lower extremity arterial system. More expensive imaging technologies such as computed tomographic angiography (CTA) and magnetic resonance angiography (MRA) are primarily useful for planning of initial vascular interventions and surveillance of prior interventions. The initial diagnosis of PAD is made cheaply, effectively, and in a risk-free fashion with the ABI, segmental pressures, and pulse volume recordings.

17.4 Medical Management of PAD

17.4.1 Diabetes Management

The ACC/AHA and Trans-Atlantic Intersociety Consensus Working Group (TASC-II) guidelines recommend aggressive treatment of diabetes mellitus with lowering of the HBA1c to less than 7%. TASC-II takes a particularly aggressive stance, arguing for attempted lowering to as close to 6% as possible [22, 23]. A common complication in diabetics with PAD is foot ulcerations. Thus, it is important that proper foot care is emphasized in this patient group with daily self-inspections of the feet as well as semi-annual podiatry visits. Additionally, lesions and ulcerations on the feet should be addressed urgently when they arise.

17.4.2 Smoking Cessation

It is also important to aggressively address smoking cessation in patients with PAD. Cigarette smoking is highly correlated with the development and progression of PAD. Smoking cessation should be undertaken in a comprehensive fashion that includes a formal smoking cessation program, counseling, behavioral techniques, nicotine replacement therapy, or other pharmacological approaches including bupropion or varenicline administration. Smoking cessation has been associated with a rapid decrease in symptomatic claudication, a decrease in mortality, lower cardiovascular events, and greater patency of revascularized arteries [34–36].

17.4.3 Lipid-Lowering Therapies

A post hoc analysis of the Heart Protection Study suggested a substantial reduction in cardiovascular events among those patients with PAD who were treated with 40 mg of simvastatin [37]. This benefit was seen even in patients without diagnosed coronary artery disease. In addition to the benefits seen in cardiovascular events, statins have been shown in two randomized trials and in one prospective cohort to modestly improve leg functioning in PAD patients [38–40]. The 2013 AHA/ACC blood cholesterol guidelines now include peripheral vascular disease as a major criterion to treat these patients with high-intensity statins (atorvastatin 40–80 mg, rosuvastatin 20–40 mg) [41].

17.4.4 Hypertension

Although recent guidelines have removed cardiovascular disease as a modifier of goal directed blood pressure management, controlling hypertension is important in PAD [42]. Despite the recent retraction of a randomized control trial of ramipril on peripheral arterial disease, previous data regarding ACEi medications, particularly ramipril, in this population has shown to reduce mortality by 19–42% [43, 44]. It is important also to recognize that beta-blockers are safe in PAD patients. There had been initial concerns regarding compromise of lower extremity perfusion in claudication patients on beta-blockers [45–47]. These fears have been disproven by multiple studies including a meta-analysis of 11 placebo-controlled trials failing to show an association between beta-blocker use and impaired leg function in patients with claudication [48]. Therefore, when required, particularly in patients who are post-myocardial infarction or suffer from left ventricular systolic dysfunction, beta-blockers should be used without hesitation in PAD patients.

17.4.5 Antithrombotic Therapy

Antiplatelet therapy with aspirin or clopidogrel is a core feature of the medical management of PAD. Specifically, in the large Antithrombotic Trialists' Collaboration meta-analysis, patients treated with antiplatelet therapy had a relative risk reduction of 23% for subsequent serious vascular events [49]. Post hoc analysis of the Clopidogrel vs. Aspirin in Patients at Risk of Recurrent Ischemic Events (CAPRIE) trial showed a 24% risk reduction in stroke, MI, or cardiovascular death in a population of patients with known PAD who were treated with clopidogrel as opposed to aspirin [50]. This result raised the question about the potential superiority of clopidogrel over aspirin in PAD patients. This has yet to be fully investigated, and current guideline recommendations by the ACC/AHA recommend using either agent [51]. Importantly, aspirin therapy may not provide significant clinical benefit in asymptomatic PAD patients who do not have a history of myocardial infarction, stroke, or claudication. The Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial showed no difference in outcomes in a diabetic population with asymptomatic PAD treated with aspirin versus placebo, though it was criticized for being underpowered [52]. In a substudy of the CHARISMA trial, higher-risk populations such as those with a history of symptomatic peripheral vascular disease, myocardial infarction, or stroke had a significant mortality benefit favoring dual antiplatelet use over clopidogrel alone, thus supporting a dual antiplatelet strategy in this specific population that has now been reflected in the current guidelines [51, 53]. The data support the use of ticagrelor 60 mg twice a day, as a viable option to improve mortality in patients with a prior history of myocardial infarction; however larger randomized trials have yet to be performed [54]. Finally, chronic anticoagulation therapy with warfarin does not have a routine role in the medical management of PAD. The Warfarin Antiplatelet Vascular Evaluation (WAVE) trial demonstrated increased rates of life-threatening bleeding among PAD patients treated with a combination of warfarin and an antiplatelet agent compared to lone antiplatelet therapy [55, 56].

17.4.6 Symptomatic Therapy

In addition to the goal of reducing cardiovascular events through risk factor modification via the techniques above, therapies exist for the treatment of symptomatic claudication. First, supervised exercise rehabilitation improves pain-free walking distance, maximal walking times, and overall walking distance in patients with PAD [32, 57–60]. The importance of a supervised exercise program cannot be stressed enough as the results from supervised programs are significantly better than non-supervised exercise programs [61]. Additionally, patients with PAD and significant physical activity in their daily lives have decreased cardiovascular events compared to their more sedentary counterparts [62]. As for pharmaceutical agents, a 3- to 6-month trial of cilostazol in dosages of 50–100 mg twice daily is recommended by the AHA/ACC for relief of symptomatic claudication and can improve walking distances [63, 64]. In a meta-analysis of six randomized trials of cilostazol versus placebo in patients with PAD, patients taking cilostazol had improvements of 34% in both maximal treadmill walking distance and calf pain severity after 3–6 months on the drug. Patients taking placebo had improvements of 21 and 24%, respectively, in the two outcomes. An important caveat to the use of this drug is its contraindication in patients with a history of congestive heart failure. This warning is based on studies showing potential adverse effects of other phosphodiesterase inhibitors in heart failure patients. Additionally, emerging data reveal ACE inhibitors and statins to have effects on functional leg outcomes in PAD in addition to their core role as risk factor modifiers [38–40, 65]. Although still prescribed, currently, the use of pentoxifylline for claudication is not strongly supported by evidence [66].

17.4.7 Interventional Therapy

When life-altering symptoms persist despite optimal medical therapy, revascularization of the lower extremity can be considered. Importantly, lower extremity revascularization is never indicated in the asymptomatic patient, regardless of the severity of PAD as measured by hemodynamic or imaging techniques [22]. However, in symptomatic patients with significant disability who have failed exercise rehabilitation and pharmacologic therapies and in whom significant functional benefit is anticipated, there are a few different options for revascularization. These options include percutaneous transluminal angioplasty, endovascular stenting, surgical endarterectomy, and lower extremity bypass surgery. The recommendations for specific types of procedures vary based on patient and stenotic lesion characteristics. When considering lower extremity revascularization for a patient, seek consultation from an experienced vascular medicine specialist.

17.4.8 Acute Limb Ischemia

Acute limb ischemia refers to a sudden (less than 2-week duration) and rapidly progressive decrease in perfusion to a limb, usually threatening its viability. This can occur in patients with pre-existing severe peripheral arterial disease who show the sudden onset of signs of critical limb ischemia. Atheromatous plaque rupture with overlying thrombosis and luminal obstruction of an at-risk arterial segment is often the

mechanism for this syndrome. Alternatively, embolism of a lower extremity can cause the development of acute limb ischemia. This is of particular concern in patients with atrial fibrillation who are not adequately anticoagulated. The classic symptoms of acute limb ischemia are illustrated by the five Ps: pain, pallor, pulselessness, paresthesia, and paralysis. When acute limb ischemia is suspected, urgent consultation with a vascular medicine specialist should be obtained. Parenteral anticoagulation should be initiated. If limb viability is in question, possible modalities for urgent revascularization include thrombolytic administration, endovascular intervention, and open surgical bypass grafting [23].

17.5 Case Studies

17.5.1 Case 1

A 62-year-old man with a history of hypertension presents to his primary care physician with a complaint of some mild discomfort in his proximal left lower extremity. The discomfort is sometimes but not always related to exertion. He describes it as an ache that occurs unpredictably, sometimes when sitting on the couch. His overall exertional tolerance is good; he is able to walk three blocks without difficulty. He is a 35-pack/year smoker with a family history of coronary artery disease in his father.

Up to 70% of patients with PAD do not present with typical exertional claudication, calf or thigh pain exacerbated by exercise and relieved by rest. Atypical leg pain or no symptoms characterize the majority of the PAD population. The patient above has atypical leg symptoms and is over 50 years old and has a history of smoking. For this reason, the first step in the evaluation of his symptoms (after a physical examination) is the easy, inexpensive, office-based ABI. Patients over 50 with a history of diabetes mellitus or smoking should be screened for PAD with an ABI. Diabetics under 50 with an additional major cardiovascular risk factor, patients over age 70, patients with known vascular disease, and patients with exertional leg symptoms or abnormal pulse examinations should also be routinely screened.

Bilateral ABI is performed revealing an ABI of 0.56 on the left and 0.63 on the right. Segmental pressures and pulse volume recordings are shown in Fig. 17.2.

Based on his ABI measurements, the patient has moderate left lower extremity PAD and moderate right lower extremity PAD. The segmental pressures performed in a vascular laboratory are typically accompanied by pulse volume recordings (PVR). This helps to localize the lesion. A thigh to brachial index of >1.1 is considered normal, whereas a calf to brachial index of >1.0 is normal. In this patient's case, the study revealed left iliac disease and probable right superficial femoral artery disease. At this point, two parallel lines of medical management should begin: intensive risk factor modification and treatment of claudication symptoms. The risk factor modification should be initiated to decrease the patient's risk of future cardiovascular events and progression of PAD. Specifically, if he is found to have diabetes, it should be aggressively managed with a target HBA1c of 7% or less. Also, one should initiate comprehensive smoking cessation therapy that includes nicotine replacement therapy, behavioral techniques, and Wellbutrin or varenicline if necessary. His blood pressure should be treated initially with an ACE inhibitor. Hydrochlorothiazide is also a reasonable first- or second-line agent in management of his hypertension. A fasting cholesterol panel may be obtained but regardless of the results, the patients should be started on high-intensity statin therapy. Finally, he should be started on either aspirin or clopidogrel as antiplatelet therapy; unless he has a history of myocardial infarction, then dual antiplatelet therapy should be initiated with aspirin and either clopidogrel or ticagrelor.

The other important approach in this patient is treatment of claudication symptoms. He should be referred, if possible, to a formalized, supervised exercise rehabilitation program. If this is unavailable, as is the case in many areas, he should be counseled to begin a home walking exercise program. A 3-month trial of 100 mg of cilostazol can be initiated as this patient does not have a history of congestive heart failure. He should be followed up regularly for monitoring of his symptoms and risk factors. Medications should be titrated and added as needed in order for the patient to meet national guideline-specified goals for his various risk factors.

The patient exhibits good medication compliance and appropriately increases his level of physical activity. His blood pressure is well controlled and is adherent to high-intensity statin therapy. Unfortunately, he continues to smoke. He notices initial improvement in his symptoms, but insidiously, over the course of 3 years, his left lower extremity symptoms become worse eventually causing him difficulty at his job as a bellman that requires him to walk hotel guests to their rooms while carrying luggage.

The patient noticed improvements initially but now appears to be failing medical therapy. Additionally, his symptoms are interfering with his daily life and making him more sedentary, increasing his risk for future cardiovascular events. At this point, it would be appropriate to refer him to a vascular medicine specialist to consider further interventional options to treat his claudication.

He is seen by a vascular medicine specialist who orders a CTA showing severe left iliac disease and moderate right SFA disease with good three-vessel runoff (evidence of patent anterior tibial, posterior tibial, and peroneal arteries). He undergoes percutaneous balloon angioplasty followed by implantation of a nitinol stent to his left iliac artery and notices significant relief of his symptoms. He vows to stop smoking.

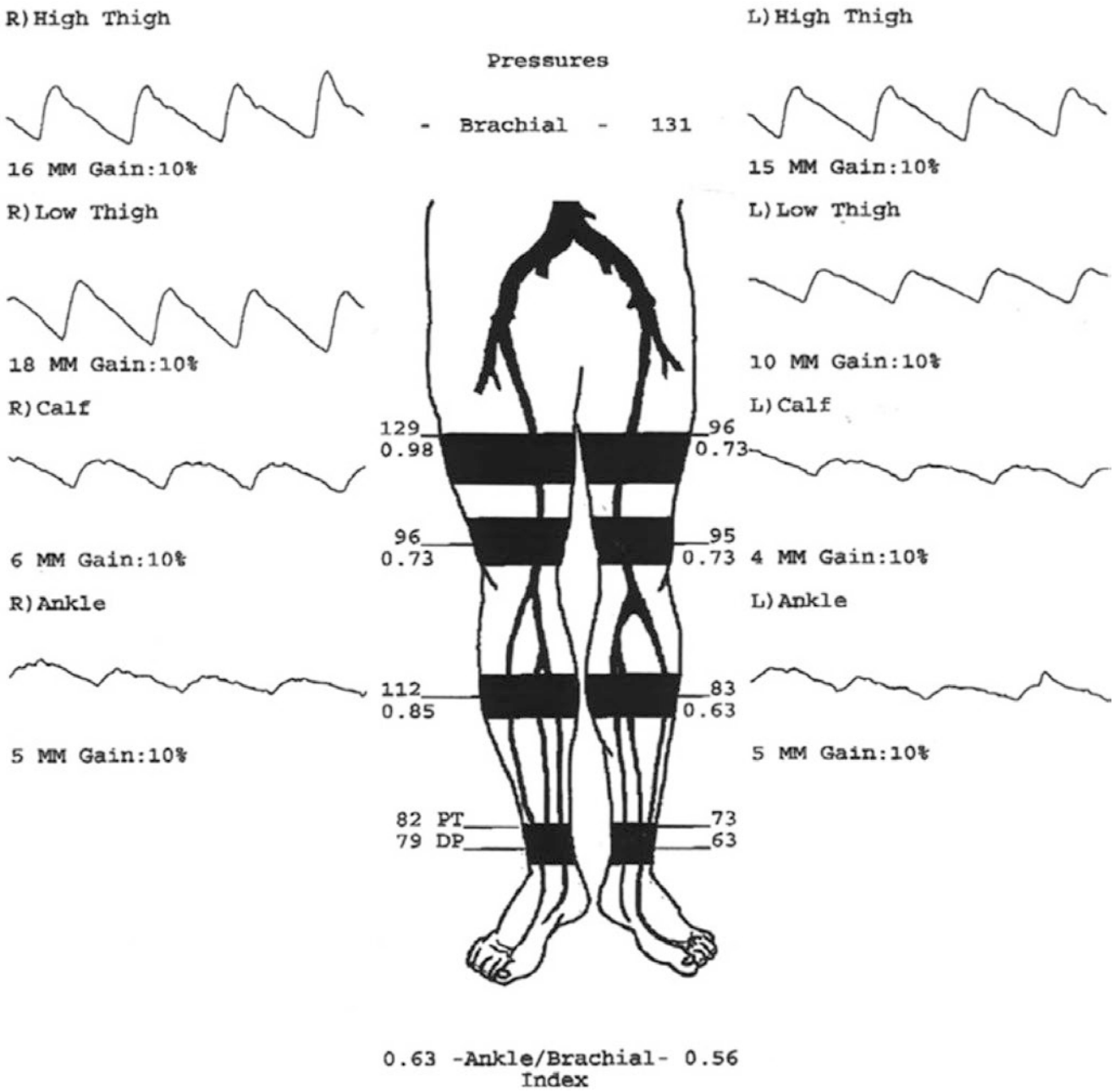

Fig. 17.2 Segmental pressures and pulse volume recordings for patient in Case 1. These results are consistent with the diagnosis of bilateral PAD at the level of the left common iliac artery (as evidenced by the dramatic blood pressure drop at the left high thigh level) and the right superficial femoral artery (as evidenced by the drop in blood pressure at the right low thigh level)

17.5.2 Case 2

A 74-year-old man with a history of diabetes mellitus and hypertension comes to the primary care office with complaints of a sore foot for 2 weeks. The patient was diagnosed with claudication secondary to PAD 3 years earlier. The patient was urged to quit smoking at that time but, unfortunately, was unable to comply. The physical examination reveals an ulceration on the great toe of the right lower extremity. Laboratory testing reveals a mildly elevated fasting glucose level of 110 mg/dL. His laboratory testing along with the finding of a waist circumference greater than 40 inches is consistent with metabolic syndrome. The patient is referred to the vascular laboratory where he is found to have a right ankle-brachial index of 0.3 and a left ankle-brachial index of 0.6.

The annual incidence of critical limb ischemia is approximately 500–1000 persons per million of population in North

America and Europe [22]. The natural history of patients with claudication over 5 years for development of CLI is relatively low at approximately 1%. However, risk factors such as persistent smoking and metabolic syndrome increase this risk. The patient described above warrants immediate medical attention for evaluation of possible revascularization in order to provide enough blood flow and tissue oxygenation to heal the wound. Consultation from a vascular medicine specialist should be obtained.

The patient underwent lower extremity angiography and was found to have a 5-cm-long soft superficial femoral artery atherosclerotic lesion that resulted in complete occlusion of the vessel. This occlusion was treated with balloon angioplasty. An 80% occlusion of the popliteal artery was also noted, and this vessel was also treated with an angioplasty balloon. Two of the three vessels below the popliteal artery were patent bilaterally. Although clinical trial data regarding combination antiplatelet therapy after peripheral percutaneous revascularization are very limited, the patient was given both aspirin and clopidogrel in order to maintain vessel patency and prevent thrombosis.

Guideline recommendations for treating patients after percutaneous revascularization for CLI include antiplatelet therapy, which decreases the rate of future vascular events. It is presumed that antiplatelet therapy also improves long-term patency of arterial segments that have been intervened upon, though this has not been rigorously studied in the lower extremities [22].

Over the course of 4 weeks, the patient's lower extremity pain resolved, and he no longer needed analgesic pain relief. He was given prescriptions for a supervised exercise claudication program as well as consultation with a nutritionist. The patient again underwent counseling regarding smoking cessation.

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Diagnosis and Management of Ischemic Stroke

18

Aslam M. Khaja

Key Points

- The diagnosis of acute ischemic stroke in the emergency room is a clinical diagnosis based on history, physical exam, and neuroimaging.
- Intravenous recombinant tissue plasminogen activator (tPA) is recommended for acute ischemic stroke within 4.5 h after onset. Intra-arterial therapy is also recommended for patients with a large vessel occlusion within 6 h of onset.
- Hypoxia, fever, hypotension, hypertension, and hyperglycemia are associated with worse outcomes after ischemic stroke and should be managed appropriately.
- The inpatient evaluation consists of vascular imaging, echocardiography, and risk factor identification/management.
- Decompressive hemicraniectomy is a lifesaving procedure and should be considered in younger patients with large strokes involving greater than 2/3 of the cerebral hemisphere.
- The first line of secondary stroke prevention is antiplatelet therapy.
- Management of risk factors such as hypertension, diabetes, cholesterol, and smoking is necessary to reduce the risk of recurrent cardiovascular events.
- Patients with intracranial atherosclerotic disease are treated with aspirin, clopidogrel, antihypertensives, and high-dose statin therapy.
- Carotid revascularization should be considered in patients with symptomatic and asymptomatic disease who meet certain criteria.
- Stroke patients with atrial fibrillation should be anticoagulated; if warfarin is contraindicated, then antiplatelets should be utilized.

18.1 Introduction

Until 1995, ischemic stroke management was a classic example of "diagnose and adios." Care of patients presenting to the hospital or clinic with symptoms of stroke consisted of aspirin followed by rehabilitation, with few disease-specific strategies directed toward optimal treatment and outcomes. The past two decades have witnessed an explosion of research into ischemic stroke. We now have specific therapies and management strategies to reduce morbidity and mortality. This chapter will first discuss the identification of patients with ischemic stroke, followed by acute treatment, inpatient management, and secondary stroke prevention.

18.2 Diagnosis

The clinical assessment remains the most efficient method to diagnose ischemic stroke in the emergency room. The history, general examination, and neurologic examination can almost always reliably determine the location of the infarct, even without the aid of neuroimaging. The goal of the initial evaluation is to diagnose an ischemic stroke and evaluate for any emergency treatments.

The first component of the clinical assessment is the history. The deficits are usually sudden in onset, during normal daily activities or upon awakening from sleep. Progression of symptoms over days or weeks is less common. Since patients presenting within the first few hours after onset can be eligible for acute reperfusion therapies, the time of onset is critical. Many times the patient can

A. M. Khaja (✉)
Neurology, Northwest Neurology, Ltd., South Barrington, IL, USA

P. P. Toth, C. P. Cannon (eds.), *Comprehensive Cardiovascular Medicine in the Primary Care Setting*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-319-97622-8_18

identify when the symptoms began. If the patient suffers from aphasia or woke up from sleep with symptoms, then determining the exact time of onset can be difficult. In this setting the time of onset is considered the time the patient was last seen normal. For example, if the symptoms were present upon awakening from sleep, then the time the patient went to sleep the night before is considered the time of onset. Additional components of the history should focus on concurrent medical problems and medications, particularly the use of anticoagulants.

The general examination is similar to other patients and begins with the "ABCs" of airway, breathing, and circulation. Vital signs including temperature and oxygen saturation are important. Examination of the head and neck can reveal signs of trauma, seizure, or carotid artery disease. The cardiac examination should focus on identifying acute MI, atrial fibrillation, or aortic dissection. The skin exam can elucidate significant systemic disease, such as a coagulopathy or hepatic dysfunction [1].

The main purpose of the neurologic examination is to localize the lesion. Patients with ischemic stroke usually present with focal neurologic signs and symptoms that fit a recognized neuroanatomic pattern. Physicians can utilize the pattern of deficits to localize the lesion and determine appropriate testing.

Common patterns of deficits in patients with ischemic stroke appear in List 1. Since the left side of the brain controls the right side of the body, the stroke in the brain is typically on the opposite side of the deficits on the body. The left hemisphere is the dominant hemisphere; even left-handed people are left hemisphere dominant 2/3 of the time. Brainstem strokes often cause "crossed findings" – i.e., deficits involving the left face and right side of the body. This is because almost all cranial nerves are ipsilateral, whereas the descending motor and sensory tracts are contralateral. For instance, a lesion in the left pons may cause left facial weakness (due to impairment of the left seventh cranial nerve) but right-sided weakness.

List 1 Common Patterns of Neurologic Deficits in Ischemic Stroke

Left Hemisphere (Dominant Hemisphere)
- Aphasia
- Right-sided weakness
- Right-sided numbness
- Right homonymous hemianopsia
- Left gaze preference

Right Hemisphere (Non-dominant Hemisphere)
- Neglect or extinction
- Left-sided weakness
- Left-sided numbness
- Left homonymous hemianopsia
- Right gaze preference

Brainstem
- Impaired consciousness
- Ataxia/incoordination
- Vertigo or dizziness
- Double vision (diplopia)
- Trouble swallowing (dysphagia)
- Slurred speech (dysarthria)
- Nystagmus

The National Institutes of Health Stroke Scale (NIHSS) score (List 2) is commonly employed by stroke neurologists to describe the deficits and determine the size of the stroke: the larger the stroke, the higher the NIHSS. The customary orientation questions are person and place. The routine commands are "Close your eyes" and "Show me 2 fingers." It is important for the examiner to not perform the tasks themselves to prevent aphasic patients from mimicking. Technically, the NIHSS score should reflect the patient's total deficits, regardless of acuity. However, in clinical use the NIHSS score is often scored to reflect the patient's new deficits. When used properly, the NIHSS not only serves to describe deficits but also helps identify the occluded vessel and determine prognosis [2]. For example, a patient with an NIHSS of 20 likely has a carotid occlusion and poor prognosis.

List 2 NIH Stroke Scale

1A. Level of Consciousness
- 0 = alert
- 1 = arousable with minor stimulation
- 2 = arousable with repeated stimulation
- 3 = unresponsive or coma

1B. Orientation Questions (Two Questions)
- 0 = answers both correctly
- 1 = one question correct
- 2 = neither question correct

1C. Commands (Two Commands)
- 0 = follows both
- 1 = follows one command
- 2 = follows neither command

2. Lateral Gaze
- 0 = normal horizontal eye movements
- 1 = partial horizontal gaze palsy
- 2 = complete gaze palsy or forced deviation

3. Visual Fields
- 0 = intact to confrontation
- 1 = partial hemianopsia
- 2 = complete hemianopsia
- 3 = bilateral hemianopsia or blind

4. Facial Movement
0 = normal
1 = minor facial weakness
2 = paralysis of the lower face or significant weakness
3 = complete unilateral facial palsy
5. Motor Function in the Arm (A = Left, B = Right)
0 = able to raise the arm for 10 s without drift
1 = the arm drifts but does not touch the bed
2 = the arm drifts down to the bed before 10 s
3 = no movement against gravity, unable to raise
4 = no movement
6. Motor Function in the Leg (A = Left, B = Right)
0 = able to raise for 5 s without drift
1 = the leg drifts but does not touch the bed
2 = the leg drifts down to the bed before 5 s
3 = no movement against gravity, unable to raise
4 = no movement
7. Limb Ataxia
0 = no ataxia
1 = ataxia in one limb
2 = ataxia in two or more limbs
8. Sensory
0 = normal
1 = mild sensory loss
2 = severe or total sensory loss
9. Language
0 = normal
1 = mild aphasia, mild loss of fluency
2 = severe aphasia, fragmented speech
3 = mute of global aphasia
10. Dysarthria
0 = normal
1 = mild dysarthria, but able to be understood
2 = moderate dysarthria, unintelligible, or mute
11. Extinction or Neglect
0 = absent
1 = mild, extinction
2 = severe neglect or inattention

It is also important to differentiate ischemic stroke from common mimics. Processes that can mimic acute stroke symptoms include seizures, migraines, encephalopathy, positional vertigo, and hypo- or hyperglycemia. In the setting on aphasia, it can become particularly difficult to distinguish between focal language impairment and other causes of altered mental status, such as delirium. Often, the aphasic patient will be awake and alert, regarding the examiner, but unable to follow commands, compared to the delirious patient who often is agitated or somnolent/lethargic [3]. Headaches are uncommon in the setting of acute ischemic stroke because the brain itself is not sensitive to pain [4]. Yet another common scenario is patients who present with serious medical comorbidities such as acute kidney injury or infection/sepsis that can cause altered mental status. Often there is confusion and decreased level of consciousness without focal neurologic deficits as described above. The absence of focal symptoms should prompt a thorough medical evaluation for possible causes of toxic/metabolic encephalopathies [5–7]. Isolated dysarthria is another presentation that often makes physicians suspicious for stroke. It is important to remember that isolated dysarthria (without other focal deficits) is usually not an ischemic stroke sign. Avoiding tunnel vision and keeping other causes such as alcohol intoxication or lack of dentures in mind helps avoid unnecessary tests and consultations.

The diagnosis of stroke can often be made on the basis of history and clinical exam alone. Neuroimaging is critical to differentiate ischemic from hemorrhagic stroke [8]. The most commonly employed modality is CT scanning. A simple non-contrast CT of the head can consistently determine the presence of intracranial hemorrhage and diagnose some nonvascular causes such as malignancy [9]. CT has important limitations. First, CT is relatively insensitive in detecting acute ischemic infarcts, as well as small cortical or subcortical strokes [10]. The inability of CT to determine acute infarcts is significant; therefore, the main utility of CT is to exclude hemorrhage and other causes. The diagnosis of acute ischemic stroke in the ED remains a largely clinical diagnosis. Magnetic resonance imaging (MRI) is increasingly utilized in the ER as the initial neuroimaging modality and is discussed later.

- The diagnosis of stroke is based on the clinical exam and history.
- Often conditions such as acute kidney injury, sepsis, or alcohol intoxication can mimic strokes. Altered mental status without focal deficits should prompt a workup for toxic/metabolic etiologies.
- The CT scan is used to distinguish between ischemic and hemorrhagic stroke since CT can often miss ischemic strokes early on.

18.3 Acute Thrombolysis and Treatment

Thrombolysis has redefined the acute management of stroke. The FDA approved recombinant tissue plasminogen activator (tPA) in 1995 based upon the results of the pivotal National Institute of Neurological Disorders and Stroke (NINDS) trial. In this study, 624,000 patients presenting within 3 h of symptom onset were randomized to treatment with IV tPA (0.9 mg/kg) or placebo. Patients treated with tPA were 30% more likely to have a favorable

outcome at 3 months compared to placebo [11]. It is interesting to note that there was no significant decrease in the NIHSS scores at 24 h. So even if patients do not immediately improve, they are still more likely to have a favorable outcome at 3 months if treated with tPA. The most significant adverse effect of tPA was intracerebral hemorrhage, which occurred in 6.4% of treated patients. The number of patients needed to treat with tPA to cause benefit is 3; whereas the number needed to harm is 30 [12]. Proper selection of patients is critical. Criteria to select patients for treatment with tPA are listed in List 3 [13]. Deviations from published guidelines may increase the rate of intracranial hemorrhage [14, 15].

List 3 Inclusion and Exclusion Criteria of Patients with Acute Ischemic Stroke Who Could Be Treated Within 3 h from Symptom Onset

Inclusion Criteria

- Diagnosis of ischemic stroke with measurable neurologic deficit
- Last seen normal <3 h before beginning treatment
- Age 18 ≥ years

Exclusion Criteria

- Any acute hemorrhage on neuroimaging
- Significant head trauma or prior stroke in past 3 months
- Symptoms suggest subarachnoid hemorrhage
- Arterial puncture at non-compressible site in past 7 days
- History of intracranial hemorrhage (not including cerebral microhemorrhages)
- Intracranial neoplasm or arteriovenous malformation
- Recent intracranial or spinal surgery
- Blood pressure > 185/110 mmHg
- Active internal bleeding
- Serum glucose <50 mg/dL
- CT evidence of hypodensity >1/3 cerebral hemisphere
- Acute bleeding diathesis, including but not limited to
  - Platelet count <100 k/mm^3
  - Heparin received in past 48 h with elevated PTT
  - INR > 1.7 or PT > 15 s
  - Current use of direct thrombin or factor Xa inhibitors

Relative Exclusion Criteria (Consider Risk vs. Benefit Carefully if One or More Are Present)

- Minor or rapidly spontaneously improving symptoms
- Pregnancy
- Seizure at onset of symptoms with postictal neurologic impairments
- Major surgery or previous trauma in past 14 days
- GI or urinary tract hemorrhage in past 21 days
- Acute MI in past 3 months
- Unruptured cerebral aneurysm
- History of hemorrhagic diabetic retinopathy

Despite the approval of tPA for acute ischemic stroke, only a small percentage of patients nationwide receive the drug. The most common exclusion is presentation outside the 3 h window [16]. Early trials of tPA beyond 3 h failed to show a benefit. However, a meta-analysis suggested a benefit to IV tPA beyond 3 h [17], and a large US trial showed a benefit of IV tPA up to 4.5 h after symptom onset [18]. As a result of this data, IV tPA has been recommended in 3–4.5 h with additional inclusion and relative exclusion criteria [19, 20].

Another rapidly expanding area of acute stroke treatment is intra-arterial therapy (IAT). IAT is attractive because of the added benefit of mechanical clot lysis via a plethora of specialized catheters and devices (Fig. 18.1). IAT also enables the administration of thrombolytic medications directly into the clot, leading to higher recanalization rates [21]. Problems with IAT include availability and time. Typically, only large centers have experienced neuro-interventionalists and a specialized treatment team.

Three early studies with either primary IAT or first-generation mechanical thrombectomy devices failed to a benefit over conventional IV tPA, despite better recanalization rates [22–24]. With the advent of more experience and stent retrievers (Fig. 18.1), studies now show improved recanalization and, most importantly, outcomes [25–29]. Based upon these trials, IAT is now recommend for patients with acute ischemic stroke who have received IV tPA and have a large stroke with large artery occlusion on vascular imaging, and treatment can be initiated (groin puncture) within 6 h of symptom onset [30]. Observing the patient after IV tPA to assess for clinical response before pursuing endovascular therapy is not required nor recommended. The use of IAT in patients who are not eligible for IV tPA, or with smaller vessel occlusions, is of unproven benefit. However, it is common practice to refer patients with large

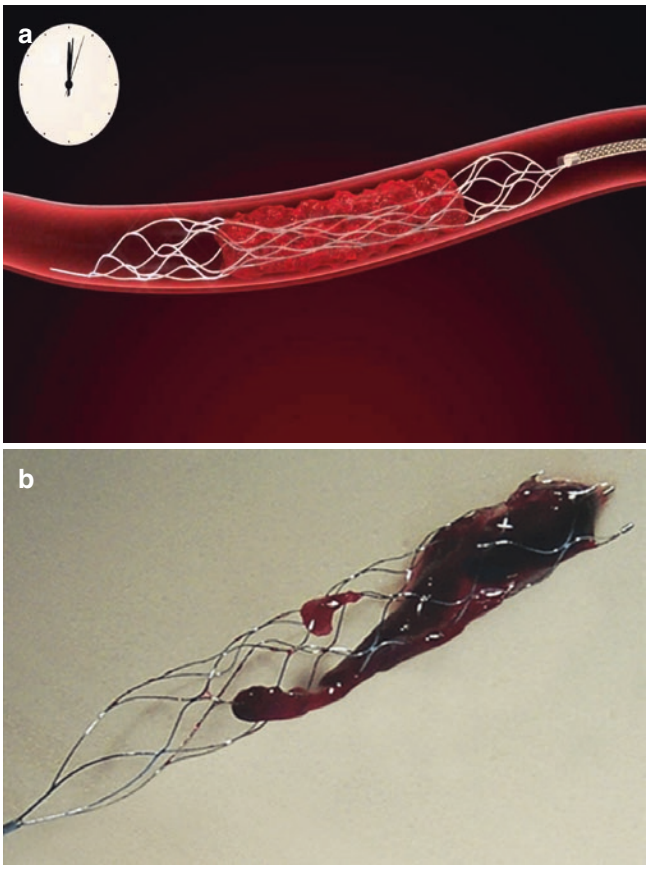

Fig. 18.1 (**a**) Examples of intra-arterial stent retrievers. Trevo Retriever (Stryker Neurovascular). A stent is deployed across the thrombus and then withdrawn slowly to remove the thrombus and recanalize the vessel. (**b**) Actual Solitaire revascularization device (Medtronic) after removal with the clot still entrapped in the mesh stent [129]

vessel occlusions who are not candidates for IV tPA for IAT because there is no other acute therapy to offer.

Because of this opportunity to help select patients, many EDs now obtain emergent vascular imaging with CT angiography when an acute ischemic stroke patient is eligible for IV tPA. The exact timing of the imaging is an area of debate. Some prefer to get the CTA along with the initial head CT done in the first few minutes. The main advantage of this approach is that patients who are eligible for IAT can be identified sooner. The major disadvantage is the delay in treatment with IV tPA. The additional imaging takes extra time (on average about 15 min) and can unnecessarily delay IV tPA treatment for all patients. Time is brain, and this delay in IV treatment could lead to worse outcomes. Therefore, many EDs will get the initial head CT, make a decision about IV tPA, and then send the patient back for CT angiography while the IV tPA is being administered. This can sometimes delay IAT, but only some IV tPA patients are eligible for IAT.

- IV tPA is approved for ischemic stroke, if used within 4.5 h of symptom onset.
- Intra-arterial thrombolysis is indicated for patients with large vessel occlusions within 6 h of symptom onset.

18.4 Inpatient General Medical Care

The inpatient care of stroke patients focuses on controlling risk factors and rehabilitation. Hypoxia can occur in patients with acute ischemic stroke, due to partial airway obstruction, hypoventilation, aspiration pneumonia, or atelectasis. Hypoxia should be treated to limit additional ischemic brain injury. Stroke patients with brainstem dysfunction or depressed consciousness are at particular risk of hypoxia due to impaired airway-protective reflexes [31]. Many times stroke patients are routinely placed on supplemental oxygen, but the benefit has not been proven [32]. The target blood oxygen saturation should be greater than or equal to 92% [33]. Endotracheal intubation should be performed if the airway is threatened. Hyperbaric oxygen has been studied in acute ischemic stroke; however, trials do not reveal improved outcomes [34].

Fever is also associated with poor neurological outcomes after stroke. Possible mechanisms include increased metabolic demands, release of neurotransmitters, and free radical production [35, 36]. Treating fever may improve prognosis [37]. Fever may be secondary to a cause of stroke, such as endocarditis, or from a complication, such as deep venous thrombosis.

Hypothermia is a promising therapy for acute ischemic stroke. Hypothermia has already been shown to improve neurological outcomes after cardiac arrest [38, 39]. Small studies have evaluated the feasibility of hypothermia in acute ischemic stroke [40–42]. Patients can be cooled with external cooling devices, such as helmets, or internal catheters. Hypothermia is also being tested in combination with other potential neuroprotective agents, such as caffeinol (a combination of caffeine and alcohol) [43]. Although promising, hypothermia is associated with significant complications, such as hypotension, pneumonia, and cardiac arrhythmias [44]. Hypothermia in acute ischemic stroke is an active area of research, but at this time, hypothermia is not recommended outside the setting of a clinical trial.

Cardiac arrhythmias and myocardial ischemia are potential complications of acute ischemic stroke [45]. Interestingly, strokes in the right hemisphere, particularly the insula, may

have an increased risk of cardiac complications. The etiology is unknown but thought to involve autonomic disturbances [46, 47]. In addition, stroke itself can cause ST segment depression, QT dispersion, inverted T waves, and prominent U waves [48, 49]. Cardiac monitoring is recommended for the first 24 h after admission, but it is usually continued for the duration of the inpatient stay. The most common arrhythmia in ischemic stroke patients is atrial fibrillation [50].

The optimal management of blood pressure in ischemic stroke patients is controversial. Both hyper and hypotension on admission are associated with increased mortality [51]. Theoretically, blood pressure lowering may reduce cerebral edema, lower the risk of hemorrhagic transformation, and prevent further vascular damage [1]. On the other hand, lowering the blood pressure may also lead to neurologic worsening by decreasing cerebral perfusion [52, 53]. One randomized, controlled trial suggests that blood pressure can be acutely lowered safely, but further study is needed [54, 55].

In the acute setting, elevated blood pressure is associated with an increased risk of hemorrhagic transformation after IV tPA [56, 57]. Outside of thrombolysis, the general consensus is to allow permissive hypertension. Guidelines for acute BP management are summarized in Table 18.1 [13]. Many experienced centers discontinue antihypertensive medications upon admission, and then blood pressure is gradually lowered during the inpatient stay.

Hyperglycemia is often seen in ischemic stroke patients. The presence of hyperglycemia and diabetes is associated with worse outcomes and neurologic deterioration [58–60]. It is unclear if hyperglycemia causes worse outcomes or is merely a marker for more severe strokes. Treatment of blood glucose levels greater than 200 mg/dL is recommended [1].

Table 18.1 Blood pressure management in acute ischemic stroke

A. In patients not eligible for thrombolysis or other acute reperfusion therapies	
Blood pressure (mmHg)	Treatment
SBP ≤220 or DBP ≤120	Observation
SBP >220 or DBP 121–140	Enalapril (IV) or hydralazine (IV) or labetalol (IV) or clonidine (IV or SC) or nicardipine infusion (IV)
DBP >140	Nicardipine infusion (IV) or nitroprusside infusion (IV)
B. In patients eligible for thrombolysis or other acute reperfusion therapies	
Blood pressure (mmHg)	Treatment
SBP ≤185 or DBP ≤110	Observation
SBP >185 or DBP >110	Labetalol (IV) or hydralazine (IV) or clonidine (IV or SC) or nicardipine infusion (IV)
DBP >140	Nicardipine infusion (IV) or nitroprusside infusion (IV)

Intensive glucose control does not seem to affect mortality and increases the incidence of hypoglycemia [61, 62]. Despite the lack of good data to guide clinical decisions, it is generally agreed that hyperglycemia after stroke should be controlled [63].

18.5 Inpatient Ischemic Stroke Evaluation

The primary goals of the inpatient evaluation are to determine the etiology of the stroke, manage neurologic complications, and prevent future events. The first goal is to determine the size of the ischemic stroke and determine the etiology. Non-contrast CT scans can determine stroke size after the acute period has passed. Because the CT scan looks at the brain structure, once 48 h has passed, the infarct is much better defined on CT. The CT scan can also identify hemorrhagic transformation, which can affect the use of antiplatelets or anticoagulants. However, it is difficult to distinguish new from old areas of infarction on CT. In addition, small lacunar or brainstem strokes may be missed [10].

Because of the limitations of CT, many centers employ MRI to evaluate stroke patients. The first important sequence is diffusion-weighted imaging (DWI), often called the "stroke sequence" (Fig. 18.2). Acute strokes will appear bright on DWI within an hour of ischemia and remain bright for approximately 2 weeks [64]. The companion image to the DWI is the ADC (apparent diffusion coefficient); acute strokes appear dark on ADC and then normalize in 5–10 days [65]. After a few hours of ischemia, FLAIR (fluid-attenuated inversion recovery) sequences identify areas of vasogenic edema, consistent with acute ischemic stroke [65]. FLAIR sequences also identify old areas of ischemia. Although CT reliably detects hemorrhage, GRE (gradient echo) images on MRI are much more sensitive for areas of small petechial and old hemorrhages [66, 67]. Because of its many advantages over CT, MRI is the imaging modality of choice in stroke patients.

After determining the size and extent of the stroke, the next step is to determine the etiology of the vascular occlusion. Clots can be divided into two basic classes. A thrombus forms at the site of the occlusion, whereas an embolus forms in one place and then travels to occlude the artery. Because ischemic stroke can be due to either process, it is important to obtain vascular imaging to evaluate the arteries and cardiac imaging to evaluate for emboli.

Carotid ultrasound (CUS) is a common technique to image the vessels of the neck. CUS is based on Doppler imaging of velocity in the carotid arteries. The advantages of CUS are that it is noninvasive, quick, and does not require contrast. As the diameter of the vessel decreases, the velocity must increase to maintain consistent flow. The degree of stenosis can be determined using velocity criteria [68].

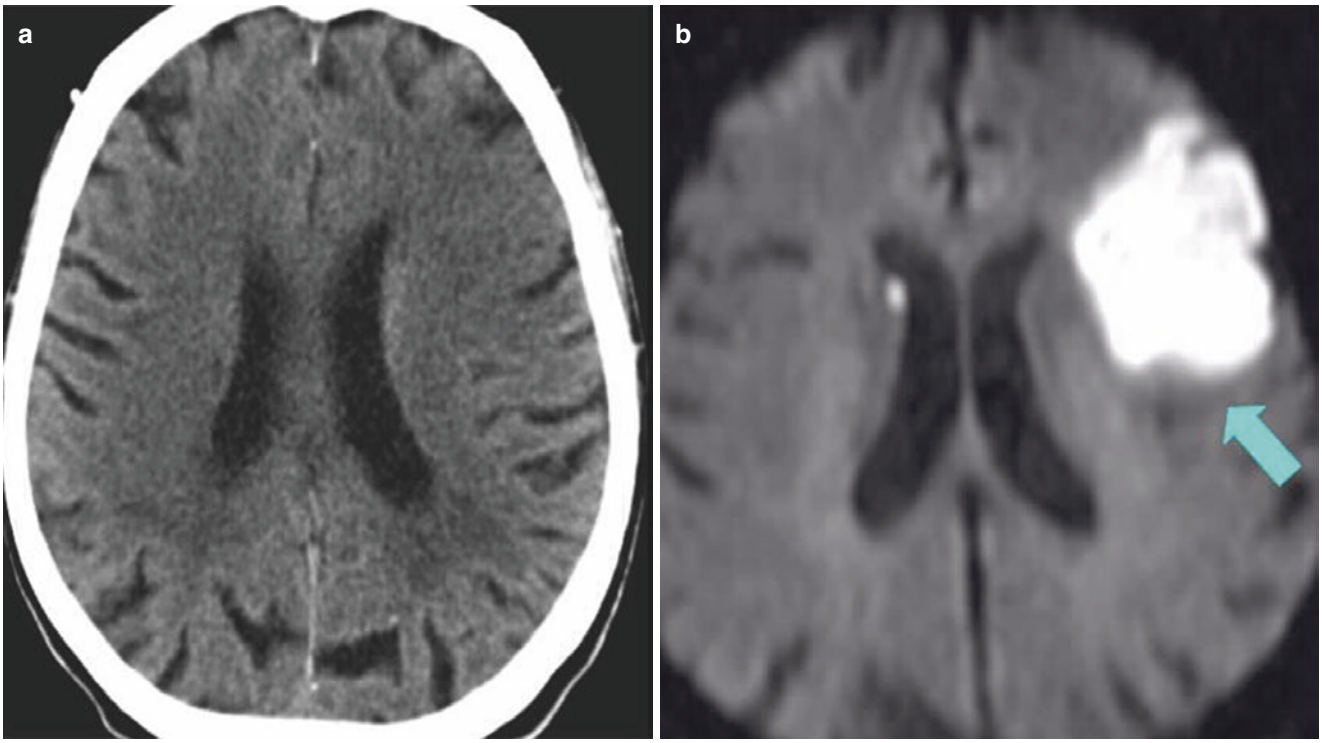

Fig. 18.2 DWI in ischemic stroke: in acute ischemic stroke, the CT scan is often normal (**a**), but the stroke can easily be seen on DWI (**b**)

Disadvantages of ultrasound are that it cannot image the entire length of the carotid or vertebral arteries and provides no information about the intracranial vessels.

A technique to image the arterial circulation of the entire head and neck is CT angiography (CTA). This is done in the CT scanner. IV contrast is injected and allows for visualization of the vessel lumen. CTA of the neck can identify areas of stenosis or occlusion anywhere along the carotid or vertebral arteries [69]. CTA of the head can be performed at the same time and provides valuable information about the intracranial circulation. The main drawback of CTA is that it requires contrast, which is nephrotoxic, and must be used with caution in patients with renal insufficiency.

Because many stroke patients undergo an MRI while in the hospital, magnetic resonance angiography (MRA) has become a convenient noninvasive method of vascular imaging. MRA is based on the flow of blood through the vessel [70]. An MRA of the head and neck will provide similar information to a CTA (Fig. 18.3).

The gold standard imaging technique remains invasive cerebral angiography. This is done in the angiography suite by direct arterial injection. Because of its invasive nature, the complications of angiography can be serious – arterial dissection, creation of emboli to cause further strokes, and even death. However, complication rates are low in the hands of experienced interventionalists [70]. Ultimately, the choice of vascular imaging is personal; different centers prefer different imaging modalities.

Since emboli leading to stroke are often cardiac in origin, echocardiography is done in almost every patient with ischemic stroke. Transthoracic echocardiography (TTE) provides information about the structure and function of the heart. Transesophageal echocardiography (TEE) provides better visualization of the atrial chambers, and particularly the left atrial appendage, where many clots form. TEE also provides information about atherosclerotic disease in the arch, which may be an additional source of emboli. TEE is preferred over TTE [71]. Most centers routinely employ TTE, with selected patients undergoing TEE. In patients with a PFO, a Doppler venous ultrasound of the lower extremities is recommended to evaluate for a paradoxical embolus. An MRV of the pelvis can also be considered.

- Ischemic stroke patient should have vascular imaging to evaluate the vessels of the head and neck for areas of stenosis or occlusion.
- CT or MR angiography provides noninvasive imaging of the vasculature.
- Invasive cerebral angiography remains the gold standard vascular imaging technique.
- Echocardiography aids in the identification of causes of cardiogenic emboli.

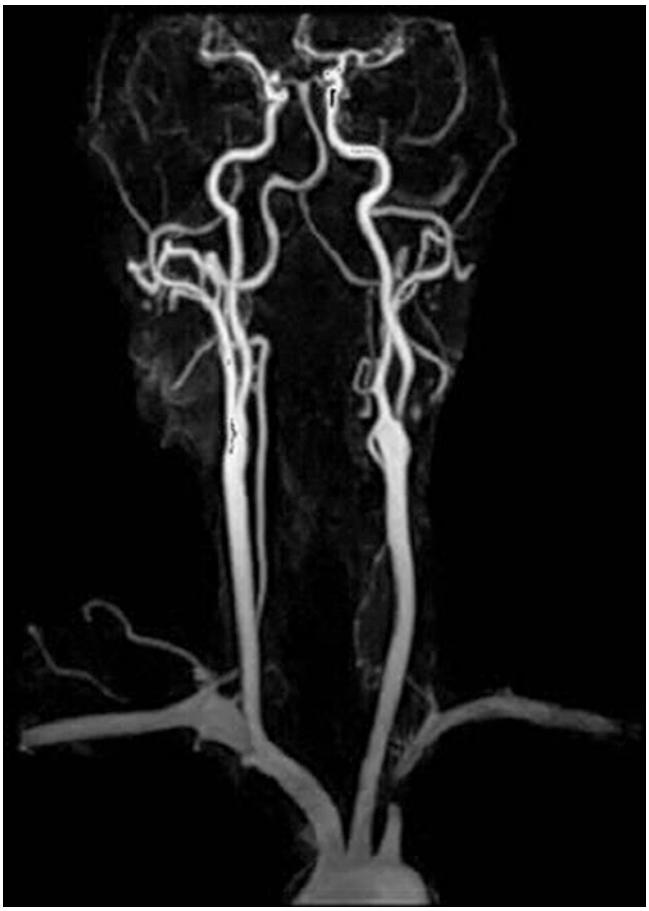

Fig. 18.3 MRA of the head and neck reveals a smooth narrowing of the left internal carotid artery (arrow)

18.6 Inpatient Management of Neurologic Complications

There are three significant acute neurologic complications of ischemic stroke. First is cerebral edema. Second is hemorrhagic transformation. Third is seizures. Consultation with a neurologist or neurosurgeon is recommended for management of acute neurologic complications.

Signs of increased intracranial pressure due to cerebral edema include depressed consciousness or worsening neurologic deficits. In some patients, cerebral edema can be severe enough to cause a shift of the intracranial structures. A particularly ominous sign is a fixed dilated pupil; this occurs with compression of the third cranial nerve.

Cerebral edema typically peaks about 4 days after stroke onset [72]. Although most strokes will have some degree of edema, relatively few have significant enough edema to warrant intervention [73]. Initial management of cerebral edema involves avoiding hypo-osmolar fluid (which theoretically may worsen edema). In addition, hypoxemia, hypercarbia, and hyperthermia may exacerbate swelling and should be managed appropriately. Antihypertensives should be avoided to maximize cerebral perfusion [1].

Large middle cerebral artery strokes may cause significant intracranial shift. The definitive treatment is decompressive hemicraniectomy. This involves removing half of the skull and cutting the dura on the side of the stroke to allow room for the damaged brain to swell outward. The bone is saved and can be reinserted later, after the edema has resolved. We now know that early hemicraniectomy (within 48 h of stroke onset) improves survival and outcomes, whereas delaying hemicraniectomy beyond 48 h improves survival but has little effect on outcomes [74, 75]. Hemicraniectomy should be considered in patients under the age of 60, with large hemispheric stroke involving greater than 2/3 of the middle cerebral artery territory [75]. However, surviving patients often have significant neurologic deficits, and quality of life after hemicraniectomy remains a topic of debate.

Management of hemorrhagic transformation depends upon the amount of bleeding and symptoms. Small petechial hemorrhages are usually asymptomatic. Large confluent hematomas can increase intracranial pressure and cause neurologic deterioration. Although hemorrhagic transformation is a well-known complication of ischemic stroke, optimal treatment strategies have not been defined. If a patient recently received tPA, the tPA should be reversed by administration of cryoprecipitate and platelets [3]. In late hemorrhagic transformation, antiplatelets and anticoagulants should be temporarily held.

Seizures are uncommon after ischemic stroke, occurring in about 5% of patients. They usually occur within 48 h of infarction. Most seizures are focal and do not generalize. Interestingly, seizures do not appear to be associated with worse outcome [76]. Little data exists about the management of seizures in ischemic stroke; therefore management is similar to seizures in other neurological illnesses.

18.7 Stroke Prevention

The key component of stroke prevention is risk factor management. The section will begin by discussing risk factor management applicable to most ischemic stroke patients, such as hypertension, diabetes, cholesterol, etc. This is followed by a discussion of antiplatelet agents, indications for anticoagulation, and the treatment for other disease states that may be discovered during the inpatient evaluation, such as carotid artery disease and intracranial stenosis.

The association between blood pressure reduction and primary stroke prevention is well established [77]. Antihypertensive medications also decrease recurrent stroke rates, regardless of whether the patient has hypertension or not [78]. Based on the current data, specific recommendations about choice of antihypertensive agents cannot be made, but antihypertensive therapy is recommended to prevent recurrent stroke and vascular events [50].

As mentioned previously, hyperglycemia has been associated with worse outcomes in ischemic stroke patients.

Glycemic control reduces the occurrence of microvascular complications [79]. Conventional reasoning would argue that glycemic control should therefore also prevent macrovascular complications and reduce vascular mortality in patients with diabetes. Interestingly, multiple studies now reveal the tight glycemic control in patients with type 2 diabetes does not reduce cardiovascular events and may actually increase mortality [80–82]. While glycemic control is probably still important in stroke prevention, aggressive glycemic control may not be the best strategy. The optimum blood glucose and hemoglobin A_{1c} concentrations to prevent recurrent strokes and cardiovascular events have not been established.

The association between hyperlipidemia and stroke risk has been to topic of much study and discussion. Prior studies have shown a weak correlation between lipid levels and stroke [83]. The pivotal study to prove that statin therapy reduced recurrent stroke patients with stroke or TIA was the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial. This study proved that atorvastatin reduced the overall incidence of strokes and cardiovascular events [84]. Patients with stroke should be treated according to the updated guidelines with lifestyle modification, dietary guidelines, and medications [85]. The new guidelines have moved away from the target LDL goals and instead focus on cardiovascular risk. The current recommendation is that patients with stroke or TIA thought to be due to atherosclerotic disease are candidates for statin therapy. Statins are suspected to have beneficial effects on the vascular endothelium, beyond cholesterol lowering. Therefore, patients with atherosclerotic ischemic stroke are reasonable candidates for statin therapy [50].

In many patients, smoking cessation is the single most effective way to decrease the risk of recurrent vascular events. Smoking approximately doubles the risk of stroke compared to non-smokers [86]. In addition, secondhand smoke may also increase the risk of cardiovascular disease [87–89]. A combination of nicotine therapy, social support, and skills training is the most effective approach to quitting smoking [90]. The increased risk of stroke disappears 5 years after smoking cessation [91, 92].

Most studies suggest a J-shaped relationship between alcohol consumption and ischemic stroke. Consumption of one or two drinks per day appears to decrease the risk of stroke. Consumption of 0 or > 5 drinks per day had an increased stroke risk [93]. The current recommendations state that light to moderate levels of alcohol consumption (two drinks/day for men, one drink/day for women who are not pregnant) may be beneficial [1]. Heavy drinkers should reduce their consumption [50].

An increasing body mass index (BMI) increases stroke risk in men [94], but the effect in women is unclear [95]. Although losing weight has not been shown to decrease stroke risk, losing weight improves blood pressure, glucose levels, and cholesterol [96]. The goal BMI is 18.5–24.9 kg/m^2 [50].

Much attention is focused on the choice of antiplatelet agents to reduce recurrent stroke. At present there are three different agents that are commonly utilized – aspirin, dipyridamole+aspirin (Aggrenox), and clopidogrel (Plavix). Aspirin has been consistently shown to reduce the risk of recurrent stroke. The dose range varies from 50 to 1300 mg/day. Both high- and low-dose aspirin have similar efficacy [97, 98]. However, higher doses of aspirin increase the risk of GI bleeding [99]. Clopidogrel is considered similar to aspirin for stroke prevention [100]. The combination of aspirin plus clopidogrel offers further benefit for stroke prevention, but this benefit is offset by an increase of intracranial hemorrhage in stroke patients and is not recommended for long-term secondary prevention [101]. In one study, dipyridamole+aspirin was shown superior to aspirin or dipyridamole alone [102].

If dipyridamole+aspirin is superior to aspirin, and clopidogrel is equivalent to aspirin, therefore dipyridamole+aspirin must be superior to both aspirin and clopidogrel. Based upon this logic, for years, stroke neurologists considered dipyridamole+aspirin (Aggrenox) the antiplatelet of choice for secondary stroke prevention. Then in 2008, the results of a trial comparing dipyridamole+aspirin to clopidogrel (the largest stroke prevention trial to date) were released. Surprisingly, there was no significant difference [103]. The decision of which antiplatelet to use should be individualized. Patients who are unable to tolerate aspirin because of GI side effect may benefit from clopidogrel. Patients suffering headaches because of dipyridamole may benefit from aspirin or clopidogrel.

Many stroke patients presenting to the hospital are often already prescribed and taking an antiplatelet agent. A common practice is to change the antiplatelet prior to discharge, on the assumption that the current antiplatelet was ineffective. For example, if a patient has a stroke on aspirin, they are changed to clopidogrel on discharge, because they have "failed" aspirin therapy. If antiplatelet agents prevented 100% of recurrent strokes, then this would be acceptable. But just because a patient was taking aspirin and has a vascular event, this does not mean that the patient did not benefit from antiplatelet therapy. There is no clear data to support the common practice of changing antiplatelet therapy in patients presenting with ischemic stroke [104]. Platelet function testing can determine the aggregation responses to arachidonic acid (aspirin mediated) or ADP (clopidogrel mediated). In one study, 43% of patients were found to be nonresponders to aspirin and 35% for clopidogrel. A subset of patients had their antiplatelet therapy modified, and interestingly these patients had higher morbidity compared to patients in which the treatment was not modified [105]. Because the clinical significance of platelet aggregation testing is uncertain, it is not recommended at this time [104].

Dissections of the carotid and vertebral arteries are common causes of stroke or TIA in the young. Often they are due to trauma but can also occur spontaneously or with minor

injuries such as vomiting or coughing [106]. Despite the prevalence, the optimal strategy for prevention is unknown. Either antiplatelet agents or anticoagulation is reasonable. Patient with recurrent events despite medical therapy should be considered for endovascular or surgical treatment [104]. Dissections usually heal over time, and most neurologists will repeat vascular imaging in 3–6 months and re-evaluate treatment. Long-term treatment is not typical.

During the inpatient evaluation, extracranial carotid artery disease is frequently found in stroke patients. Atherosclerotic disease of the carotid artery tends to affect the internal carotid artery (ICA) near the bifurcation of the common carotid into the internal and external carotid arteries. A lesion is considered symptomatic if the stroke or TIA is on ipsilateral hemisphere. If there is no stroke on the side of the stenosis, then the lesion is considered asymptomatic. The decision to potentially intervene is based upon three factors: (1) degree of stenosis, (2) symptomatic vs. asymptomatic, and (3) sex of the patient. If the ICA stenosis is less than 50%, there is no benefit to intervention, and nothing further is required. Consultation with a vascular surgeon is recommended if the following criteria are met – men with symptomatic stenosis of 50–99%, women with symptomatic stenosis of 70–99%, and men with asymptomatic stenosis of 60–99% [107]. No studies have shown a clear benefit for women with asymptomatic stenosis. Revascularization is also not recommended when the carotid is completely occluded. However, even patients who are not candidates for revascularization may benefit from additional counseling by a specialist.

Two main options exist for carotid revascularization, carotid endarterectomy (CEA) and carotid artery stenting (CAS). In a CEA, an incision is made in the neck exposing the ICA. The artery is opened and the plaque cleaned out by hand. In recent years carotid artery stenting (CAS) has become another available option. This is done endovascularly, similar to cardiac stenting. The procedures are essentially equivalent. There is some evidence that patients over the age of 70 may benefit more from CEA and younger patient from CAS [108]. The choice of intervention is mainly dependent upon referral patterns and physician preference. No intervention is of proven benefit in extracranial vertebrobasilar disease. Patient with recurrent events despite medical management should be considered for endovascular stenting or other surgical procedures even though the data is lacking [104]. Routine preventive therapy as discussed elsewhere is still recommended for all patients with atherosclerotic disease. The timing of revascularization is dependent upon multiple factors such as the size of the stroke, presence of hemorrhage, and degree of stenosis. In general, the recommendation is that revascularization be performed within 2 weeks of the stroke [30].

Intracranial atherosclerotic disease is also frequently encountered in ischemic stroke patients. Patients with >50% symptomatic intracranial stenosis should be treated with aspirin, antihypertensives with goal SBP < 140 mmHg, and high-intensity statin treatment. Clopidogrel 75 mg daily is often added as well [104]. Dual antiplatelet therapy is continued for about 90 days at which point the patient is switched to a single agent. Intracranial stenting is not recommended because of a higher risk of stroke and death [109]. Intracranial stenting or angioplasty is considered investigational in patients with recurrent symptoms despite maximal medical therapy. Anticoagulation is no longer recommended for intracranial atherosclerotic disease [110].

Occasionally, stroke patients admitted to the hospital are started on heparin to decrease the risk of neurologic deterioration and recurrent stroke. Several studies have shown no benefit of routine anticoagulation [3]. Antiplatelet therapy remains preferred over anticoagulation to prevent recurrent stroke, except in certain circumstances.

The most common indication for anticoagulation in ischemic stroke patients is atrial fibrillation (AF). AF is the most common cardiac arrhythmia in the elderly [50]. Clinical trials have consistently shown a benefit to anticoagulation over placebo, aspirin, and aspirin plus clopidogrel in ischemic stroke patients [111–113]. The goal INR is 2.0–3.0. In patients not eligible for warfarin, antiplatelet therapy still reduces stroke risk. Approximately 10% of stroke patients will have new-onset AF detected during their hospital admission, but longer outpatient monitoring protocols have uncovered even more cases of occult AF [114–116]. In patients with acute ischemic stroke or TIA without a clear cause, prolonged rhythm monitoring is very reasonable [104].

Other indications for anticoagulation in ischemic stroke patients are acute MI with LV thrombus, rheumatic mitral valve disease, mechanical prosthetic heart valves, or bioprosthetic heart valves. Cardiac conditions in which anticoagulation or antiplatelet therapy is appropriate are dilated cardiomyopathy with a low EF and mitral regurgitation due to mitral annular calcification [50]. In addition, patients with arterial dissection are often placed on warfarin for 3–6 months, although data to support this practice is lacking [50].

The choice of medication to achieve therapeutic anticoagulation should be individualized. Warfarin, apixaban, dabigatran, rivaroxaban, etc. are all reasonable choices. Cost, tolerability, patient preference, drug interactions, and renal function should all be incorporated into the decision. Often we run into similar issues with anticoagulation as we do with antiplatelets. Patients can present with ischemic stroke despite therapeutic anticoagulation with warfarin or a newer agent. Options in this situation would be to either add antiplatelet therapy to anticoagulation or switch the anticoagulant. The addition of aspirin to warfarin has been shown to increase risk of major bleeding with no significant reduction

in ischemic events [117]. An exception would be patient with AF and coronary artery disease, where antiplatelet therapy may be beneficial [99]. No studies that show a benefit to switching the anticoagulation in patients with ischemic events despite therapeutic anticoagulation, although this is often done as an emotional decision with good intentions. Such patients may be candidates for left atrial appendage closure.

The timing of when to start anticoagulation is an important but understudied part of poststroke care. The secondary prevention benefits of anticoagulation should be weighed against the increased risk of hemorrhagic conversion. Based upon available evidence, the ACCP recommends starting anticoagulation within 14 days of acute ischemic stroke [118]. In patients with a high risk of hemorrhagic conversion, it is reasonable to delay anticoagulation beyond 14 days. More studies are needed to identify subgroups of patients who may benefit from urgent anticoagulation.

Recently multiple trials have shown that percutaneous closure of the left atrial appendage with the Watchman™ device may be superior to warfarin to prevent ischemic strokes with a lower risk of hemorrhage [119–121]. The device may also be beneficial in patients with AF who are not candidates for anticoagulation [122]. Further study is ongoing, and patients with AF should be evaluated by cardiology to determine if the patient is a candidate.

Anticoagulation with warfarin has been shown to be superior to antiplatelet therapy (aspirin alone and aspirin+clopidogrel) in AF [123, 124]. However, patients with AF who are not candidates for anticoagulation should be treated with antiplatelet therapy. Aspirin has been shown to reduce the risk of strokes in AF [125, 126]. The combination of aspirin and clopidogrel further lowers the risk of ischemic events, but there is increased risk of hemorrhage, and therefore there is no significant difference between the two options [127, 128].

18.8 Summary

Ischemic stroke patients typically present with sudden onset of focal neurologic symptoms that follow a recognized neuroanatomic pattern. Every patient should get neuroimaging in the ER, usually a non-contrast CT, mainly to exclude hemorrhage. Ischemic strokes will appear on CT a few hours after symptom onset.

In patients with acute ischemic stroke, the time of onset is critical. IV tPA is recommended for acute ischemic stroke within 4.5 h of symptom onset. Intra-arterial therapy is beneficial in patients with large vessel occlusion within 6 h of onset.

The management of hypoxia, fever, and hyperglycemia is important and should not be overlooked. Permissive hypertension for the first few days may help optimize cerebral perfusion. Neuroimaging during the inpatient stay provides valuable information about stroke size and location. CT is often used. MRI has many advantages over CT, as it can distinguish acute from chronic infarcts and small strokes that are often missed by CT. Stroke patients should receive vascular imaging. Carotid ultrasound is a minimum, but CTA or MRA is preferred since these modalities allow for noninvasive imaging of the entire vasculature of the head and neck. The gold standard remains invasive cerebral angiography. Echocardiography is recommended to evaluate for cardiac sources of emboli.

Significant inpatient complications of ischemic stroke are cerebral edema, hemorrhagic transformation, and seizures. Decompressive hemicraniectomy improves morbidity and mortality in large hemispheric strokes when done within 48 h of large ischemic strokes.

Management of blood pressure, glucose, cholesterol, smoking, and obesity is much more effective than antiplatelet therapy for stroke prevention. Antiplatelets are generally indicated for ischemic stroke prevention. Carotid revascularization should be considered in men with symptomatic stenosis (50–99%) and women with symptomatic (70–99%) stenosis. Anticoagulation should be reserved for patients with conditions such as atrial fibrillation and mechanical heart valves.

- Control of risk factors such as hypertension, hyperglycemia, hyperlipidemia, smoking, alcohol, and obesity is the most effective method to prevent recurrent stroke.
- Antiplatelet therapy is indicated in most patients with ischemic stroke.
- Carotid revascularization with CEA or CAS should be considered in men with symptomatic stenosis of 50–99% and women with 70–99% stenosis.
- Patient with intracranial atherosclerotic disease should be treated with aspirin, clopidogrel, antihypertensives, and high-dose statin therapy.
- Indications for anticoagulation include atrial fibrillation and prosthetic heart valves.

List 4 Additional Inclusion and Exclusion Criteria of Patients with Acute Ischemic Stroke Who Could Be Treated Within 3–4.5 h from Symptom Onset

Inclusion Criteria

Diagnosis of ischemic stroke with measurable neurologic deficit

Last seen normal within 3–4.5 h before beginning treatment

Relative Exclusion Criteria

Age > 80 years

Severe stroke (NIHSS > 25)

Taking oral anticoagulant regardless of INR

History of both diabetes and ischemic stroke

18.9 Case Studies

18.9.1 Case Study #1

A 60-year-old African-American male presents to the emergency room with acute onset of left-sided weakness and numbness upon awakening at about 6 am. He has a past medical history of diabetes and hypertension. Medications are aspirin, HCTZ, and metformin. Vital signs are unremarkable except for a BP of 170/95. On examination he has a left facial droop and dysarthria. Cranial nerves are otherwise intact. He is able to raise his left arm and leg off the bed, but they drift to the bed in a few seconds. He has impaired sensation too on the left (NIHSS 7). CT of the head shows a hypodensity in the right internal capsule suspicious for acute stroke. Laboratory studies are normal. He is outside the window for IV tPA because he was last seen normal at 10 pm the night before when he went to bed.

He is admitted for further workup and treatment. His total cholesterol is 180 mg/dL, and LDL is 110 mg/dL. He has an MRI and MRA, which reveal an acute infarct in the right internal capsule and 60% stenosis of his right internal carotid artery. Transthoracic echocardiography reveals an EF of 55% and mild mitral regurgitation. During the next few days in the hospital, his sensation returns to normal, and his strength improves to only subtle weakness on his left side. He is started on antihypertensives. Since he is thought to have an atherosclerosis-related stroke, he is started on statin therapy.

Because the RICA stenosis meets the criteria (>50% symptomatic stenosis), he consult a vascular surgeon, who feels he is a candidate for CEA. He undergoes the CEA next week without complications.

18.9.2 Case Study #2

An 80-year-old Caucasian female has acute onset of aphasia and right-sided weakness at 6 pm while eating dinner. The onset is witnessed by the family. Her past medical history is hypertension and hyperlipidemia. Medications are aspirin, atorvastatin, and metoprolol. Upon examination her vital signs are normal except for BP 180/100. She has a left gaze deviation, right homonymous hemianopsia, and right facial droop. She is alert and follows commands but is unable to speak. She has no movement or response to pain on his right side (NIHSS 18). CT of the head shows small vessel ischemic disease but no acute intracranial abnormality.

She is a candidate for IV tPA and treatment is started at 7:30 pm. She is then sent for a CTA that shows an occlusion of the LMCA. The neuro-interventionalist on call is notified, and she is taken to cerebral angiography, which confirms the thrombus, and it is removed successfully with a stent retriever. She is admitted to the ICU; her metoprolol and aspirin are held. Overnight telemetry shows paroxysmal atrial fibrillation. MRI and MRA the next day show patchy areas of acute infarction in the left hemisphere.

During her hospital stay, her visual fields improve, and she is able to raise her right arm and leg off the bed. She is discharged to inpatient rehabilitation. Two weeks after the stroke, she is started on anticoagulation for atrial fibrillation.

18.9.3 Case Study #3

A 64-year-old female presents with acute onset of left-sided weakness. Past medical history is type 2 diabetes, hypertension, and hyperlipidemia. She presents outside the window for IV tPA. MRI confirmed a stroke in the subcortical white matter in the right hemisphere. MRA revealed a stenosis in the right middle cerebral artery estimated to be about 70%. She was started on aspirin 81 mg daily, clopidogrel 75 mf daily, and Lipitor 80 mg daily. She was discharged to acute rehab.

She comes back in to the office in 1 month and is doing well. She follows up again in about 2 months, and she is switched to single antiplatelet therapy with clopidogrel alone since she has completed 90 days of dual antiplatelet therapy for intracranial atherosclerotic disease.

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Aortic Aneurysms

19

Nicole M. Bhave, Eric M. Isselbacher, and Kim A. Eagle

19.1 Introduction

Aortic aneurysms are relatively common, and their management frequently involves cardiologists, primary care physicians, and surgeons. It is therefore important not only to understand the basic pathological mechanism and current treatment recommendations but also to recognize the different variants and their complications and to know the indications for aortic repair. This chapter will focus on the pathogenesis of aortic aneurysm, different types and classifications, prevalence and mortality associated with it, and current medical and surgical management guidelines.

19.2 Aorta

The aorta begins at the annulus of the aortic valve and ends at the bifurcation into the common iliac arteries. Anatomically, the aorta is divided into thoracic and abdominal components. The thoracic aorta is further divided into the ascending, arch, and descending segments and the abdominal aorta into the suprarenal and infrarenal segments (Fig. 19.1) [1]. The aortic arch gives rise to the brachiocephalic, left common carotid, and left subclavian arteries.

N. M. Bhave
Division of Cardiovascular Medicine, University of Michigan Medical School, Ann Arbor, MI, USA

E. M. Isselbacher
Cardiology Division and Department of Medicine, Massachusetts General Hospital, Boston, MA, USA

K. A. Eagle (✉)
Division of Cardiovascular Medicine, Cardiovascular Center, University of Michigan Medical School, Ann Arbor, MI, USA
e-mail: keagle@med.umich.edu

The aorta, the largest and strongest artery in the body, is composed of three layers: the intima (thin inner layer), media (thick middle layer), and adventitia (thin outer layer). In adults, the aortic diameter is approximately 3 cm in the ascending portion, 2.5 cm in the descending portion, and 1.8–2 cm in the abdomen. The diameter of the normal aorta does increase slightly with age [2]. Its diameter also varies with body size and gender.

19.3 Aortic Aneurysms

The term *aneurysm* refers to a pathological dilatation of one or more segments of a blood vessel. A *true aneurysm* involves all three layers of the vessel wall and is distinguished from a *pseudoaneurysm*, in which the dilated portion extends outside the aortic media [3]. Dilatation is considered to be present with a diameter above the norm for age and body surface area. The term aneurysm has been defined as a 50% increase above the expected normal diameter of that given arterial segment, but no precise size cutoff is currently well enough accepted to define thoracic aortic aneurysms [4]. The reported incidence of aortic aneurysms is increasing, likely due to improvements in screening and advances in imaging techniques. Aneurysms are usually described in terms of their location, size, morphological appearance, and origin. The morphology of an aortic aneurysm is typically either *fusiform* (symmetrical dilatation involving the full vessel circumference) or *saccular* (localized dilatation involving only one side). Aortic aneurysms are also classified according to location, i.e., abdominal versus thoracic. Aneurysms of the descending thoracic aorta are often contiguous with infradiaphragmatic aneurysms and are referred to as *thoracoabdominal aortic aneurysms*. The etiology, natural history, and treatment guidelines of aortic aneurysms differ according to the location (thoracic versus abdominal), and, consequently, they will be discussed separately.

P. P. Toth, C. P. Cannon (eds.), *Comprehensive Cardiovascular Medicine in the Primary Care Setting*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-319-97622-8_19

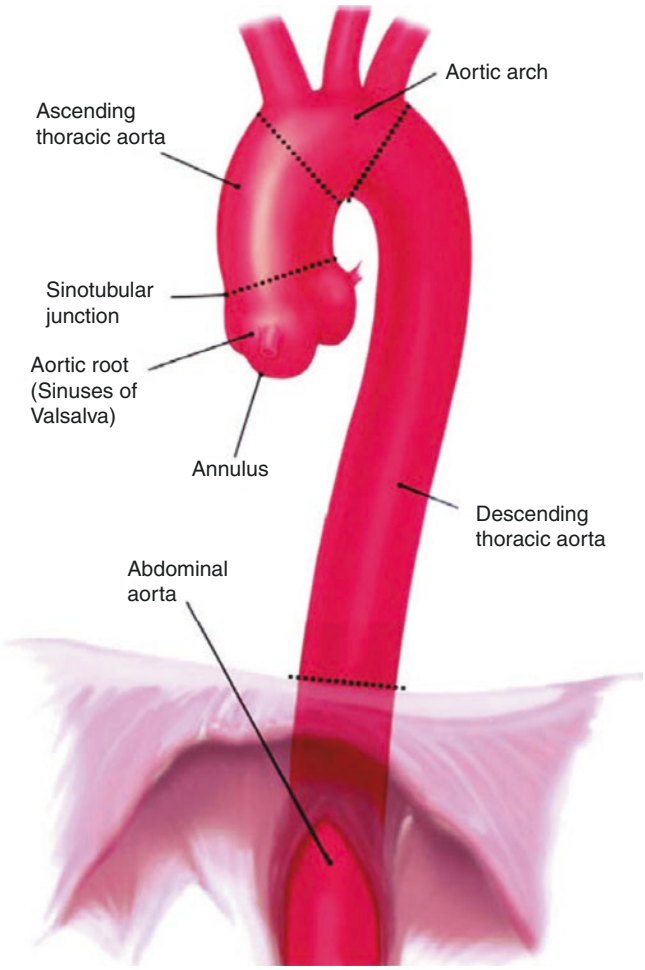

Fig. 19.1 Anatomy of thoracic and proximal abdominal aorta [1]

19.4 Thoracic Aortic Aneurysm

Thoracic aortic aneurysms are much less common than abdominal aortic aneurysms; the incidence is estimated to be around 4.5 cases per 100,000 patient-years [5]. They are detected most commonly in the sixth and seventh decades of life; males are affected approximately two to four times more often than females [6]. In the case of aortic root aneurysms, patients are often younger (age 30–50 years), with a 1:1 sex ratio [5]. Thoracic aneurysms are classified by the segment of aorta involved: aortic root, ascending aorta, arch, or descending aorta (Fig. 19.1). In a contemporary series, the reported frequency of involvement of the thoracic aortic segment was 60% for the aortic root and/or ascending aorta, 40% for the descending aorta, 10% for the arch, and 10% for the thoracoabdominal aorta (with some involving >1 segment) [1].

19.4.1 Etiology and Pathogenesis

Aortic aneurysms result from conditions that cause degradation or abnormal production of the aortic wall's structural components (elastin and collagen). The causes of aortic aneurysms may be broadly categorized as degenerative diseases, inherited or developmental diseases, infections, vasculitides, and trauma (Table 19.1) [3]. Aneurysms of the ascending thoracic aorta most often result from medial degeneration (previously termed *cystic medial necrosis*), in which degeneration of elastic fiber and collagen appears histologically as empty spaces filled with mucoid material [1]. Medial degeneration leads to circumferential weakening and dilatation of the aortic wall, which in turn results in the development of fusiform aneurysms involving the ascending aorta and/or the aortic root. When such aneurysms involve the aortic root, the anatomy is often referred to as *annuloaortic ectasia* [1].

Medial degeneration occurs normally to some extent with aging, and the process is accelerated by hypertension [11]

Table 19.1 Etiology of thoracic aortic aneurysms [1, 3]

Causes	Remarks
Hereditary fibrillinopathies	
Marfan syndrome	Classic disorder with medial degeneration due to mutations in the fibrillin-1 gene. Aortic aneurysms typically occur at the aortic root level but can occur throughout the aorta. Accounts for 6% of aortic dissections
Ehlers–Danlos syndrome	Defects in type III collagen cause hyperelasticity; aortic root disease is uncommon
Loeys–Dietz syndrome	Autosomal-dominant disorder causing disruptions in TGF-β signaling; patients have early-onset, rapidly progressive aortic aneurysmal disease and are at risk for aortic dissection at smaller aortic diameters than typical for aneurysms of other etiologies
Familial TAA syndrome	Autosomal-dominant mode of inheritance but marked variability in expression and penetrance; males present at a younger age
Hereditary vascular disease	
Bicuspid aortic valve	Approximately 40–50% have dilatation of the aortic root or ascending aorta; medial degeneration regarded as the main cause [7–9]
Vascular inflammation	
Takayasu arteritis	Results in aortic dilatation in 15% of cases; occurs mostly in women
Syphilis	Spirochetal infection of the aortic media causes obliterative endarteritis of the vasa vasorum; currently rare due to antibiotic treatment
Giant cell arteritis	Typically affects the temporal or cranial arteries but can also produce thoracic aortic aneurysms (~12%), often years after the initial vasculitis diagnosis [10]
Ankylosing spondylitis	Associated with inflammation of fibrocartilage, potentially directed at tissues rich in fibrillin-1
Behçet's disease	Leads more to local aneurysm formation and perforation than dissection
Kawasaki syndrome	Coronary artery aneurysms are typical, but also other arterial segments can be involved; more circumscript aneurysm formation
Deceleration trauma	
High-speed accidents	Results in partial or complete transection of the aorta (usually at the aortic isthmus) that produces a pseudoaneurysm

but is particularly prevalent in patients with Marfan syndrome, Ehlers–Danlos syndrome type IV, congenital bicuspid aortic valves, and familial thoracic aortic aneurysm syndromes [1]. Marfan syndrome, the prototype of medial degeneration, is an autosomal-dominant heritable disorder of connective tissue caused by mutations in the gene for fibrillin-1, a structural protein that is the major component of microfibrils of elastin. More than 1800 mutations have been identified in this large gene [12]. There is also a strong association between bicuspid aortic valve and ascending thoracic aortic aneurysms, and medial degeneration has been found to be the underlying cause of the aortic dilatation [5]. In Loeys–Dietz syndrome, medial degeneration is more diffuse than in Marfan syndrome, and significantly more collagen deposition occurs [13].

19.4.2 Clinical Manifestations

Most thoracic aortic aneurysms are asymptomatic and are therefore discovered incidentally on imaging studies (chest radiograph, CT scan, or echocardiogram) ordered for other indications [14]. Symptomatic thoracic aortic aneurysms may present either with a local mass effect or with a vascular consequence of the aneurysm. Vascular consequences include dilatation of the aortic root or ascending aorta that results in incomplete aortic valve closure secondary to leaflet tethering, which in turn results in aortic regurgitation; the aortic regurgitation can produce a diastolic murmur detectable on physical examination or, if severe, congestive heart failure [5]. A local mass effect by aneurysms may cause symptoms of compression or erosion of adjacent tissue, such as compression of the trachea or mainstem bronchus (causing cough, dyspnea, wheezing, or recurrent pneumonitis), compression of the esophagus (causing dysphagia), or compression of the recurrent laryngeal nerve (causing hoarseness) [1].

Rarely, chest or back pain may occur with non-dissecting aneurysms as a result of stretching of the aortic tissue, direct compression of other intrathoracic structures, or erosion into adjacent bone [1]. The most feared consequences of thoracic aortic aneurysms are aortic dissection or rupture, both of which are potentially lethal. Aortic dissection is typically accompanied by the sudden onset of severe thoracic pain, usually felt retrosternally in case of ascending aortic involvement or posteriorly, between the scapulae, when the descending aorta is involved. Acute aneurysm expansion, or subacute contained rupture, which may herald frank rupture, can cause similar pain [3].

19.4.3 Diagnosis

A variety of noninvasive and invasive methods are useful for the diagnosis and evaluation of thoracic aortic aneurysms.

19.4.3.1 ECG

An ECG is an important test, especially in patients with chest pain, and may help differentiate pain from acute angina/myocardial infarction versus non-coronary pain.

19.4.3.2 Chest Radiography

Chest radiography may be the first test to suggest the diagnosis of a thoracic aortic aneurysm. Most aneurysms are characterized by widening of the mediastinal silhouette, enlargement of the aortic knob, or tracheal deviation [15]. In the PA view, an enlarged ascending aorta may produce a convex contour of the right superior mediastinum (Fig. 19.2). In the lateral view, there may be a loss of the retrosternal air space. Aneurysms confined to the aortic root can be obscured by the cardiac silhouette and may not be evident on a chest radiograph [5]. Additionally, smaller aneurysms and even some large ones may not produce any abnormalities on chest radiography, so this technique cannot be used to exclude the diagnosis of aortic aneurysm [1]. Similarly, one cannot typically distinguish whether an enlarged aortic silhouette represents a tortuous aorta or the presence of an aneurysm. Consequently, an enlarged aortic silhouette on chest radiography should prompt a further workup (e.g., CT scan or MRI) in the appropriate clinical setting [1].

19.4.3.3 CT, MRA, and Aortography

Contrast-enhanced computed tomographic angiography (CTA), magnetic resonance angiography (MRA), and conventional invasive aortography are sensitive and specific tests for the assessment of aneurysms [16]. However, given the relatively invasive nature of aortography, CTA and MRA are preferred in most cases to define both aortic and branch vessel anatomy (Fig. 19.3). Among patients with known bicuspid aortic valves, the 2010 ACC/AHA guidelines recommend that the aortic root and ascending aorta be

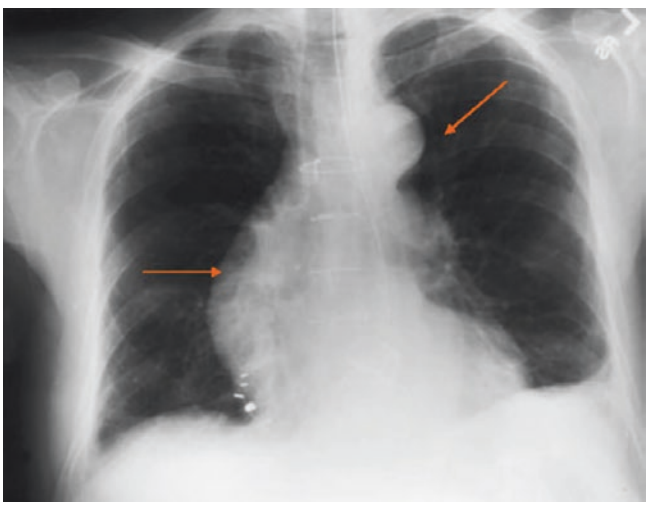

Fig. 19.2 Chest radiograph of a patient with a very large aneurysm of the ascending thoracic aorta [4]

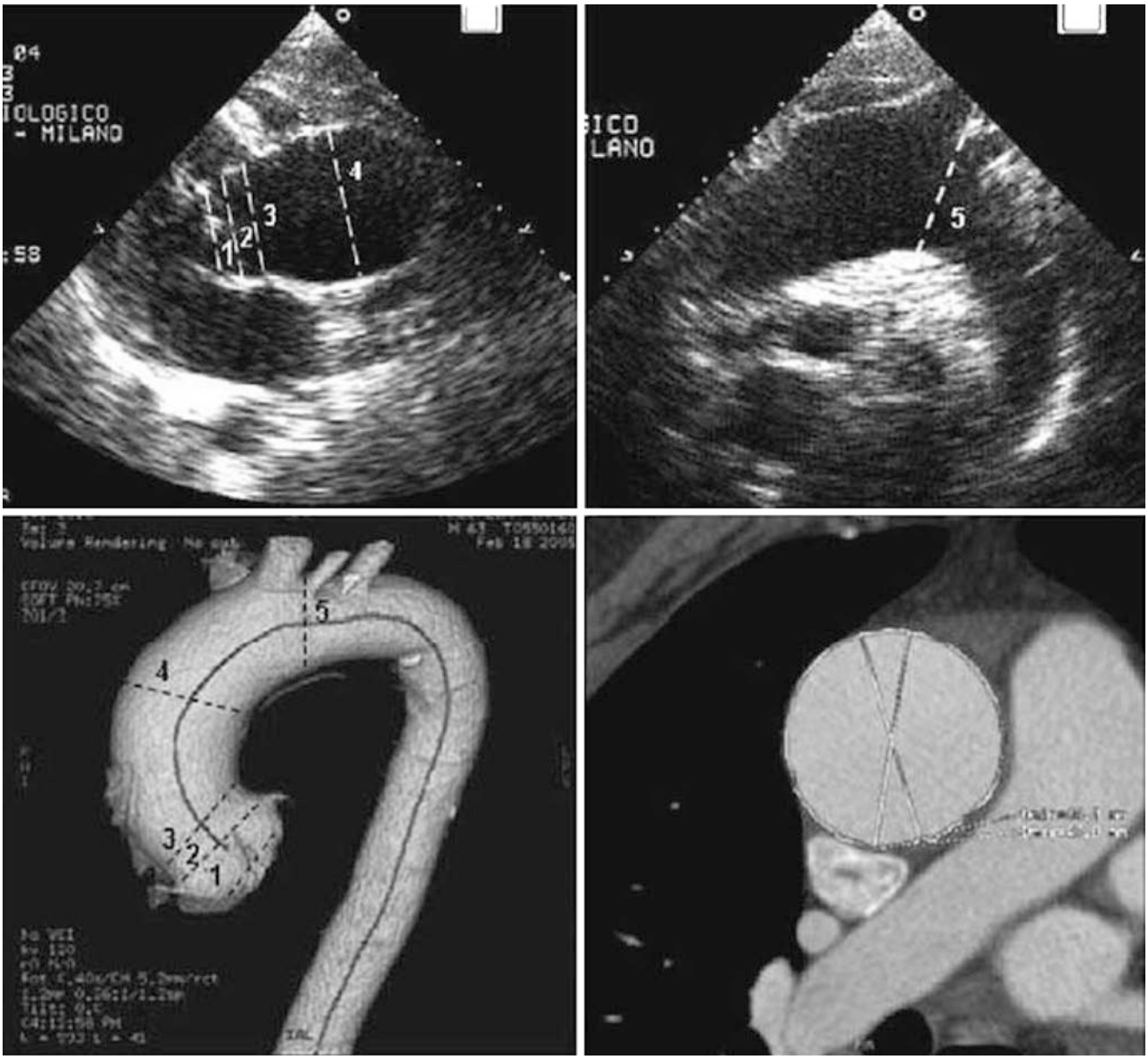

Fig. 19.3 Example of measurement of the ascending aortic dimensions on transthoracic echocardiography (upper panels) and CTA (lower panels; [17])

assessed with imaging [18]. Every patient with an aortic aneurysm detected by echocardiography or suspected based on chest radiography should undergo an initial CTA or MRA examination of the entire aorta (thoracic and abdominal), because multiple aneurysms occur in 13% of patients diagnosed with a thoracic aneurysm [3].

19.4.3.4 Echocardiography

Transthoracic echocardiography (TTE) is effective for imaging the aortic root and proximal ascending aorta (Fig. 19.3), but it does not consistently visualize the mid or distal ascending aorta well, nor does it visualize the descending aorta well [1, 16, 17]. Therefore, after baseline CTA or MRA, patients with Marfan syndrome and bicuspid aortic valve can then be followed by serial evaluation with TTE on a yearly basis with repeat CTA or MRA less frequently if the CTA/MRA shows normal aortic size and morphology beyond the aortic root [1]. Transesophageal echocardiography (TEE) can image almost the entire thoracic aorta quite well, although there is typically a blind spot in the distal ascending aorta and proximal arch. However, given that TEE is a semi-invasive procedure, it is not favored for the routine imaging of those with stable (non-dissecting) thoracic aneurysms [3].

19.4.4 Natural History

The natural history of thoracic aortic aneurysms is related to location and the etiology, which in turn predict the rate of growth and propensity for dissection or rupture. Therefore, it is appropriate to image aneurysms serially to document size and growth and perform surgery when aneurysms are large enough to be considered at significant risk for rupture and/or dissection [1, 3]. Studies focusing on the natural history of thoracic and thoracoabdominal aneurysms have found that the odds of rupture are increased by chronic obstructive pulmonary disease (COPD) (RR, 3.6), advanced age (RR, 2.6 per decade), and aneurysm-related pain (RR, 2.3) [19].

Davies et al. reported a mean growth rate of 0.1 cm/year for the thoracic aortic aneurysms measuring 3.5 cm [20]. In this longitudinal study of more than 31 months, they found that the rate of growth was higher for aneurysms of the descending aorta versus ascending aorta, for dissected aneurysms versus non-dissected aortas, and for those with Marfan syndrome versus those without. In a multivariate logistic regression analysis, initial aneurysm diameter, Marfan syndrome, and female gender were found to be significant predictors of dissection or rupture. Initial aneurysm diameter is the single most important predictor of dissection, rupture, or death in several studies (Table 19.2) [19–22]. The critical point at which rupture or dissection occurred was at 6 cm for the ascending aorta and 7 cm for the descending aorta. Rupture or dissection occurs at smaller sizes in patients with Marfan and Loeys–Dietz syndromes [21, 23]. Accordingly, it is important to intervene before an aneurysm reaches this critical point (Table 19.2).

19.5 Management

19.5.1 Surgical Treatment

Symptomatic aortic aneurysms require surgery regardless of the size. Prophylactic surgical repair is often recommended to prevent the morbidity and mortality associated with aneurysm dissection/rupture (Table 19.3). Significant risks are associated with thoracic aortic surgery, particularly in the arch and descending aorta. Mortality rates are in the range of 3–5% for elective surgical repair [25, 26] and 4–29% in the setting of emergent surgical repair for type A dissection [27].

Table 19.2 Complications based on aortic size [21]

Aortic size				
Yearly risk	>3.5 cm	>4 cm	>5 cm	>6 cm
Rupture (%)	0.0	0.3	1.7	3.6
Dissection (%)	2.2	1.5	2.5	3.7
Death (%)	5.9	4.6	4.8	10.8
Any of the above (%)	7.2	5.3	6.5	14.1

Therefore, the decision to operate is determined by the expected natural history of the aneurysm and the anticipated risk of the proposed surgical procedure. For most ascending thoracic aortic aneurysms of ≥5.5 cm in diameter and/or descending thoracic aortic aneurysms of 6 cm or greater, surgery is indicated (Table 19.3) [1, 2, 5, 18, 20, 21]. Among those with an increased operative risk (e.g., the elderly or those with significant comorbidities), the threshold for recommending surgery is raised (often by 1 cm) [22]. Similarly, among patients who are at increased risk of aortic dissection or rupture (e.g., due to Marfan syndrome or a familial thoracic aortic aneurysm syndrome), aortic repair may be recommended at smaller diameters.

Table 19.3 Criteria for resection of thoracic aortic aneurysms [18, 22, 24]

Rupture
Acute aortic dissection
Ascending aortic involvement requires urgent surgical repair
Descending aortic involvement requires a complication-specific approach
Symptomatic states
Pain consistent with aortic origin and unexplained by other causes
Compression of adjacent organs, especially the trachea, esophagus, or left mainstem bronchus
Significant aortic regurgitation in conjunction with ascending aortic aneurysm
Documented enlargement
Growth ≥0.5 cm/year or substantial growth and aneurysm is rapidly approaching absolute size criteria
Absolute size (cm)
Marfan syndrome
Root/ascending: surgical repair at a diameter of ≥5.0 cm or less if a family history of dissection; consider prophylactic replacement if diameter exceeds 4.0 cm in a female patient contemplating pregnancy
Descending: endovascular stent grafting if feasible at 5.5 cm
Thoracoabdominal aneurysm: open repair at 6.0 cm or less if endovascular options limited
Loeys–Dietz: 4.2 cm (measured by TEE), 4.4–4.6 cm (measured by CT/MRA)
Bicuspid aortic valve
Root/ascending aortic aneurysm without surgical valve disease: surgical repair at 5.5 cm; consider at 5.0 cm if additional risk factors for dissection present or if patient is at low risk for surgery and surgery is performed by an experienced team at a center of expertise
Root ascending aortic aneurysm with surgical valve disease: valve surgery with concomitant aortic repair if aortic diameter ≥4.5 cm
Isolated thoracic aortic aneurysm in the absence of bicuspid aortic valve or genetic syndrome
Root/ascending or arch: ≥5.5 cm (also consider if aortic root or ascending aortic area in cm^2 divided by the patient's height in meters exceeds 10)
Descending: endovascular stent grafting if feasible at 5.5 cm
Thoracoabdominal aneurysm: open repair at 6.0 cm if endovascular options limited

19.5.1.1 Open Surgical Repair Versus Endovascular Stent Graft

Choice of aortic repair technique depends on the location of the aneurysm and the distal extent of aortic involvement, as well as the underlying pathology, patient comorbidities and life expectancy, and desired anticoagulation status. In general, patients requiring open surgical repair of an ascending thoracic aneurysm should undergo coronary angiography and echocardiography to determine whether concomitant coronary revascularization or aortic valve and root replacement or repair is warranted [18]. Open thoracic aortic aneurysm repair requires cardiopulmonary bypass to support the circulation distal to the aneurysm. The aneurysmal segment is replaced with a prosthetic Dacron® tube graft of appropriate size.

Endovascular stent-graft implantation, or thoracic endovascular aortic repair (TEVAR), is an alternative approach for the repair of descending thoracic aneurysms in selected patients with favorable aortic anatomy. This technique has the advantage of being far less invasive than open surgery, with potentially fewer postoperative complications and lower morbidity [1]. The comparison of endovascular stent grafting with open surgical repair compiled for FDA analysis showed favorable early outcomes [28], and the devices were approved in 2005 and are now widely used [4]. Although at the time of this writing, no randomized controlled trials have yet compared TEVAR with open surgery [29], a recent meta-analysis including 11 studies and 673 patients reported a technical success rate of 91% and a mortality rate of 3%, with relatively low rates of paraplegia and stroke, both approximately 3% [25]. A 2014 study based on the National Inpatient Sample, including 8967 patients undergoing elective thoracic aortic aneurysm repair, showed a significantly lower mortality rate for TEVAR versus open repair (3.6% vs. 4.5%, respectively), accompanied by lower risks of cardiac, neurologic, and respiratory complications in the TEVAR group [26].

19.5.2 Medical Management

Asymptomatic patients with aneurysms below the size threshold for surgery are initially managed medically (Table 19.3), with risk factor reduction, control of hypertension, smoking cessation, and serial imaging studies to monitor aortic growth and size. The target blood pressure is <140/90 mmHg, and it is reasonable to reduce blood pressure to lower goals (such as systolic blood pressure 105–120 mmHg) if tolerated [1, 18]. Reports of medical therapy in patients with Marfan syndrome have demonstrated that propranolol administration is associated with improvements in both aortic growth and 10-year survival [30]. Whether these benefits can truly be extrapolated to the non-Marfan population with thoracic aneurysms remains unknown.

In a non-randomized evaluation of angiotensin-converting enzyme inhibitors, Yetman and colleagues [31] noted a decrease in aortic growth for Marfan patients receiving enalapril compared with those receiving beta-blockers. Losartan, an angiotensin II type I receptor (AT1) blocker, was shown to prevent aortic aneurysm in a mouse model of Marfan syndrome, possibly secondary to its capacity to reduce transforming growth factor beta (TGF-β) expression and signaling [32]. Subsequently, a randomized trial of losartan versus the beta-blocker atenolol among children and young adults with Marfan syndrome with aortic root dilatation showed no significant difference between the treatments; in both groups, aortic root size relative to body surface area decreased [33]. A 2015 placebo-controlled trial of losartan versus placebo in children and adults with Marfan syndrome showed no significant effect of losartan on aortic root dilatation [34], although a 2013 randomized trial in adults showed that losartan slowed aortic root growth when added to baseline therapy [35]. In both studies, >80% of patients were on beta-blockers. There is some experimental evidence that HMG–CoA reductase inhibitors (statins) may potentially have a protective effect in thoracic aortic aneurysm [1, 36], but in the clinical literature, the effect of statins on aneurysm expansion and overall mortality remains unclear [37, 38]. However, treatment with a statin is recommended in patients with a significant burden of aortic atherosclerosis, particularly if the aortic arch is involved, in the interest of stroke prevention [21].

Associated cardiovascular risk factors should be aggressively controlled, and activities and lifestyle should be modified if needed. Generally, patients with thoracic aortic aneurysms should avoid heavy lifting, pushing, and pulling activities that involve the Valsalva maneuver [21]. Patients should be informed about potential acute symptoms and instructed how to respond appropriately. Pregnancy is discouraged in patients with Marfan syndrome, especially if the aortic root diameter exceeds 40 mm. In the case of pregnancy in a female Marfan patient with an aortic root diameter of 40 mm or greater, close clinical and echocardiographic surveillance is necessary as well as treatment with beta-blockers, and prophylactic repair of an aorta >40 mm in a Marfan patient planning a pregnancy may be considered [18, 39].

The natural history of thoracic aortic aneurysm is generally that of expansion, so almost all patients require regular surveillance imaging. It is appropriate to obtain a first follow-up imaging study after 6 months and, if the aneurysm is stable, subsequent imaging studies on an annual basis or perhaps less frequently if the aneurysm has been stable for several years. However, should there be a significant increase or rapid growth in aortic diameter, the interval between imaging studies should be decreased to 3 or 6 months [1]. One suggested protocol for surveillance is given in Table 19.4 [3]. For younger patients and patients

Table 19.4 Suggested imaging surveillance for patients with thoracic aortic aneurysms [40]

Aortic pathology	Additional initial workup	First follow-up imaging	Subsequent imaging
Newly diagnosed TAA	Echocardiography to evaluate aortic valve structure and function	CTA or MRA at 6 months	Annual CTA or MRA if stable
			Annual echocardiography if initial study demonstrated moderate to severe aortic stenosis or insufficiency
Rapidly growing TAA (assuming surgery is planned in the near future)	Echocardiography	CTA or MRA at 3 months unless indication for operation exists	CTA and MRA at 6 months if stable and then annually thereafter
	Right and left heart catheterization		CTA or MRA every 3 months if growing further
	Carotid duplex		
	Pulmonary function testing		
Residual distal aortic dissection after repair of type A dissection	None	CTA or MRA 3 months postoperatively	Annual CTA or MRA scan if stable distal aortic dimension
Known TAA in setting of pregnancy	Echocardiography	6–8 weeks with repeat echocardiography	Echocardiography every 6–8 weeks including into first 3 postpartum months
			CTA or MRA postpartum and then algorithm per rapidly growing TAA

who will be imaged frequently, MRA may be preferable to CTA because it does not involve ionizing radiation. In patients with significant renal insufficiency, the iodine-based contrast used for CTA may cause acute kidney injury. Patients with stage IV–V chronic kidney disease and patients with acute kidney injury should not receive gadolinium-based contrast for MRA, given the risk of nephrogenic systemic fibrosis [41], but non-contrast MRA can be performed in these patients. CTA may be better tolerated than MRA in patients with claustrophobia.

19.6 Abdominal Aortic Aneurysm (AAA)

The abdominal aorta is the most common site of arterial aneurysm. Since the abdominal aorta tends to be about 2 cm in diameter, a true abdominal aortic aneurysm measures 3 cm or more [4]. Given the variation in normal aortic diameter, the diagnosis of abdominal aortic aneurysm should be adjusted for age, gender, and body surface area [4]. Hence, using the diameter ratio may be better, particularly in smaller people such as women and those of short stature [42]. Similar to thoracic aortic aneurysms, abdominal aortic aneurysms are also classified according to their shape (fusiform or saccular) and the segment involved, as discussed above. Abdominal aortic aneurysms are much more common than thoracic aortic aneurysms and occur 5–10 times more frequently in males than in females. Age is an important risk factor [3]. The incidence of abdominal aortic aneurysm rises rapidly after 55 years of age in males and 70 years of age in females [1]; however, this may vary depending on the type of diagnostic imaging used, the diagnostic criteria applied, and the age and gender distribution of the population screened.

19.6.1 Etiology and Pathogenesis

Smoking is the strongest independent risk factor for abdominal aortic aneurysm, followed by older age, hypertension, hyperlipidemia, and atherosclerosis [43]; according to one study, current smokers are more than seven times more likely to have an abdominal aortic aneurysm than nonsmokers [42]. Smoking increases not only the risks of aneurysm expansion and rupture but also the risk associated with aneurysm repair. Sex and genetics are the strongest non-modifiable risk factors. Males are ten times more likely than females to have an abdominal aortic aneurysm of 4 cm or greater [1]. However, females and those with a family history of abdominal aortic aneurysm have a higher risk of rupture [3]. Race also appears to influence the prevalence of AAAs. In a Veterans Affairs Study, abdominal aneurysms occurred approximately twice as frequently in whites compared to blacks [44]. Vasculitis (such as Takayasu arteritis, giant cell arteritis, spondyloarthropathies, rheumatoid arthritis) and infectious diseases (such as tuberculosis or mycotic aneurysms) are less commonly associated with abdominal aneurysms.

Classically, degenerative atherosclerotic disease has been considered the underlying cause of abdominal aortic aneurysms, but more recent data suggest that many aneurysms form in response to altered expression patterns of tissue matrix metalloproteinases that diminish the integrity of the arterial wall [4]. Matrix metalloproteinases are enzymes that are produced by smooth muscle and inflammatory cells, can degrade elastin and collagen, and may participate in abdominal aortic aneurysm formation. There is growing evidence that atherosclerotic and inflammatory abdominal aortic aneurysms share a common underlying pathophysiology [11]. The wall of the infrarenal abdominal aorta is thinner,

has fewer adventitial vasa vasorum than the thoracic aorta, is more prone to atherosclerosis, and therefore is the most common site of abdominal aneurysm formation [42].

19.6.2 Clinical Manifestations

In most cases, abdominal aortic aneurysms are asymptomatic, expand silently, and are discovered incidentally on routine physical examination or on imaging studies ordered for other indications [1, 3]. Up to 50% of abdominal aneurysms can be recognized on plain abdominal radiographs by a calcified aneurysmal wall [42]. Younger patients are more likely to be symptomatic at the time of diagnosis [3]. In symptomatic abdominal aneurysms, pain is the typical complaint and is usually located in the hypogastrium or lower back. The usual description is steady and gnawing in nature, lasting hours to days [1, 3].

Sudden worsening of pain or development of new pain may herald expansion or impending rupture of an aneurysm, whereas frank rupture is associated with abrupt onset of back pain along with abdominal pain and tenderness [3]. Most patients have a palpable, pulsatile abdominal mass, unless they are hypotensive because of blood loss. The classic pathognomonic triad of abdominal/back pain, a pulsatile abdominal mass, and hypotension is seen in only few cases [4]. Hemorrhagic shock and its complications may ensue rapidly in cases of rupture.

19.6.3 Physical Examination

The sensitivity of physical examination to detect a pulsatile mass varies and increases with the size of the aneurysm, from 29–61% for abdominal aneurysms 3.0–3.9 cm in diameter to 76–82% for aneurysms 5.0 cm or larger [45]. Generally, it is easier to detect a pulsatile mass in a thin individual who does not have a tense abdomen and more difficult to detect in an overweight or obese patient [45]. Contrary to a once popular belief, gentle palpation of AAAs is safe and does not precipitate rupture [42].

19.6.4 Diagnosis and Sizing

A number of diagnostic imaging modalities are available for detecting and serially monitoring abdominal aortic aneurysms.

19.6.4.1 Plain Film

Fifteen to eighty-five percent of abdominal aneurysms are discovered because of incidentally discovered curvilinear aortic wall calcification on a plain abdominal radiograph that was obtained for other purposes [4]. However, it is not the current standard of care to use plain radiographic studies for screening or surveillance of aneurysms.

19.6.4.2 Ultrasonography

B-mode or real-time abdominal ultrasonography is perhaps the most practical way to screen, assess, and follow abdominal aneurysms because it is relatively inexpensive and noninvasive, and does not require the use of a contrast agent ionizing radiation [1]. Diagnostic specificity for the presence of an infrarenal aortic aneurysm is nearly 100%, with sensitivity ranging from 92 to 99% [4]. Suprarenal aneurysms may be more difficult to detect because bowel gas can obscure that portion of the aorta. Given the limited ability to visualize the extent of disease (cephalic and/or pelvic) and define the anatomy of mesenteric and renal arteries, ultrasound is insufficient for planning operative repair [3].

19.6.4.3 Computed Tomographic Angiography (CTA) Scanning and Magnetic Resonance Angiography (MRA)

CTA and MRA provide detailed information about the site, size, shape, extent, and local anatomic relationships of the aneurysm and are therefore valuable when planning abdominal aneurysm repair [4]. They are also better than ultrasonography in imaging suprarenal aortic aneurysms. Their cost, use of ionizing radiation (CTA), intravenous contrast media (CTA and MRA), and inconsistent availability (MRA) are major disadvantages that make these tests less practical for screening. Nevertheless, their high accuracy in sizing aneurysms makes them excellent modalities for serially monitoring changes in aneurysm size [1]. Because of improved techniques, their relatively noninvasive nature, and relative cost advantage over transcatheter angiography, CTA and MRA have emerged as the current "gold standards" in the preoperative and postoperative evaluation of abdominal aneurysms [46].

19.6.5 Screening

Aortic diameter can be measured accurately by ultrasound imaging in more than 97% of subjects, and screening by this method has the potential to reduce the incidence of aortic rupture [4]. The effectiveness of population-based ultrasound screening has been evaluated in several studies, often with specific targeting of high-risk groups, such as those with hypertension, coronary disease, or tobacco use. In a population-based study, the Multicenter Aneurysm Screening Study Group in the United Kingdom randomized 67,770 men aged 65–74 years to screening and non-screening groups. Patients found to have abdominal aortic aneurysms of 3 cm or greater were followed up with serial

ultrasound scans for a mean of 13 years. There were 381 aneurysm-related deaths in the control group versus 224 in the screening group, yielding an estimated cause-specific mortality reduction of 42% and all-cause mortality reduction of 3% [47]. Another study addressed the potential usefulness of repeated screening for abdominal aneurysms and reported that a normal ultrasound at age 65 effectively excludes the risk of a clinically significant aneurysm for life [48]. Current recommendations from the American College of Cardiology and American Heart Association are that men of age 60 and older with first-degree relatives with AAA, and men ages 65–75 who have ever smoked, undergo physical examination and ultrasound screening for AAA [4]. Based on a systematic review of recently published international data, the US Preventive Services Task Force (USPSTF) has recommended one-time screening for AAA by ultrasonography in men aged 65–75 years who have ever smoked. The USPSTF felt that there was insufficient evidence to recommend screening of women, but it is worth noting that only one of the four trials in their recent review enrolled any female participants [49]. A practice guideline from the Society of Vascular Surgery has recommended screening all women aged 65 years and older with a family history of AAA or personal history of smoking and all men aged 65 or older; men with family history of AAA may be screened as early as 55 years [50].

19.6.6 Natural History

The natural history of abdominal aortic aneurysms is distinguished by gradual and/or sporadic expansion in diameter and by the accumulation of mural thrombus. The major risk posed by an expanding abdominal aortic aneurysm is rupture and its associated mortality risk [1]. Among the participants in the United Kingdom Small Aneurysm Trial who suffered a ruptured abdominal aneurysm, 79 out of 103 died without abdominal aneurysm repair (25% died before reaching a hospital and 51% died at the hospital without undergoing surgery), and of those who had surgery, the operative mortality was 46%, yielding an overall 30-day survival of 11% [51]. Therefore, the goal is to prevent rupture by having patients undergoing elective aortic repair (with a mortality of only 4–6%) when aneurysms are considered to be at significant risk of rupture [1].

In a classic report, Szilagyi et al. noted that the risk for spontaneous rupture was a direct function of aneurysm size [52]. Additional factors also may influence the rupture rate, such as hypertension, COPD and/or tobacco abuse, female gender, and a family history of aortic aneurysms (particularly when a woman with an aortic aneurysm is present in the proband [4]). Nevertheless, baseline aneurysm size remains the single most important predictor of aneurysm growth rate and rupture, and the risk of rupture increases with aneurysm size, with larger aneurysms expanding more rapidly than small ones [53]. The mean rate of expansion within a population is extremely variable, and, according to one study, the mean expansion rate of ruptured versus non-ruptured aneurysms was 0.82 and 0.42 cm/year, respectively [54]. Thus, a small AAA that expands ≥0.5 cm over 6 months of follow-up is considered at high risk for rupture [4].

19.7 Management

19.7.1 Surgical Treatment

Operative mortality for elective aneurysm repair is 4–6% overall and as low as 2% in low-risk patients [1]. However, operative mortality rises to 19% for urgent aortic repair and reaches 50% for repair of a ruptured aneurysm. The decision to operate must weigh the expected natural history of the aneurysm and life expectancy of the patient against the anticipated morbidity and mortality of the proposed surgical procedure. Aneurysm size is the primary indicator for repair of asymptomatic aneurysms. The 2011 update to the 2005 ACC/AHA guidelines on peripheral arterial disease recommends surgical repair of abdominal aortic aneurysms ≥5.5 cm in diameter in asymptomatic patients [4]. The Society for Vascular Surgery's 2009 practice guideline on AAA concurs with this recommendation [50]. Both sets of guidelines suggest considering repair in selected patients with aneurysms in the 5.0–5.4 cm range [4, 50].

19.7.1.1 Open Aortic Aneurysm Repair Versus Endovascular Aortic Aneurysm Repair (EVAR)

The choice of endovascular stent-graft repair (EVAR) versus open surgery depends on the patient's condition, personal preference, and life expectancy, as well as the urgency of the procedure and the surgeon's experience [42]. Open aortic aneurysm repair is performed by a midline transabdominal approach (or an extraperitoneal incision in the left flank), whereas EVAR can be performed under regional or even local anesthesia and can avoid a major transabdominal procedure. Procedural mortality of endovascular repair is lower than with open surgical repair, but based on the results of randomized controlled trials, there is no long-term mortality advantage of one strategy over the other [55–57]. Patients undergoing EVAR require close surveillance for endoleaks, and they are more likely to require reintervention than patients undergoing open surgery. Following EVAR, late rupture remains a concern [55, 56]. The 2005 ACC/AHA guidelines and 2009 Society for Vascular Surgery guidelines recommend long-term surveillance for endoleaks with CTA and/or ultrasound following EVAR [4, 50].

19.7.2 Preoperative Risk Assessment

Because atherosclerosis is a common finding in patients with abdominal aneurysms, the likelihood of concomitant coronary artery disease (CAD) increases significantly [3]. Thus, patients undergoing major vascular surgery, such as open surgical repair in the presence of concomitant CAD, are at high risk of perioperative cardiac events. Indeed, one-half of all perioperative deaths from aneurysm repair result from myocardial infarction [1, 3]. However, studies on prophylactic coronary revascularization in stable CAD and high-risk patients (with preoperative extensive stress-induced ischemia) undergoing vascular surgery did not demonstrate improved outcomes [58, 59]. The ACC/AHA 2014 guidelines for perioperative management do not recommend (and indeed discourage) the routine use of prophylactic coronary revascularization in stable CAD before noncardiac surgery [60]. However, patients with active cardiac conditions such as unstable coronary syndromes, decompensated heart failure, significant arrhythmias, or severe valvular disease should undergo evaluation and treatment before noncardiac surgery. Treatment for patients requiring percutaneous coronary intervention (for MI or ACS) who need subsequent surgery should be based on the urgency of procedure and risk of bleeding [60].

Current data does not support indiscriminate use of beta-blockers in patients undergoing vascular surgery because several randomized trials have failed to demonstrate benefit of these agents, in contrast to earlier studies. In fact, beta-blockers may increase the risk of perioperative hypotension and stroke [60], as they inhibit a patient's ability to mount a physiologic tachycardia in the setting of common perioperative conditions such as hypovolemia, anemia, and sepsis. The ACC/AHA recommends continuing beta-blockers perioperatively in patients who are on these medications chronically. It is reasonable to consider perioperative beta-blockade in patients undergoing vascular surgery who are at high cardiac risk owing to the finding of significant myocardial ischemia on preoperative testing, as well as in patients who have two or more clinical markers for perioperative cardiac events (heart failure, coronary artery disease, history of stroke or transient ischemic attack, serum creatinine $\geq$2 mg/dL, and insulin-dependent diabetes mellitus). Beta-blockers should be initiated preoperatively and titrated carefully to avoid severe bradycardia and/or hypotension. Postoperatively, management of beta-blockers should be guided by the clinical scenario; for example, in the context of hypotension or blood loss, it may be prudent to discontinue beta-blockers at least for a short period of time, regardless of how long the patient has been on therapy [60]. There is a protective effect of perioperative statin use during noncardiac surgery, especially vascular surgery. In a meta-analysis of 15 studies evaluating the overall effect of preoperative statin therapy, a 44% reduction in mortality was observed [60].

19.7.3 Medical Management

Medical management of AAA involves early detection, surveillance, and aggressive risk factor modification. It is widely recognized that patients with abdominal aneurysms have significantly more cardiovascular risk factors such as smoking, hypertension, hypercholesterolemia, and atherosclerosis of other vessels than do age- and gender-matched controls [6]. Therefore, finding a AAA presents an opportunity to start risk factor modification. Smoking cessation and management of hypertension are the mainstays of medical therapy. Given the increased risk of aneurysm rupture among active smokers and hypertensive patients, cigarette smoking must be discontinued, and hypertension should be controlled [42].

Beta-blockers have long been considered an important therapy for reducing the risk of aneurysm expansion and rupture and have numerous benefits in patients with cardiovascular disease [3]. In aneurysm-prone animal models, propranolol has been shown to reduce the risk of aneurysm development and to reduce aneurysm diameter [61, 62]. In humans, the data are mixed. Small trials found that beta-blockers did not slow the growth rate of most small aneurysms [63]. However, in one study, slower growth rates were noted in a beta-blocker subgroup that had aneurysms >5.0 cm at enrollment, suggesting that the beta-blocker had a beneficial effect [54]. Therefore, beta-blockers should be considered for patients with larger aneurysms or in hypertensive aneurysm patients who are managed medically [4]. Treatment with statins, although not proven to affect aneurysm expansion or rupture, may prolong survival by their effect on low-density lipoprotein (LDL) and cardiac and cerebrovascular disease. Given the strong association of abdominal aortic aneurysm with coronary artery disease in epidemiological studies, AAAs and other forms of peripheral arterial disease are considered a coronary heart disease equivalent. Based on the 2013 ACC/AHA cholesterol treatment guidelines, AAA patients should therefore be prescribed high-intensity statin therapy or moderate-intensity statin therapy if >75 years of age or if there is a contraindication to high-intensity therapy [64].

Follow-up surveillance imaging to monitor the size of aortic aneurysms is a critical aspect of management in patients not treated surgically. The 2011 ACC/AHA guidelines recommend that patients with abdominal aneurysms measuring 4.0–5.4 cm in diameter be monitored by ultrasound or CTA every 6–12 months, whereas for abdominal aneurysms <4.0 cm in diameter, monitoring by ultrasound examination every 2–3 years is reasonable [4].

19.8 Case Studies

19.8.1 Case Study 1: Thoracic Aortic Aneurysms

A 32-year-old man with Marfan syndrome and a strong family history of aneurysmal disease was referred to our center for a newly discovered cardiac murmur. Initial examination revealed a tall, lean man with long arm span. His fingers were long and slender and had a spider-like appearance (arachnodactyly). He had reduced vision because of dislocations of lenses (ectopia lentis). Vital signs were stable; heart rate was mildly bradycardic at 55 beats per minute. Cardiac auscultation revealed a mid-systolic click followed by a late systolic murmur. Standing and the Valsalva maneuver made the click and murmur louder and earlier in systole. Two-dimensional echocardiography not only confirmed the clinical impression of mitral valve prolapse with mitral regurgitation but also revealed aortic root dilatation. The patient subsequently underwent magnetic resonance angiography (MRA), which showed a thoracic aortic aneurysm involving the aortic root and ascending thoracic aorta (4.4 cm at the sinuses and 4.1 cm at the ascending aortic level). He was started on an angiotensin receptor blocker and had a repeat MRA 6 months later, which did not a show significant change in the size of aneurysm. He was subsequently followed with annual imaging. The above case illustrates the importance of the initial examination and appropriate surveillance studies to look for both valvular and aortic effects of Marfan syndrome.

19.8.2 Case Study 2: Abdominal Aortic Aneurysms

A 70-year-old male with a past medical history of chronic obstructive pulmonary disease, hypertension, dyslipidemia, and colon cancer was referred for management of a rapidly expanding abdominal aortic aneurysm. The aneurysm was diagnosed 3 years previously, when a CT scan was done for cancer staging. At that time, the size of the aneurysm was only 4 cm in diameter. After the colon surgery, the patient was lost to follow-up. He was then admitted for acute-onset back pain, along with abdominal pain and tenderness.

He had continued to smoke (2 packs/day, duration 50 years) and was noncompliant with his antihypertensive and statin medications in the 2 years prior to presentation. On examination, his vitals were stable; however, there was a tender, pulsatile abdominal mass. Ultrasonography showed an infrarenal abdominal aortic aneurysm of 5.8 cm, which was subsequently confirmed with CT scan. The patient underwent urgent endovascular aortic aneurysm repair (EVAR). The above case illustrates that aneurysms can rapidly increase in size especially in patients with risk factors for atherosclerosis (especially smoking) and can present acutely with rupture or impending rupture.

19.9 Conclusions

Aortic aneurysms are a major cause of mortality in the United States. The incidence of aortic aneurysms is increasing with improvements in screening as well as advances in imaging. Care of aortic aneurysm patients often involves physicians from different specialties such as primary care, hospitalists, cardiologists, radiologists, emergency physicians, and, ultimately, surgeons. Knowledge of the etiology, natural history, and prognosis helps guide optimal management, (i.e., medical and/or surgical treatment), frequency and mode of surveillance, and patient education about expected outcomes and screening of family members. It is well known that most aortic aneurysms are clinically silent and discovered incidentally, but occasionally the aorta undergoes rapid expansion, rupture, or dissection, and such presentations of aortic aneurysms are potentially lethal. Emergent surgery for aortic aneurysm is associated with a substantial morbidity and mortality, and so the goal is to operate electively before reaching the critical point of rupture/dissection.

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Erectile Dysfunction

20

Thorsten Reffelmann and Robert A. Kloner

20.1 Definition, Prevalence, and Causes of Erectile Dysfunction

Erectile dysfunction is commonly defined as the inability to attain or maintain a penile erection sufficient for satisfactory sexual intercourse. The prevalence, as estimated in a cross-sectional national probability survey in the United States (men aged 40 years and more, May 2001–January 2002), was 22% with significant increase with aging [1]. A similar prevalence of 19.2% was found in an urban area in Germany (30–80 years of age), with an increase from 2% among the youngest group to 53% in the oldest group [2]. Twenty-six new cases per 1000 men were the estimated annual incidence of erectile dysfunction determined in the Massachusetts Male Aging Study (40- to 69-year-old men) [3].

There are numerous causes of erectile dysfunction that should be considered when a patient first presents with this problem. Apart from neurologic and anatomic disorders and conditions following spinal cord injury, many medical diseases are commonly associated with some degree of erectile dysfunction. For example, endocrine disorders associated with erectile dysfunction do not merely comprise hypogonadism, thyroid disorders, or hyperprolactinemia, but also diabetes mellitus, which, as a cardiovascular risk factor, may also be classified as vasculogenic erectile dysfunction. Table 20.1 presents an overview, compiled from various references (4–15), of associated disorders and conditions to be considered for a patient suffering from erectile dysfunction. Of note, also various drugs frequently used in clinical practice may be associated with some degree of erectile dysfunction.

Table 20.1 Conditions and disorders to be considered in patients with erectile dysfunction [4–15]

	Associated conditions
Vascular-type erectile dysfunction	1. Cardiovascular risk factors: Arterial hypertension Smoking Diabetes mellitus Dyslipidemia, hypercholesterolemia Obesity sedentary lifestyle 2. Endothelial dysfunction, atherosclerosis
Medical disorders	1. Renal failure, dialysis, hepatic failure, sickle cell disease, leukemia 2. Endocrine disorders: Hypogonadism (testosterone level <230 ng/dl usually benefit from replacement therapy) Hyperprolactinemia Thyroid disease Diabetes mellitus
Neurological conditions	1. Spinal cord injury, nerve damage due to prostate surgery, cerebrovascular insult, multiple sclerosis 2. Neuropathy (e.g., diabetic)
Anatomical disorders	1. Peyronie's disease, trauma, priapism
Psychogenic/psychiatric disease	1. Depression, anxiety disorder, etc.
Drugs (selection)	1. Thiazide diuretics, spironolactone, digoxin, antidepressants, β-blockers, centrally acting antihypertensives, fibrates, phenothiazines, histamine-2-receptor antagonists, allopurinol, indomethacin, tranquilizer, chemotherapeutics, etc. (whether statins induce erectile dysfunction is controversial) 2. Alcohol

20.2 Cardiovascular Risk Factors in Erectile Dysfunction

Why should erectile dysfunction, a disorder at first sight belonging to the medical discipline of urology, be discussed in a book dealing with cardiovascular medicine? As early as 1985, this question was asked in a modified fashion in an article published in Lancet entitled "Is Impotence an Arterial

T. Reffelmann
Medizinische Klinik II, Klinikum Idar-Oberstein,
Idar-Oberstein, Germany

R. A. Kloner (✉)
Huntington Medical Research Institutes, Pasadena, CA, USA
e-mail: rkloner@goodsam.org

P. P. Toth, C. P. Cannon (eds.), *Comprehensive Cardiovascular Medicine in the Primary Care Setting*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-319-97622-8_20

Disorder?" [16]. The paper reported the prevalence of atherogenic risk factors in 440 men suffering from erectile dysfunction. Smoking (64%), diabetes mellitus (30%), and hyperlipidemia (34%) were significantly more common in patients with erectile dysfunction in comparison with a male population of similar age.

In the Massachusetts Male Aging Study, the incidence of erectile dysfunction increased markedly with each decade of age, and clearly, heart disease, diabetes, and hypertension were identified as major risk factors in this prospective analysis [3]. An investigation of 154 patients suffering from erectile dysfunction in the United States reported a prevalence of 44% for hypertension, 23% for diabetes mellitus, 16% for tobacco use, 79% for obesity, and 74% for elevated low-density lipoprotein cholesterol levels (>120 mg/dL) [17].

Endothelial dysfunction might be the common denominator of erectile dysfunction and atherosclerotic risk factors. A generalized vascular process involving atherosclerosis and endothelial dysfunction appears to be the basis for many forms of erectile dysfunction. Endothelial dysfunction, measured as flow-dependent and flow-independent vasodilation of the brachial artery, was strongly associated with first symptoms of erectile dysfunction prior to manifestation of atherosclerotic disease in a cohort of 30 patients in comparison with age-matched controls [18]. In some cases, erectile dysfunction may be a warning sign of silent cardiac disease before symptoms of heart disease are present [19]. Among patients with diabetes mellitus type 2, erectile dysfunction was identified as a predictor of silent coronary artery disease apart from traditional risk factors [20]. In general, endothelial dysfunction is supposed to precede the morphologic development of atherosclerotic lesions; some studies estimated 2–5 years as the mean time window between first symptoms of erectile dysfunction and a coronary artery event [21–25]. As a consequence, the association with erectile dysfunction might suggest that the presence of erectile dysfunction can predict the development of atherosclerotic disease in an early stage, in particular in younger men (<50 years old). Notably, a retrospective analysis, including more than 24,000 men with and without erectile dysfunction, demonstrated a twofold increased risk for acute myocardial infarction among men with erectile dysfunction in comparison to men without erectile dysfunction after adjustment for age, smoking, obesity, and medication [26]. Thus, detecting the underlying cardiovascular disease in men with erectile dysfunction and then treating the underlying risk factors may help to prevent future clinical manifestations of atherosclerotic disease.

20.3 Brief Overview: Physiology and Pathophysiology of Erectile Function

The process of penile erection involves the sequence of tumescence and detumescence regulated by a complex neurophysiological process involving coordinated relaxation and contraction of smooth muscle cells within the corpora cavernosa of the penis. Increasing blood flow toward the corpus cavernosum while simultaneously reducing the outflow results in a penile erection.

Release of nitric oxide from non-adrenergic, non-cholinergic nerves and endothelial cells as a result of sexual stimulation enhances the activity of the enzyme guanylate cyclase of penile artery smooth muscle cells. This enzyme catalyzes the formation of 3′5′-cyclic guanosine monophosphate (cGMP), which serves as a second messenger leading to reduced intracellular Ca^{2+}-activity and relaxation of the penile arteries, arterioles, and sinusoids. Total blood volume within the tunica albuginea increases as draining venules are compressed by the rigid tunica albuginea. This results in a penile erection. The breakdown of cGMP is catalyzed by isoform 5 of the enzyme phosphodiesterase-5. Thus, when cGMP formation via guanylate cyclase decreases, falling concentrations of intracellular cGMP are accompanied by penile detumescence.

While alteration of various steps within this physiological model might conceivably worsen erectile function, the availability of nitric oxide appears to be crucial for initiation and maintenance of an erection. As a reduced availability of nitric oxide and, consequently, compromised endothelial-dependent vasodilation is a central characteristic of endothelial dysfunction, one might easily imagine that endothelial dysfunction may be the pathophysiological link to compromised erectile function.

20.4 Evaluation of a Patient Presenting with Erectile Dysfunction

Even if various diseases are to be considered as a potential cause of erectile dysfunction (Table 20.1), erectile dysfunction associated with a generalized vascular process will play a prominent role in the patient population in the primary care setting. Of note, during routine outpatient cardiology visits, a prevalence of erectile dysfunction of 75% among patients with chronic stable coronary artery disease, as evaluated by a standardized questionnaire, was estimated [27]. Most of these patients had never discussed issues related to sexual function with their doctor. It appears to be important that the

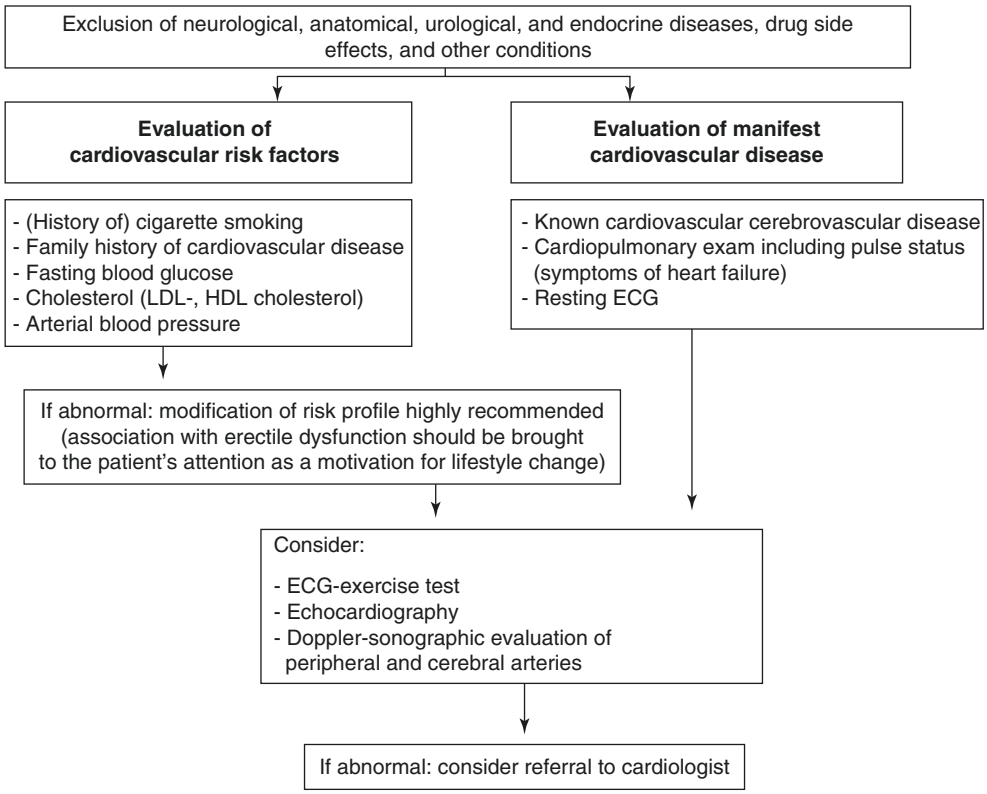

Fig. 20.1 Algorithm for the evaluation of a patient presenting with erectile dysfunction

primary care physician or cardiologist should give patients at risk for erectile dysfunction, in particular cardiovascular patients, the opportunity to discuss potential problems regarding sexual functioning, depending on the patient's readiness to discuss these issues.

On the other hand, patients complaining of erectile dysfunction should be thoroughly evaluated regarding cardiovascular risk factors and potential silent cardiovascular disease. A detailed medical history, including sexual and psychosocial history, and evaluation of a potential genetic predisposition to cardiovascular disease, as well as a complete list of drugs the patient takes, are necessary. A history of hypertension, dyslipidemia, smoking, diabetes mellitus, obesity, and lack of physical activity are crucial to elicit during the work-up. Exertional dyspnea or anginal symptoms should be investigated. A careful clinical exam, including genitourinary examination, and also a complete cardiovascular (including blood pressure, heart rate measurement and assessment of peripheral pulses, complete pulse status), pulmonary, and neurologic exam are indispensable. If special medical diseases as a cause for erectile dysfunction (Table 20.1) are suspected, laboratory tests or further technical work-up may be required. If no obvious cause, such as neurologic, endocrine, or anatomic disorders, can be detected, a detailed cardiovascular work-up is worthwhile in order to see whether the classification as vascular-type erectile dysfunction is plausible and whether cardiovascular risk factors or manifest cardiovascular disease are also present. Laboratory work-up includes fasting glucose levels, creatinine, triglyceride, cholesterol, high-density lipoprotein and low-density lipoprotein cholesterol, and total testosterone (before 11 a.m.). In Fig. 20.1, we propose a practical approach to the patient. In particular, an ECG-exercise test may be helpful in detecting silent coronary artery disease, abnormal blood pressure regulation, and overall physical fitness. In some cases, referral to a cardiologist, either for further diagnostic testing or for stabilization of the medical condition, might be necessary. If the ECG-exercise test remains inconclusive, stress echocardiography, cardiac CT scan, or stress MRI may be considered according to the cardiologist's recommendation.

20.5 Treatment of Cardiovascular Risk Factors: Therapy for Erectile Dysfunction

The statistical association between cardiovascular risk factors and erectile dysfunction as well as pathophysiological concepts suggests that reducing modifiable cardiovascular risk

factors may also improve erectile function. Even if this is not undoubtedly proven for the majority of risk factors, the association between risk factors and erectile dysfunction might be a relative concrete motivation for the patient to modify his risk profile, change lifestyle, and, in some cases, also initiate medical interventions. The following facts could help when discussing these issues with a patient.

Smoking cigarettes can lead to endothelial dysfunction, which provides a link to the close relation with erectile dysfunction in smokers. The risk for erectile dysfunction appears to be approximately twofold increased in smokers in comparison with non-smokers [10, 28]. One can conjecture that cessation of tobacco use could reverse erectile dysfunction, as in one study (in contrast to others), the prevalence of erectile dysfunction in former smokers was not different from individuals that had never smoked [10, 29, 30].

Increasing physical activity, among other *lifestyle changes*, can significantly reduce the risk of developing erectile dysfunction, as reported in a prospective cohort study in men aged 40–70 years [31]. It is interesting that the same investigation reported that weight loss, reduction of alcohol consumption, and also smoking cessation had little beneficial effects on erectile dysfunction when initiated at higher age. Presumably, lifestyle change, once atherosclerosis has already developed, may be too late to reverse erectile dysfunction, but it might prevent its progression. Therefore, change of lifestyle should be strongly encouraged as early as possible.

For diabetic patients, a strong association between glycemic control and the prevalence of erectile dysfunction seems to be well established, even if there are no prospective trials showing reversal of erectile dysfunction after intensified treatment of diabetes [32].

Treatment of hyperlipidemia, as either primary or secondary prophylaxis, should be recommended for any patients with dyslipidemia. Dietary measures should be the first step to correct the altered lipid balance. While fibrates, which nowadays are not routinely recommended for the most common lipid disorders, can also induce erectile dysfunction as a drug-specific side effect, information regarding the effect of statins on erectile function is controversial. In general, statins seem to have positive effects on endothelial function [33]. In a similar manner, small studies also reported a positive effect on erectile function, in particular in conjunction with phosphodiesterase-5 inhibitors [34]. Case series from Spain and France, however, also demonstrated a low, but significant incidence of erectile dysfunction probably related to statin therapy [35]. Furthermore, Solomon et al. reported new-onset erectile dysfunction in 22% of men on statins for 6 months; however, this was not a placebo-controlled finding [36]. Thus, even if treatment of high cholesterol levels is strongly recommended in this risk population, a positive effect on erectile function is not undoubtedly proven [37–39].

Arterial hypertension should consequently be treated to achieve adequate target levels of blood pressure, because it is closely related to endothelial dysfunction. However, there is no scientific proof that this has the potential to reverse erectile dysfunction. To the contrary, some antihypertensive drugs, in particular thiazide diuretics and slightly less frequently β-blockers, may worsen erectile function as a side effect (compare Table 20.1). Nonetheless, with the currently available spectrum of antihypertensive drugs, it should be possible to find an effective combination without these side effects. Angiotensin-converting enzyme inhibitors appear to be neutral, while angiotensin-receptor blockers were actually reported to slightly improve erectile function [40–42]. Calcium antagonists have a low risk of deteriorating erectile function, but sometimes they increase prolactin levels which could have negative effects.

Some recent concepts suggested that treatment of erectile dysfunction by PDE-5 inhibition could also reduce cardiovascular mortality, in particular in diabetics [43, 44]. These studies emphasize that endothelial dysfunction is common in patients with erectile dysfunction and may be treated by PDE-5 inhibition with potential beneficial effects on cardiovascular mortality. However, these concepts have to be investigated in systematic prospective studies before specific recommendations can be developed.

20.6 The Cardiovascular Patient Presenting with Erectile Dysfunction

In patients with manifest cardiovascular disease, erectile dysfunction is quite common. A healthy sexual life significantly contributes to quality of life, which is particularly true for the cardiovascular patient. Nonetheless, there is substantial uncertainty among patients and doctors whether a patient, e.g., after a myocardial infarction, may engage in sexual activity without increased cardiovascular risk. Furthermore, patients asking for treatment of erectile dysfunction may long have abstained from sexual activity, and it may not be evident whether physical activity during sexual intercourse is adequate for their cardiovascular status. Therefore, patients asking for medical treatment for erectile dysfunction should not only be checked for potential drug interactions and contraindications when prescribing oral treatment but also be evaluated to determine whether they can safely expend the physical activity needed for sexual activity.

The level of physical exertion during sexual intercourse may vary depending on several factors; in healthy males a peak heart rate of 110–127 per min was measured during intercourse with their usual female partner in a laboratory setting [45]. As a rule of thumb, historically, the stair-climbing

test was introduced to simulate the level of physical activity during intercourse by Larson et al., who demonstrated an increased heart rate of 115 ± 7 per min and a systolic blood pressure of 164 ± 7 mmHg during sexual intercourse and a heart rate of 118 ± 6 per min and a systolic blood pressure of 144 ± 6 mmHg with stair-climbing in patients with coronary artery disease [46]. In these investigations, 10 min of brisk walking was followed by climbing two flights of stairs, which approximates 5–6 METs, and may provide a general impression of the level of energy expenditure during sexual intercourse.

To quantify the level of physical exertion, the metabolic equivalent of energy expenditure at the resting state (MET, approximately 3.5 mL/kg/min oxygen consumption) is usually used for various physical activities (e.g., climbing two flights of stairs equals approximately 3 METs and digging in the garden 5 METs). Bohlen et al. found that 2.5–3.3 METs are attained during sexual stimulation and orgasm (maximum 5.4 METs) [45].

Therefore, an exercise test might approximate the potential cardiac stress during sexual activity. A patient achieving 3–5 METs on exercise testing without signs of ischemia or arrhythmias is most likely not at risk for developing ischemia during intercourse.

20.7 Risk Stratification (First, Second, and Third Princeton Consensus Panel)

A cardiovascular patient asking for treatment options for erectile dysfunction should first be given a realistic estimate of a potential risk of sexual intercourse depending on his cardiovascular condition. For most patients, the risk of a cardiac event will be very low. The recommendations from the first, second, and third Princeton Consensus Conference [47–49] may be applied because they provide an approach that is useful in daily practice. Cardiovascular patients are categorized into three groups (Table 20.2): the low-risk, high-risk, and indeterminate-risk group (for details see [47–50]: the first and second Princeton recommendations tended to be slightly more careful when categorizing the patients into the three groups). In the indeterminate-risk group, further diagnostic testing or therapeutic stabilization of the cardiovascular condition is required before the patient can be re-evaluated and categorized into either low-risk group or high-risk group. For most of these patients, referral to a cardiologist is appropriate to clarify the cardiovascular disease by further diagnostic testing (echocardiography, exercise testing, for some patients cardiac catheterization) and to plan treatment options including revascularization and adequate medical treatment.

Table 20.2 Categorization of cardiovascular patients

Low-risk group	Indeterminate-risk group	High-risk group
≤2 atherogenic risk factors,	≥3 atherogenic risk factors	Unstable angina/refractory angina
Controlled hypertension	Moderate, stable angina	Uncontrolled arterial hypertension
Mild, stable angina (consider exercise test)	Myocardial infarction (2–8 weeks after the acute event)[a]	Congestive heart failure (NYHA IV)
After successful coronary revascularization (either percutaneous coronary interventions or bypass surgery, without remaining ischemia)	Congestive heart failure NYHA III[a] Stroke, peripheral vascular disease	Myocardial infarction (within the last 2 weeks)
After uncomplicated myocardial infarction (> 6–8 weeks)[a]		Recent stroke
Mild valvular disease ← Further diagnostic testing, interventional or medical treatment		Further diagnostic testing → Moderate to severe valvular heart disease or hypertrophic obstructive cardiomyopathy
Congestive heart failure NYHA I-II		High-risk arrhythmia

Modified recommendations according to the first, second, and third Princeton Consensus Panel [47–49]
[a]In contrast to the Princeton I and II recommendations, the Princeton III recommendation considers NYHA I–II as low risk, NYHA III as indeterminate risk, and NYHA IV as high risk; the period after MI without intervention in the indeterminate group is now 2–8 weeks in Princeton III

Patients in the low-risk group, e.g., those with asymptomatic, medically controlled arterial hypertension, mild valvular disease, or patients with reduced left ventricular function who are in functional NYHA class I-II, can be assured of a very low risk of a cardiovascular event during sexual intercourse, and treatment for erectile dysfunction can be safely prescribed. Patients with mild angina pectoris should undergo noninvasive evaluation including exercise-ECG. If five metabolic equivalents of the task without angina pectoris are achieved or angina occurs only at very high levels of exertion, the risk appears to be low. Nonetheless, in some patients the antianginal drug regimen may need to be modified to accommodate drug therapy for erectile dysfunction (e.g., no nitrates when a phosphodiesterase-5 inhibitor is prescribed). In patients with successful revascularization, i.e., percutaneous coronary interventions or bypass grafting, an exercise test should be used to document that there is no remaining ischemia. Traditionally, it has been recommended that sexual activity be avoided for 6–8 weeks after an acute myocardial infarction. In those who have undergone successful revascularization with no remaining exercise-induced ischemia, this period can be reduced to 3–4 weeks or even to 1 week provided that the patient can achieve 3–5 metabolic equivalents on exercise testing [49, 50]. Of note, exercise training (cardiac rehabilitation program) after myocardial infarction and also β-blockers may reduce the risk of a cardiac event during sexual activity.

For high-risk patients, adequate treatment must be initiated before sexual activity may be recommended. Revascularization is required for unstable angina and medical treatment for uncontrolled hypertension and congestive heart failure. Cardiac valve disease may require heart valve replacement, and for malignant ventricular arrhythmia an implanted cardioverter/defibrillator may be adequate. In any case, stabilization of the cardiovascular condition is necessary before any treatment for erectile dysfunction is prescribed.

20.8 Treatment of Erectile Dysfunction

Phosphodiesterase-5 inhibitors, such as sildenafil, vardenafil, and tadalafil (in some countries avanafil), have become first-line treatments for many patients with different degrees and etiologies of erectile dysfunction. Efficacy has been demonstrated in a broad spectrum of causes, including diabetes and hypertension [51]. After initial concerns, safety, in particular cardiovascular safety, of these drugs is well documented, when contraindications are taken into account [52–54].

Phosphodiesterase-5 inhibitors have become first-line treatment options for erectile dysfunction in a broad spectrum of patients. By inhibiting isoform 5 of the enzyme phosphodiesterase, which is abundant in penile smooth muscle cells, vasodilation, and thereby blood flow into the corpus cavernosum, is enhanced and prolonged, which in turn explains their positive effect in erectile dysfunction.

The most important contraindication to the use of phosphodiesterase-5 inhibitors is the concurrent medication of a nitric oxide donor, e.g., nitroglycerine as an antianginal drug (or short- and long-acting nitrates) or riociguat for the treatment of pulmonary hypertension. The combination of both drugs may result in life-threatening hypotension due to generalized vasodilation. Any patient on a phosphodiesterase-5 inhibitor must be informed about this absolute contraindication [55].

Sildenafil has a half-life of about 4 h, and 6 half-lives (24 h) were recommended as an interval before any nitrate may be given. Vardenafil has a similar half-life; therefore, a 24-h interval between vardenafil intake and application of nitrates may be sufficient. For tadalafil with 17.5 h half-life, the interval should be at least 48 h. After avanafil intake, an interval of 12 h should elapse until administration of nitrates [56]. Alternative antianginal drugs that could be evaluated depending on co-medication, their potential effect on erectile function, and comorbidities are β-blockers, calcium antagonists, and ranolazine and in some cases also ivabradine [55].

In general, combination of phosphodiesterase-5 inhibitors with a broad spectrum of antihypertensive agents is well tolerated [57–59]. Blood pressure-lowering effects of phosphodiesterase-5 inhibitors are small. Zusman et al. reported a non-dose-dependent reduction of systolic and diastolic arterial blood pressure after sildenafil of 7–10 mmHg [60]. Combination with calcium channel blockers, β-blockers, angiotensin-converting enzyme inhibitors, and other antihypertensive drugs are well tolerated in hypertensive patients. A resting blood pressure of 90/60 mmHg is the prerequisite for initiation of a phosphodiesterase-5 inhibitor. Caution is mandatory when phosphodiesterase-5 inhibitors are combined with α-blockers, as hypotensive effects might be stronger than expected. In addition, the drug sacubitril/valsartan, now introduced for the treatment of congestive heart failure, should only be used with caution in combination with phosphodiesterase-5-inhibitors, due to the blood pressure-lowering effects.

For some patients, sublingual apomorphine (dopamine agonist, available in some countries) may be an alternative, in particular when the patient is on nitrates. Even if the efficacy rate is slightly lower, the therapeutic potential was demonstrated in a broad spectrum of patients, including cardiovascular patients and diabetics. Baseline hypotension, however, is an absolute contraindication. As vagal tone (sometimes leading to nausea) might be increased by sublingual apomorphine, caution is advisable in patients with baseline bradycardia and atrioventricular conduction disturbances.

Other therapies, such as intracavernosal self-injection and intraurethral alprostadil, or vacuum pumps and penile protheses are second- or third-line treatment options for the majority of patients.

20.9 Summary

Atherogenic risk factors are extremely common in the patient population suffering from erectile dysfunction. Many forms of erectile dysfunction may be classified as vascular-type or vasculogenic erectile dysfunction and are closely related to endothelial dysfunction. Therefore, patients with erectile dysfunction should be encouraged to minimize their risk profile by lifestyle changes and in some cases by medical therapy. It is worthwhile initiating a cardiovascular diagnostic work-up when a patient presents with erectile dysfunction, as cardiovascular risk factors or manifest cardiovascular disease, such as silent myocardial ischemia, can be detected in a substantial percentage of patients. Any cardiovascular patient asking for treatment of erectile dysfunction should be closely evaluated before any treatment is prescribed. Recommendations of the first to third Princeton Consensus Conference are useful in daily practice. An exercise test may be required in some patients to see whether the patient is able to tolerate physical exercise at a level usually performed during sexual intercourse without evidence for ischemia or arrhythmia. Phosphodiesterase-5 inhibitors and for some patients sublingual apomorphine are effective treatment options. Phosphodiesterase-5 inhibitors must not be combined with any nitric oxide donor as this may lead to potentially life-threatening hypotension.

20.10 Case Studies

20.10.1 Case Study 1

A 56-year-old man asks his family doctor for some pills for treatment of erectile dysfunction. The problem had developed over the last 3 years. He is in a stable relationship with his wife, and both partners discussed whether treatment with these tablets could improve their sex life. He is apparently healthy, has no history of cardiovascular diseases, and is not on any medical treatment. He stopped smoking 3 years ago (30 pack years). The clinical exam (height 5.8 ft/178 cm, weight 199 pounds/90 kg), including cardiopulmonary exam and pulse status, is unremarkable except for blood pressure.

The cardiovascular risk profile is further characterized: fasting glucose, 5.0 mmol/L; blood pressure, 165/100 mmHg; LDL-cholesterol, 4.6 mmol/L; HDL-cholesterol, 1.1 mmol/L; triglycerides, 1.5 mmol/L; no family history of vascular disease; and resting ECG, normal.

The patient is asked to return to the outpatient office to re-evaluate his blood pressure, and after two more measurements, the diagnosis of arterial hypertension was confirmed. The association of vascular risk factors with his primary problem, erectile dysfunction, is discussed with the patient. He is encouraged to reduce weight, start a low-cholesterol diet, and increase physical activity. Furthermore, the use of statins to lower LDL cholesterol, as a primary prophylactic measure, is discussed. Because he has multiple risk factors and is physically inactive, the patient is referred to a cardiologist for further evaluation of potential secondary causes of his arterial hypertension and for an exercise test to determine whether he can achieve 3–5 METs (metabolic equivalent of energy expenditure) needed for sexual activity.

An exercise-ECG does not provide evidence for myocardial ischemia, no secondary causes of arterial hypertension are found, and an echocardiogram is normal. Blood pressure treatment is initiated using an angiotensin-receptor blocker, and a statin is added. The patient increased his physical activity and tried to lose weight, which seemed to improve his general well-being.

A phosphodiesterase-5 inhibitor, prescribed for the treatment of erectile dysfunction, worked well, as reported at the next follow-up visit.

20.10.2 Case Study 2

A 62-year-old man with a medical history of myocardial infarction and subsequent coronary bypass grafting 6 years ago asks his family doctor for some treatment for erectile dysfunction. The patient is in a stable cardiovascular condition. His daily medication includes aspirin, a β-blocker, angiotensin-converting-enzyme inhibitor, and a statin. Sometimes during very heavy exercise and emotional stress, he develops angina, which is promptly relieved by sublingual nitroglycerine.

The doctor tells the patient that phosphodiesterase-5 inhibitors, which nowadays are commonly prescribed for the treatment of erectile dysfunction, cannot be used, as the patient sometimes uses nitroglycerine. The concomitant use of phosphodiesterase-5 inhibitors and a nitrate may lead to a life-threatening blood pressure drop.

However, the doctor recommends further cardiological work-up to see whether there are further treatment options for his stable angina. A scintigraphic investigation demonstrates myocardial ischemia at a higher level of exertion. Cardiac catheterization reveals a high-grade graft stenosis. Stent implantation was successful. Thereafter the patient feels well and does not suffer from further angina even at relative high levels of exertion. The patient does not use nitroglycerine any more. After 4 weeks, the patient returns to the office. He reports about his improved cardiac condition and asks what treatment options for his erectile dysfunction might be considered. As the patient is stable without further use of nitrates, the prescription of nitroglycerine is stopped and a phosphodiesterase-5 inhibitor is prescribed for treatment of erectile dysfunction, which worked well. Furthermore, they discuss to reduce the ß-blocker step-by step and try to control blood pressure by a sartan instead of the angiotensin-converting-enzyme inhibitor.

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Part IV

Cardiac Disease

Valvular Heart Disease

21

Garrick C. Stewart, Yee-Ping Sun, and Patrick T. O'Gara

Key Points

- The initial recognition of valvular heart disease most commonly occurs in the primary care setting after appreciation of a cardiac murmur and referral for echocardiography.
- Once valvular heart disease is identified, the clinical history and examination, as well as serial echocardiography, are crucial elements in ensuring timely referral for valve surgery.
- Compensatory remodeling often allows chronic severe valvular heart disease to have a long latent phase, but onset of clinical symptoms is a turning point marking cardiac decompensation.
- Severe aortic stenosis accompanied by symptoms of angina, syncope, dyspnea, or frank heart failure has a poor prognosis without valve replacement. There is no strict age limit for aortic valve replacement.
- Transcatheter aortic valve replacement (TAVR) is a less invasive option for valve replacement in patients with suitable anatomy who are at increased risk for open heart surgery.
- Congenitally bicuspid aortic valve predisposes to early aortic stenosis, aortic regurgitation, and/or aortic root and ascending aortic dilatation.
- Aortic regurgitation may be caused by either aortic valve or aortic root pathology.
- Mitral regurgitation (MR) begets mitral regurgitation and may result from disease affecting any part of the mitral valve apparatus—from the valve leaflets, annulus, and chordae tendineae to the papillary muscles and left ventricle.
- Though mitral valve prolapse has a generally benign course, it is the most common cause of severe MR requiring surgical treatment in North America. For patients with severe primary (degenerative) MR, valve repair is preferred over valve replacement.
- Percutaneous balloon mitral valvotomy is the treatment of choice for appropriate anatomic candidates with rheumatic mitral stenosis.
- The choice between mechanical and bioprosthetic heart valve weighs valve durability against the risks of anticoagulation.
- Antibiotic prophylaxis against infective endocarditis is recommended for patients with a prosthetic valve, previous endocarditis, complex congenital heart disease, or cardiac transplantation.

Primary valvular heart disease (VHD) remains a source of significant morbidity and mortality. The prevalence of heart valve disease in the US population is 2.5%, and over 100,000 undergo a heart valve procedure each year [1]. Valvular heart disease is often first identified when a murmur is appreciated during a primary care visit and subsequently characterized by echocardiography [2, 3] (Fig. 21.1). Optimal management of VHD requires close collaboration among primary care physicians, cardiologists, and cardiac surgeons. With timely recognition and appropriate referral to cardiac specialists, the majority of patients with VHD can lead a normal life span (Table 21.1).

G. C. Stewart · Y.-P. Sun · P. T. O'Gara (✉)
Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
e-mail: pogara@partners.org

P. P. Toth, C. P. Cannon (eds.), *Comprehensive Cardiovascular Medicine in the Primary Care Setting*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-319-97622-8_21

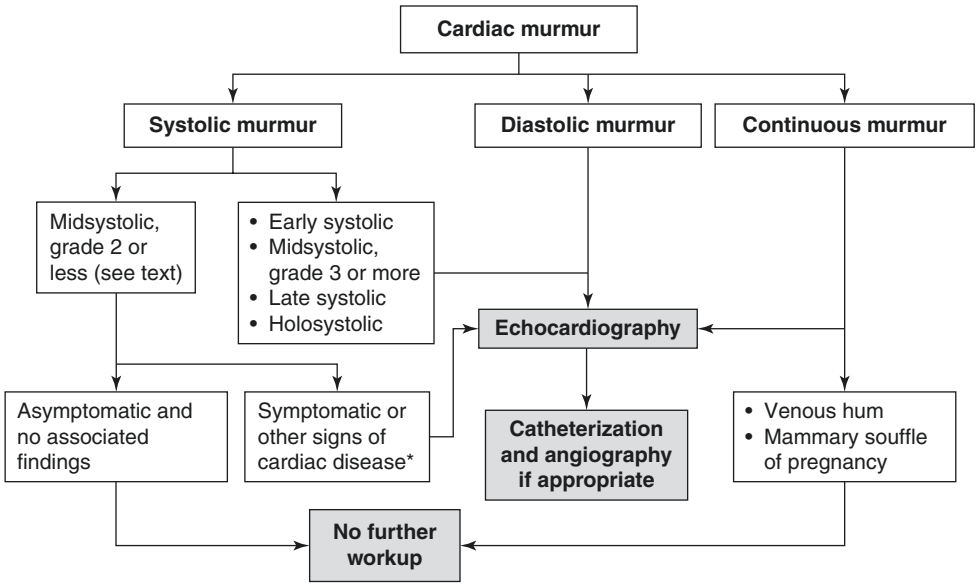

Fig. 21.1 Strategy for evaluation of heart murmurs (From Bonow et al. [3] AHA/ACC Valve Guideline)

Table 21.1 Stages of valvular heart disease. Classification of valvular heart disease (VHD) now included four stages (A through D) highlighting antecedent risk factors, progressive VHD severity without symptoms, and severe disease, which can be present with or without symptoms

Stage	Definition	Description
A	At risk	Patients with risk factors for development of VHD
B	Progressive	Patients with progressive VHD (mild-to-moderate severity and asymptomatic)
C	Asymptomatic severe	Asymptomatic patients who have the criteria for severe VHD: C1: Asymptomatic patients with severe VHD in whom the left or right ventricle remains compensated C2: Asymptomatic patient with severe VHD, with decompensation of the left or right ventricle
D	Symptomatic severe	Patients who have developed symptoms as a result of VHD

From Nishimura et al. [4] AHA/ACC Valve Guidelines

21.1 Aortic Stenosis

21.1.1 Etiology

Aortic stenosis (AS) accounts for one-quarter of all chronic VHD, and symptomatic cases in adults occur almost twice as often in males. Common etiologies of valvular AS include fibro-calcific degeneration, congenitally bicuspid valve, and rheumatic heart disease. Fibro-calcific AS is the most common cause of AS among adults in the United States. Over 30% of adults >65 years of age exhibit aortic valve sclerosis, while approximately 2–3% have more severe stenosis. Aortic sclerosis involves thickened or calcified valve cusps, often with a systolic ejection murmur, without significant outflow obstruction or evidence of left ventricular hypertrophy (LVH). On histology these valves appear thickened, inflamed, and calcified, similar to atherosclerosis. Interestingly, age, male sex, smoking, diabetes mellitus, hypertension, chronic kidney disease, and hypercholesterolemia are all risk factors for calcific AS. Both calcific AS and aortic sclerosis appear to be a marker for coronary heart disease events [5]. Recent studies suggest degenerative AS is the end result of an active disease process involving inflammation, fibrosis, and calcification, rather than the inevitable consequence of aging.

Congenitally bicuspid aortic valves are present in 1–2% of the population. The abnormal valve architecture makes the leaflets susceptible to ordinary hemodynamic stresses, ultimately leading to thickened, calcified leaflets and narrowing of the orifice. AS develops earlier in bicuspid valves, usually in the fifth or sixth decades, whereas in trileaflet aortic valves, AS develops in the seventh or eighth decade of life. Bicuspid aortic valves are also associated with aortic regurgitation, aortic root and ascending aortic dilatation, and aortic coarctation.

Rheumatic disease may affect the aortic leaflets and lead to commissural fusion, fibrosis, and calcification, with narrowing of the valve orifice. Rheumatic AS is almost always accompanied by involvement of the mitral valve or concomitant aortic regurgitation. By the time AS becomes severe, superimposed calcification may make it difficult to determine underlying valve architecture and the precise etiology. In addition to valvular AS, other causes of left ventricular (LV) outflow obstruction include hypertrophic obstructive cardiomyopathy, a congenitally unicuspid aortic valve, discrete congenital subvalvular AS resulting from a fibromuscular membrane, and supravalvular AS. The various causes of LV outflow obstruction can be differentiated by careful physical examination and transthoracic echocardiography.

21.1.2 Pathophysiology

Obstruction to LV outflow produces a pressure gradient between the ventricle and the aorta. The ventricle responds to this pressure overload by concentric hypertrophy, which is initially adaptive because it reduces wall stress. This hypertrophy may accommodate a large pressure gradient for years before it becomes maladaptive and LV function declines, with chamber dilatation and reduced cardiac output. A mean gradient >40 mmHg or an effective aortic valve orifice of <1 cm^2 is considered severe AS. Cardiac output, while normal at rest, may fail to rise appropriately with exercise. Coronary flow reserve may be reduced because of the increased oxygen demand of the thick-walled LV, the increased transmural pressure gradient, and the longer distance the blood must travel to reach the subendocardium. This may result in subendocardial ischemia even in the absence of epicardial coronary artery disease. The loss of appropriately timed atrial contraction, such as occurs with atrial fibrillation, may cause rapid progression of symptoms because of the reliance on atrial systole to fill a stiff and hypertrophied LV.

21.1.3 Symptoms

Most patients with AS have gradually increasing LV obstruction over many years with a long latent phase and no symptoms. Even with severe AS, the hypertrophied LV can produce the elevated pressures necessary to maintain an adequate stroke volume. Symptoms from AS are rare until the valve orifice has narrowed to <1 cm^2. The onset of symptoms usually indicates severe AS and heralds the need for replacement because of the markedly reduced survival in symptomatic severe AS [6].

Exertional dyspnea, angina pectoris, and syncope are the cardinal symptoms of AS. Oftentimes an insidious history of fatigue and dyspnea may be present, accompanied by a reduction in activity. Dyspnea primarily results from the elevated LV filling pressures necessary to fill the noncompliant, hypertrophied LV during diastole. Angina typically occurs later because of a mismatch between myocardial oxygen supply and demand from the thickened LV. Exertional syncope may result from vasodilatation during exercise coupled with the inability to augment cardiac output or from arrhythmia. Because of variable rates of AS progression, all patients with known AS should report any changes in symptoms to their physician.

Symptoms of frank LV failure, such as orthopnea, paroxysmal nocturnal dyspnea, and pulmonary edema, are not present until the advanced stages of AS with LV systolic dysfunction. Signs of low cardiac output, such as marked fatigue, cyanosis, and cachexia, are not present until AS reaches the end stage, as are severe pulmonary hypertension, RV failure, and systemic venous congestion leading to hepatomegaly. In patients with severe, symptomatic AS, sudden cardiac death may occur in the setting of hypotension or arrhythmia due to ischemia, LV hypertrophy, or impaired LV function.

21.1.4 Physical Findings

The hallmark of AS is a carotid pulse that rises slowly to a delayed and sustained peak (pulsus parvus et tardus). In the elderly, stiffened arterial walls may mask this finding, while patients with concomitant aortic regurgitation may have preservation of arterial pulsation due to elevated stroke volumes. The LV apical impulse may be displaced laterally and sustained due to LV hypertrophy and prolonged systolic ejection in the face of valve obstruction.

The murmur of AS is a systolic ejection murmur commencing shortly after S1, rising in intensity with a peak in mid -ejection, and then ending just before aortic valve closure. It is characteristically low-pitched, harsh, or rasping in character and best heard at the base of the heart in the second right intercostal space. It is transmitted upward along the carotid arteries, though it may sometimes be transmitted downward to the apex where it may be confused with the murmur of MR (Gallavardin effect). The intensity of the murmur does not necessarily correspond to the severity of AS. The murmur of AS is diminished with Valsalva maneuver and standing, in contrast to the murmur of LV outflow tract obstruction in hypertrophic cardiomyopathy which gets louder with these maneuvers.

When AS becomes more severe, the aortic component of S2 diminishes and may even disappear. Often S2 becomes paradoxically split in severe AS because of prolonged LV ejection. An S4 is audible at the apex and reflects LV hypertrophy with an elevated LV end-diastolic pressure. An S3 generally occurs late in the course of AS when LV dilatation is present. The best predictors of AS severity on physical exam are a late peak to the systolic murmur, a single S2 (absent aortic valve closure sound), and a pulsus parvus et tardus.

21.1.5 Diagnostic Testing

21.1.5.1 ECG

Most patients with AS have evidence of LV hypertrophy. In advanced cases there may be ST depression and T-wave inversion in the lateral leads. There is no correlation between ECG findings and severity of obstruction. The absence of LV hypertrophy does not exclude severe obstruction.

21.1.5.2 Chest X-ray

The chest radiograph usually shows a normal heart size. There may be post-stenotic dilation of the ascending aorta

or a widened mediastinum if aneurysmal dilatation is present in patients with a bicuspid aortic valve. Aortic valve calcification may be identified on the lateral film. In the later stages of AS, the LV dilates leading to a widened cardiac silhouette, often accompanied by pulmonary congestion.

21.1.5.3 Echocardiography

Key findings include LV hypertrophy and in patients with valvular calcification (most adults with symptomatic AS) bright, thick echoes on the aortic valve. Eccentric closure of valve cusps is characteristic of congenitally bicuspid aortic valves. Valve gradient and area are estimated by Doppler measurement of transaortic velocity (Fig. 21.2). Severe AS is defined as a valve area <1 cm^2, moderate as 1.0–1.5 cm^2, and mild AS as 1.5–2.0 cm^2. Echocardiography is useful for identifying coexisting valvular disease and differentiating valvular AS from other forms of LV outflow tract obstruction. There may be aneurysmal enlargement of the aortic root or ascending aorta in up to 20–30% of patients with bicuspid aortic valves. Dobutamine stress echocardiography may be useful for the evaluation of patients with severe AS and reduced LV systolic function (EF < 35%).

21.1.5.4 Cardiac Catheterization

Noninvasive assessment with echocardiography is now standard, but catheterization may be helpful if there is a discrepancy between the clinical and echocardiographic findings. Concerns have been raised about the risk of cerebral embolization during attempts to cross the aortic valve to directly measure the transaortic gradient. Coronary angiography is indicated to detect coronary artery disease in patients >45 years old who are being considered for valve replacement. Coronary CT angiography is often performed for this indication.

21.1.6 Natural History

In the era before widespread surgical treatment, average time to death after onset of AS symptoms includes angina pectoris, 3 years; syncope, 3 years, dyspnea, 2 years; and congestive heart failure, 1–2 years (Fig. 21.3). Sudden death is very uncommon (<1% per year) in asymptomatic adult patients with severe AS. Obstructive calcific AS is a progressive disease with an average annual reduction in valve area of approximately 0.1 cm^2. Death in patients with severe AS most commonly occurs in the seventh and eighth decades. Asymptomatic patients with severe calcific AS should be followed carefully for the development of symptoms and with serial echocardiograms for evidence of deteriorating LV function.

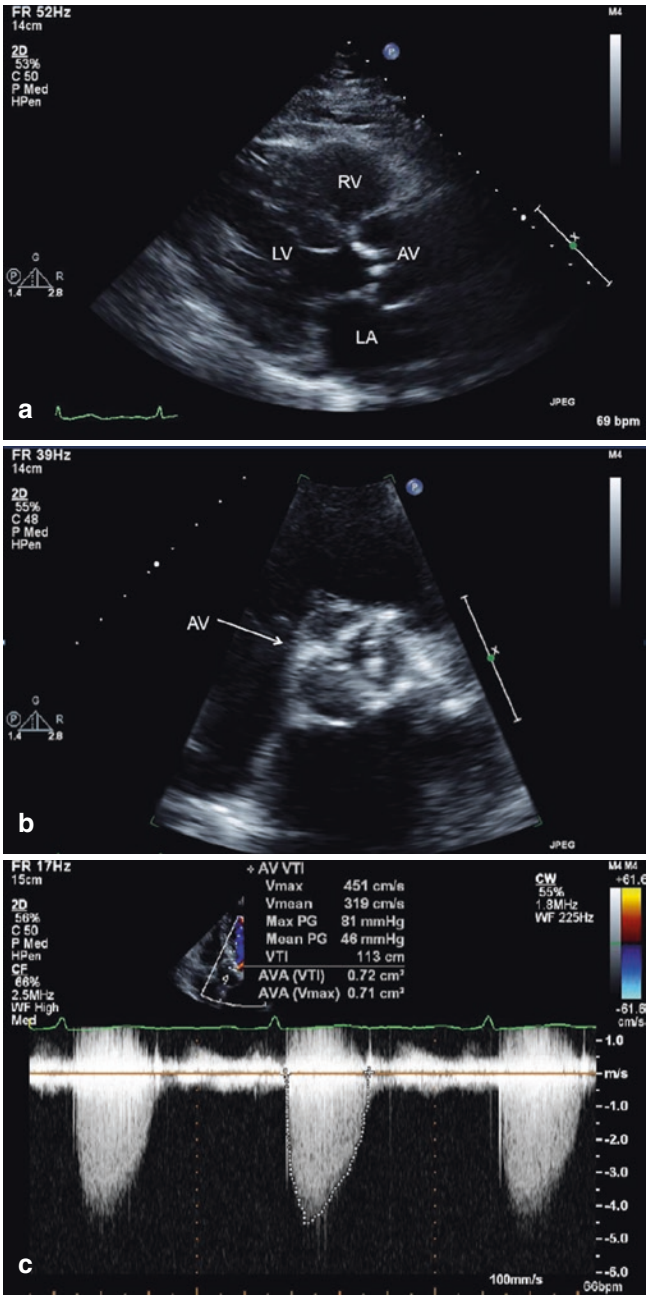

Fig. 21.2 Echocardiographic appearance of severe aortic stenosis. Panel A is a parasternal long-axis view showing a severely thickening and severely restricted aortic valve. Panel B is a parasternal short-axis view at the level of the aortic valve during systole showing a severely calcified and restricted trileaflet aortic valve. Panel C is a continuous wave spectral Doppler assessment of flow across a severely stenotic aortic valve with a peak velocity 4.5 m/s and mean gradient 46 mmHg. The aortic valve area can be calculated by echocardiography (utilizing the pulse wave Doppler velocity in the left ventricular outflow tract, left ventricular outflow tract diameter, and the continuity equation). This calculated aortic valve area is well validated to correlate with other measurements of aortic valve area. In the case shown here, the echocardiographically derived calculated aortic valve area is ~0.7 cm^2, consistent with severe aortic stenosis. AV, aortic valve; AVA< aortic valve area; LA, left atrium; LV, left ventricle; RV, right ventricle; Vmax, peak velocity

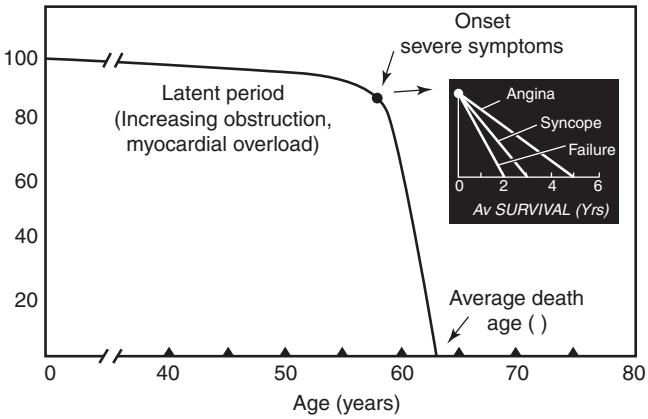

Fig. 21.3 Natural history of aortic stenosis. There is a long latent period during which survival is similar to patients without aortic stenosis. Once symptoms develop, survival declines dramatically. Half of patients do not survive 5 years after angina onset, 3 years after syncope, and only 2 years after heart failure develops in the absence of aortic valve replacement surgery (From Ross and Braunwald [6])

21.1.7 Treatment

21.1.7.1 Medical Treatment

In patients with severe AS, strenuous physical activity should be avoided even in the asymptomatic phase. Hypertension medications such as ACE inhibitors or beta-blockers are generally safe for asymptomatic patients. Nitroglycerin may be helpful in relieving angina pectoris in patients with known CAD, though it should be used with caution for fear of hypotension with severe AS. If congestive heart failure is present, diuretic therapy may be helpful to regulate fluid retention. Statin therapy has not been shown to retard the progression of AS in randomized trials. Ultimately, medical therapy alone is ineffective treatment for severe symptomatic AS.

21.1.7.2 Surgical Treatment

Surgery is indicated in patients with symptomatic severe AS (<1.0 cm^2), in those who have LV dysfunction (EF < 50%), and in those patients with AS and an aneurysmal or expanding aortic root (>4.5 cm or increase in size >0.5 cm/year), even if they are asymptomatic [4, 7, 8] (Fig. 21.4). Surgery may be postponed in patients with severe, asymptomatic AS and normal LV function, as they may do well for years [9]. The risk of surgery exceeds that of sudden death in asymptomatic patients. In patients without heart failure, the overall operative mortality for surgical aortic valve replacement (SAVR) is approximately 2–3%. SAVR may also be performed in patients with moderate AS undergoing coronary artery bypass grafting. SAVR should be carried out before LV failure develops. At this late stage with low EF and stroke volume, the transaortic gradient may be reduced. The operative mortality may exceed 15% in such patients and LV dysfunction may persist after AVR. Operative mortality depends to a substantial extent on preoperative clinical and hemodynamic status. Because many patients with calcific degenerative AS are elderly, attention to pulmonary, renal, and hepatic function is required. Age alone is not a contraindication to AVR. The overall 10-year survival for patients with AVR is approximately 60%.

21.1.7.3 Transcatheter Aortic Valve Replacement

Transcatheter aortic valve replacement (TAVR) has revolutionized the management of patients with AS [4]. TAVR is now considered for patients at prohibitive, high, or intermediate surgical risk for SAVR [10] (Fig. 21.5). Typically TAVR is performed via the femoral artery, although alternative access sites can be used. Balloon aortic valvuloplasty is performed on the calcified valve orifice followed by insertion of a stented valve bioprosthesis (Fig. 21.6). Early and late results for TAVR have been excellent, though there remains concern about vascular injury, stroke (2%), need for permanent pacing (8–10%), prosthetic valve thrombosis (10–12%), and long-term durability [11–13]. The choice between surgical and transcatheter AVR is determined by a multidisciplinary heart valve team that includes cardiologists, interventionalists, imaging specialists, and cardiac surgeons.

21.2 Aortic Regurgitation

Chronic aortic regurgitation (AR) may be caused by disorders of either the aortic valve leaflets or root. The most common causes of primary valvular AR include rheumatic heart disease, bicuspid aortic valve, and infective endocarditis. Significant valvular AS may coexist with AR due to stiff, retracted leaflets, particularly in rheumatic disease and in some patients with calcific degeneration. In patients with primary valvular AR, the aortic annulus may dilate secondarily, further worsening AR. Primary aortic root disease without involvement of the valve leaflets may also cause AR. Common etiologies of aortic root enlargement with AR include Marfan syndrome with associated cystic medial degeneration, connective tissue diseases, syphilitic aortitis, or aortic dissection.

The total volume of blood ejected by the heart is increased in AR. There is, however, significant regurgitation back into the LV due to aortic valve incompetence leading to a decrease in effective forward stroke volume. Over time the LV dilates and thickens to accommodate the increased regurgitant volume, maintaining forward flow at a reduced wall tension. Eventually, these adaptive measures fail and the ejection fraction and forward stroke volume decline. Deterioration of LV function often precedes symptom development. At autopsy the hearts of patients with severe AR are among the largest encountered.

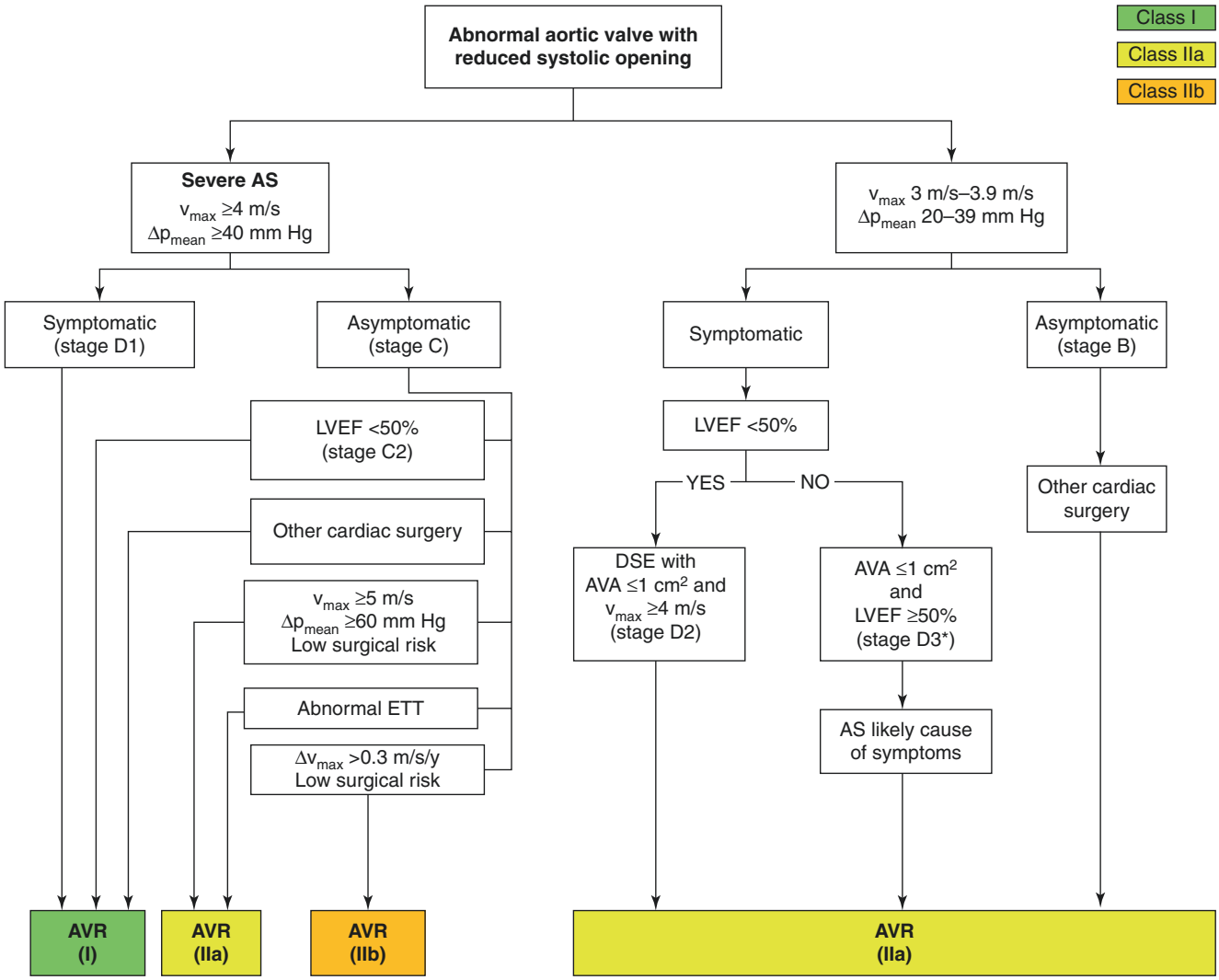

Fig. 21.4 Indications for aortic valve replacement in aortic stenosis. Arrows show the decision pathways that result in a recommendation for aortic valve replacement (AVR). Periodic monitoring is indicated for all patients in whom AVR is not yet indicated, including those with asymptomatic aortic stenosis (AS) (stage D or C) and those with low-gradient AS (stage D2 or D3) who do not meet the criteria for intervention. *AVR should be considered with stage D3 AS only if valve obstruction is most likely the cause of symptoms, stroke volume index is <35 ml/m^2, indexed aortic valve area (AVA) is ≤0.6 cm^2/m^2, and data are recorded when the patient is normotensive (systolic pressure <140 mmHg). AS, aortic stenosis; AVA, aortic valve area; AVR, aortic valve replacement; BP, blood pressure; DSE, dobutamine stress echocardiography; ETT, exercise treadmill test; LVEF, left ventricular ejection fraction; ΔP_{mean}, mean pressure gradient; and V_{max}, maximum velocity (From Nishimura et al. [4] AHA/ACC Valve Guidelines)

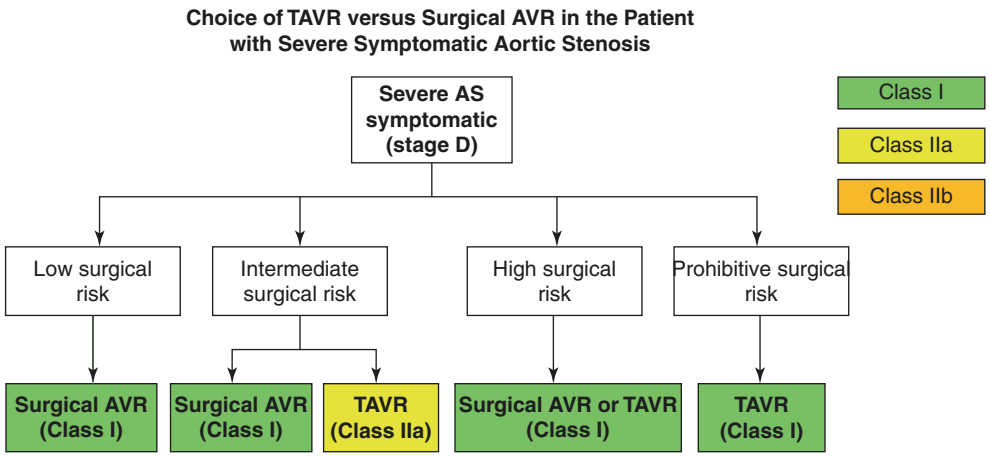

Fig. 21.5 Choice of TAVR versus surgical AVR in the patient with severe symptomatic aortic stenosis. AS, aortic stenosis; AVR, aortic valve replacement; and TAVR, transcatheter aortic valve replacement (From Nishimura et al. [8] AHA/ACC Focused Update of the Valve Guidelines)

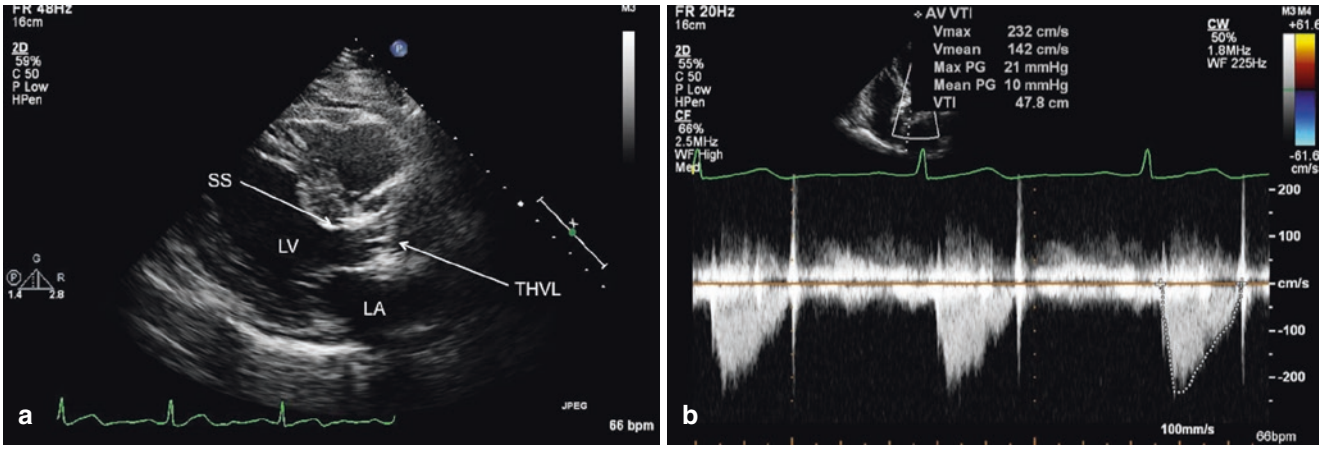

Fig. 21.6 Echocardiographic appearance of a transcatheter aortic valve. Panel A is a parasternal long-axis view of a patient who has undergone placement of an Edwards SAPIEN 3 transcatheter heart valve. The stent struts are well visualized and help identify the presence of a transcatheter heart valve on echocardiography. The leaflets of the transcatheter heart valve are seen here but are often obscured on echocardiography by the stent struts. Panel B is a continuous wave spectral Doppler assessment of flow across the transcatheter heart valve. The peak velocity is now 2.3 m/s and mean gradient 10 mmHg (normal for this valve type), which are dramatically reduced from the pre-transcatheter heart valve shown in Fig. 2. AV, aortic valve; AVA, aortic valve area; LA, left atrium; LV left ventricle; SS, stent struts; THVL, transcatheter heart valve leaflets

21.2.1 Symptoms

Chronic severe AR may have a long latent period with patients remaining asymptomatic for as long as 10–15 years [14]. Some patients may have an uncomfortable awareness of their heartbeat, particularly when lying down, or head pounding due to the increased stroke volume. Exertional dyspnea from reduced cardiac reserve is usually the first symptom, followed by orthopnea, paroxysms of nocturnal dyspnea, and excessive diaphoresis. Angina, particularly at night, may also be present even in the absence of coronary artery disease. Systemic congestion with ankle edema and hepatomegaly may be present late in the disease course.

21.2.2 Physical Findings

Physical examination in chronic severe AR centers on signs of an increased stroke volume and detection of conditions predisposing to AR. The arterial pulse rises rapidly and collapses suddenly. Capillary pulsations in the nail bed may be appreciated when pressure is applied to the nail tip (Quincke's pulse). A "pistol-shot" sound can be heard over the femoral artery, and a to-and-fro murmur may be audible when the femoral artery is lightly compressed with the stethoscope. The arterial pulse pressure is widened and often accompanied by an elevated systolic pressure. Palpation of the heart in chronic severe AR reveals a heaving, laterally displaced LV impulse. Both an apical diastolic thrill and systolic thrill at the base of the neck may be present. In some patients with severe AR, the carotid pulse may be bisferiens, with two systolic waves separated by a trough.

In patients with severe AR, the aortic valve closure sound (A2) may be absent. The murmur of AR is a high-pitched, blowing decrescendo murmur. It is often loudest along the left sternal border, though it may be heard along the right sternal border in patients with aortic root disease. The murmur of AR is often best appreciated with the patient leaning forward and after a breath hold following forced expiration. A mid-systolic flow murmur may also be heard at the base from increased stroke volume. A low-pitched mid-diastolic rumble, known as the Austin Flint murmur, may be produced in severe AR from displacement of the anterior mitral valve leaflet. Vigorous handgrip, which increases systemic resistance, augments the murmur of aortic regurgitation.

21.2.3 Diagnostic Testing

With chronic AR, the ECG will often have LV hypertrophy, left atrial abnormality, and a left axis deviation. With acute AR, the ECG may only have sinus tachycardia. Chest radiography often reveals cardiomegaly in chronic AR because of significant eccentric hypertrophy. Echocardiography is helpful in evaluating valve morphology and aortic root abnormalities. Doppler interrogation of the aortic valve and descending aorta helps quantify AR severity. Most importantly, echocardiography can identify LV enlargement and reduced systolic function, which may trigger operative intervention even before the onset of frank symptoms in chronic severe AR.

21.2.4 Treatment

Early symptoms of dyspnea and exercise intolerance often respond to treatment with diuretics and vasodilators, such as

dihydropyridine calcium channel blockers, ACE inhibitors, ARBs, or hydralazine. The use of vasodilators to prolong the asymptomatic phase of chronic severe AR is controversial. Vasodilators, however, are an important means of controlling hypertension in this population (goal systolic blood pressure <140 mmHg). Nitrates may be used to control angina from AR but are less effective than in coronary artery disease. Patients with severe AR should avoid isometric exercises.

Management of chronic severe AR often hinges on the timing of operation. In most cases of AR, valve replacement instead of repair is required. Patients with chronic severe AR usually do not become symptomatic until after LV dysfunction develops. Onset of symptoms equates with the need for AVR. The presence of new-onset heart failure indicates cardiac decompensation, irrespective of echocardiographic evidence of LV dysfunction. When delayed too long (>1 year after symptom onset or echocardiographic evidence of LV dysfunction), surgical therapy may not restore LV function. In deciding when to operate on asymptomatic patients, the risks of the operation must be weighed against the risks of delaying surgery. Operation should be carried out in asymptomatic patients with LV ejection fraction <50% or an LV end-systolic dimension of >50 mmHg. Low surgical risk patients with severe AR can be considered for operation with evidence of progressive LV enlargement on echocardiography (end-diastolic dimension ≥65 mm). Asymptomatic patients wihtout an indication for operation should be followed with echocardiographic surveillance every 6–12 months to insure operation before irreversible LV dysfunction develops. Surgical techniques for severe AR have evolved considerably. Operations for isolated valvular AR involve prosthetic valve replacement. Primary aortic root disease without valvular involvement may respond to aortic root replacement with a native valve-sparing method. Survival after surgery depends in large part on the stage of disease and ventricular function at the time of operation. The overall mortality for isolated AVR is 2–3%. However, in patients with an enlarged or dysfunctional LV, operative mortality is higher, and late mortality is approximately 5% per year. Because prognosis is poor with medical management alone, even patients with LV failure and low ejection fraction (e.g., 30%) should be considered for operation.

21.2.5 Acute Aortic Regurgitation

With acute aortic regurgitation, patients appear gravely ill and have tachycardia, significant dyspnea, and often hypotension. It is a medical emergency requiring rapid stabilization and surgery and is rarely encountered in the primary care setting. Most cases of acute severe AR are caused by infective endocarditis, but other causes include aortic dissection and trauma. Because compensatory eccentric hypertrophy has not had time to develop, a wide pulse pressure from increased stroke volume may not be present, and there may only be a short diastolic murmur. Once acute AR is suspected, prompt echocardiography and transfer to a center with cardiac surgical capabilities is imperative. Hemodynamic monitoring and therapy with intravenous vasodilators may be required to stabilize patients before surgery. Prompt surgical treatment may be lifesaving in acute severe AR.

21.3 Mitral Regurgitation

21.3.1 Etiology

Mitral regurgitation (MR), the most common heart valve disease, may arise from disorders affecting any part of the mitral valve apparatus. The mitral valve apparatus is composed of the anterior and posterior mitral valve leaflets, the annulus, the chordae tendineae, the papillary muscle, and the adjacent left ventricular myocardium [15] (Fig. 21.7). Primary MR refers to abnormalities related to the leaflets and/or chordae, whereas in secondary (functional) MR, the regurgitation is due to a disorder that leads to leaflet tethering usually with annular dilatation such as dilated or ischemic cardiomyopathy (Table 21.2).

Acute MR can occur in the setting of acute myocardial infarction with papillary muscle dysfunction or rupture, after blunt chest wall trauma, or in the course of infective endocarditis. Transient acute MR may result from papillary muscle ischemia, often presenting with angina accompanied by significant shortness of breath or pulmonary edema. Chronic MR may result from rheumatic disease, mitral valve prolapse/flail, mitral annular calcification, hypertrophic obstructive cardiomyopathy, and dilated cardiomyopathy. Chronic MR may also result from geometric changes in the LV after myocardial infarction, including remodeling that leads to leaflet tethering and fibrosis of the papillary muscles (ischemic MR). Chronic severe MR is often progressive with left atrial (LA) and LV remodeling leading to further leaflet displacement, more regurgitation, and a vicious cycle. MR begets MR.

21.3.2 Pathophysiology

With chronic MR, resistance to LV emptying is reduced since blood can eject into a compliant, enlarged low-pressure left atrium. Both LV filling and stroke volume are augmented since there is a greater return of blood from the LA such that forward LV output is preserved. As LV volume increases over time, contractile function begins to deteriorate. Since ejection fraction rises in chronic severe MR in the presence of normal LV function, even a modest reduction (<60%) reflects significant

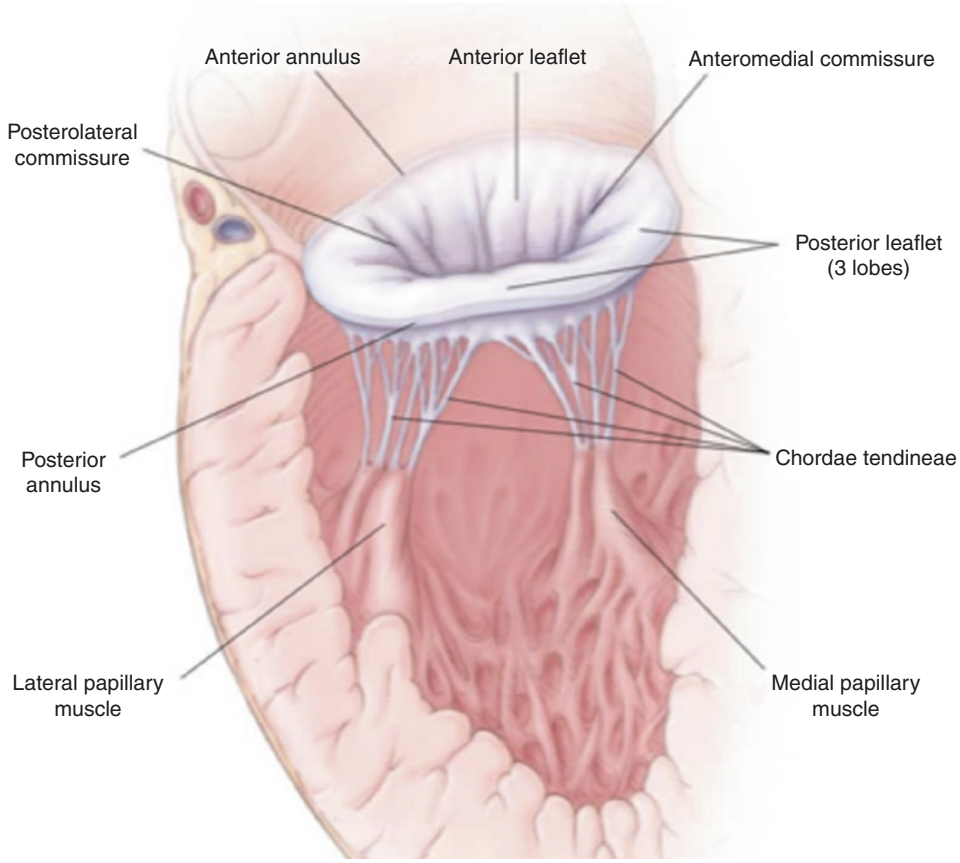

Fig. 21.7 Mitral valve. The mitral valve consists of the mitral annulus, anterior and posterior leaflets, chordae tendineae, and papillary muscles. Mitral regurgitation (MR) may be due to a disease that primarily affects the valve leaflets (primary MR), such as mitral valve prolapse or rheumatic mitral valve disease, or may result from alterations in the function or structure of the left ventricle (secondary MR), such as those induced by ischemic disease or dilated cardiomyopathy

Table 21.2 Causes of chronic mitral regurgitation

Primary
Myxomatous degeneration (mitral valve prolapse)
Infective endocarditis
Trauma
Systemic lupus erythematosus (Libman-Sacks lesion)
Rheumatic fever
Secondary
Coronary artery disease/ischemic cardiomyopathy
Dilated cardiomyopathy
Hypertrophic cardiomyopathy with outflow obstruction

dysfunction. In acute MR, the LV ejects blood into a small, noncompliant left atrium leading to a rapid rise in LA pressure during systole. This in turns increases pulmonary venous pressures and can lead to pulmonary edema. The difference in LA compliance and size explains why chronic MR (increased compliance) can be well tolerated and why acute MR (reduced compliance) is not.

21.3.3 Symptoms

Patients with MR in the compensated phase of their disease are typically asymptomatic and can tolerate even relatively strenuous exercise. With acute onset MR or in the late stages of chronic MR, symptoms of left-sided heart failure predominate, including exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and fatigue. Palpitations are commons and may signify the onset of atrial fibrillation. In severe chronic MR with pulmonary hypertension, symptoms of right heart failure may also be present.

21.3.4 Physical Findings

In patients with chronic severe MR, the LV is hyperdynamic with a brisk systolic impulse that may be laterally displaced and accompanied by an S3 gallop. Chronic MR is marked by a blowing holosystolic murmur with a reduced S1, which may be obscured by murmur onset. This systolic murmur may sometimes be accompanied by a rumbling mid-diastolic murmur from the large volume of blood filling the LV. The murmur of severe chronic MR is usually at least III/VI in intensity and loudest at the apex with radiation to the axilla. In patients with ruptured chordae, the systolic murmur often radiates away from the prolapsing or flail leaflet. If the posterior leaflet is affected, the murmur radiates to the base, whereas anterior leaflet involvement will produce a regurgitant jet directed posteriorly and thus a murmur transmitted to

the back. The murmur of chronic MR is increased with isometric exercise (hand grip) and reduced during the strain phase of the Valsalva maneuver. MR may be distinguished from tricuspid regurgitation since the latter is usually soft (less than II/VI), is best heard at the left lower sternal border, varies in intensity with inspiration, and is accompanied by large "V"-waves in the jugular venous pulsation. A ventricular septal defect also produces a holosystolic murmur, which varies inversely in intensity with defect size, is usually accompanied by a palpable thrill, and also does not vary with inspiration.

21.3.5 Diagnostic Testing

ECG often reveals LA enlargement, but right atrial (RA) enlargement may be present when pulmonary hypertension is severe. Chronic severe MR is associated with atrial fibrillation. There may also be signs of LV hypertrophy. Chest x-ray may reveal an enlarged cardiac silhouette in the late stages of chronic MR because of massive LV and left atrial dilation. Calcification of the mitral annulus may be visualized, particularly on lateral views. Transthoracic echocardiography with Doppler is indicated to assess the etiology and severity of MR. Serial assessment of global LV function and size are of particular importance in following patients with chronic severe MR.

21.3.6 Treatment

21.3.6.1 Medical

The use of vasodilators for treatment of chronic severe MR is only indicated in the presence of systemic hypertension. MR in the setting of heart failure with reduced ejection fraction may be improved by evidence-based treatments such as ACE inhibitors/ARBs, beta-blockers, diuretics, and cardiac resynchronization therapy. Asymptomatic patients with severe MR and normal LV size and function should avoid isometric exercise.

21.3.6.2 Surgical

In selecting patients for surgery for chronic severe MR, the slowly progressive nature of the disease must be weighed against the immediate and long-term risks of operation. The risks are substantially lower for valve repair compared to replacement for treatment of primary degenerative MR, such as that due to prolapse or flail. Repair involves valve reconstruction using a variety of techniques and insertion of an annuloplasty ring. In addition to reducing the need for anticoagulation and the risk of late prosthetic valve failure, repair preserves the integrity of the subvalvular apparatus, which maintains LV function to a greater degree. Surgery for secondary MR, on the other hand, may in some circumstances employ valve replacement preferentially [16].

Surgery for chronic severe, primary MR is indicated once symptoms occur (Fig. 21.8). Surgery is indicated in asymptomatic patients with LV ejection fraction <60% or end-systolic dimension >40 mm. Other indications for early repair of degenerative MR include recent onset atrial fibrillation, pulmonary hypertension (>50 mmHg at rest), or a progressive increase in LV size or decrease in LF function on serial imaging [4]. Indications for surgery have expanded given the outstanding results of mitral valve repair. In patients <75 years old with normal LV function and no coronary disease, there is <1% perioperative mortality with repair with reoperation rates ~1% per year for 10 years after surgery. The risk of surgery rises in patients with reduced LV function, particularly in those with LV ejection fraction <30%, because of persistence or worsening of LV dysfunction postoperatively. When surgery is contemplated, cardiac catheterization may be helpful in delineating discrepancies between echocardiography and clinical exam, along with identifying patients who may also require coronary revascularization. Multiple studies are underway exploring percutaneous, catheter-based treatments for chronic mitral regurgitation. For patients with degenerative primary MR, a transcatheter edge-to-edge clip can reduce MR and stimulate reverse remodeling, offering an alternative to surgical repair in select, high surgical risk patients [17].

Decision-making for patients with severe secondary MR is quite challenging and best done by an experienced multidisciplinary heart team. Optimal medical and device therapy for chronic heart failure are the mainstays of therapy. Surgery has not been shown to prolong life in this context, though it may help reduce symptom severity.

21.4 Mitral Valve Prolapse

Mitral valve prolapse (MVP) is a common (2.4% of population), highly variable clinical syndrome resulting from one of several disorders of the mitral valve apparatus [18]. Among these are excessive or redundant mitral leaflet tissues associated with myxomatous degeneration, which may be related to disorders of collagen formation or heritable connective tissue disorders such as Marfan and Ehler-Danlos syndromes. In most patients with MVP, the underlying cause is unknown. Myxomatous degeneration of the heart valves is often confined to the mitral valve, most commonly the posterior leaflet. In many patients elongated, redundant chordae may contribute to regurgitation. MVP may lead to stress on the papillary muscle and result in papillary dysfunction from ischemia. Ruptured chordae tendineae and annular dilation also contribute to regurgitation, further stressing the diseased valve apparatus, creating a vicious cycle.

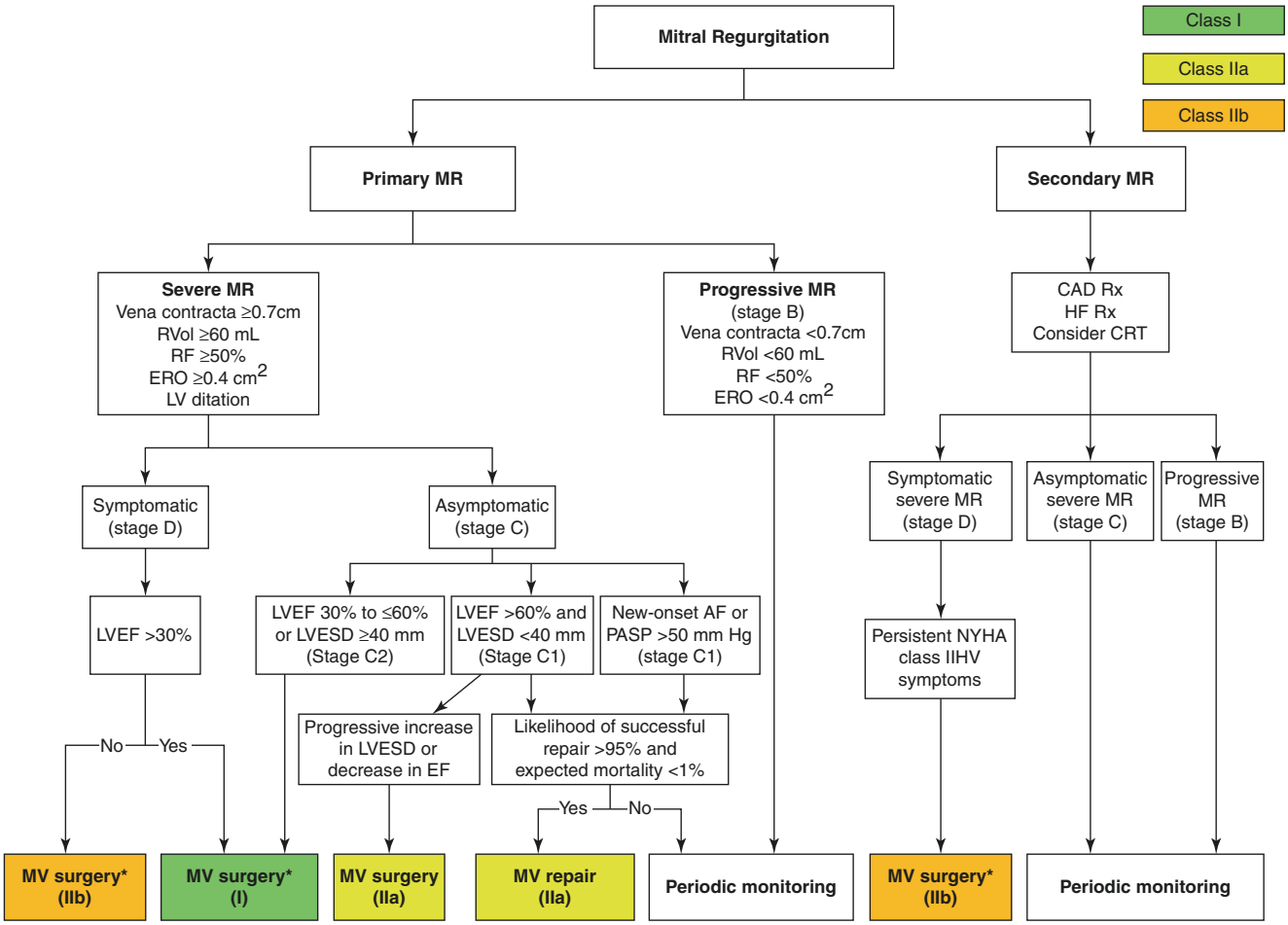

Fig. 21.8 Indications for surgery for mitral regurgitation. *Mitral valve repair is preferred over mitral valve replacement when possible. AF indicates atrial fibrillation; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; EF, ejection fraction; ERO, estimated regurgitant orifice; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation; MV, mitral valve; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; RF, regurgitant fraction; RVol, regurgitant volume; and Rx, therapy (From Nishimura et al. [8] AHA/ACC Focused Update of the Valve Guidelines)

MVP is more prevalent in females, most commonly between ages 15 and 30. Their clinical course is typically benign. MVP has also been observed in patients >50 years old, who are predominantly males and in whom MR is more severe and often requires surgery. MVP encompasses a broad spectrum of severities, ranging from a systolic click and murmur and mild prolapse of the posterior leaflet to severe MR with massive bileaflet prolapse. Most patients are asymptomatic and remain so for their entire lives. However, in North America, MVP is now the most common cause of severe MR requiring surgical treatment. MVP may be associated with arrhythmias such as premature ventricular contractions, paroxysmal supraventricular tachycardia, AF, and ventricular tachycardia, which may lead to palpitations, light-headedness, or syncope. Sudden death is a rare complication, usually occurring only with severe MR and LV dysfunction. Many patients have a difficult to evaluate chest pain syndrome, which is often substernal and unrelated to exertion. MVP may also have an association with migraine headaches.

On physical examination, the most important finding is a mid-to-late systolic click thought to be produced by the sudden tensing of slack, the elongated chordae tendineae, or the prolapsing mitral leaflet reaching its maximum excursion. Systolic clicks may be followed by a late systolic murmur, which is occasionally "whooping" or "honking" and best heard at the apex. Any maneuver that reduces LV volume, such as standing or the Valsalva maneuver, will exaggerate the propensity of the mitral valve to prolapse and move the click and murmur earlier during systole. Squatting or isometric exercises, in contrast, will cause an increase in LV volume, reduce prolapse, and move the click and murmur later in systole. Some patients will have either a click, or murmur, but not both together.

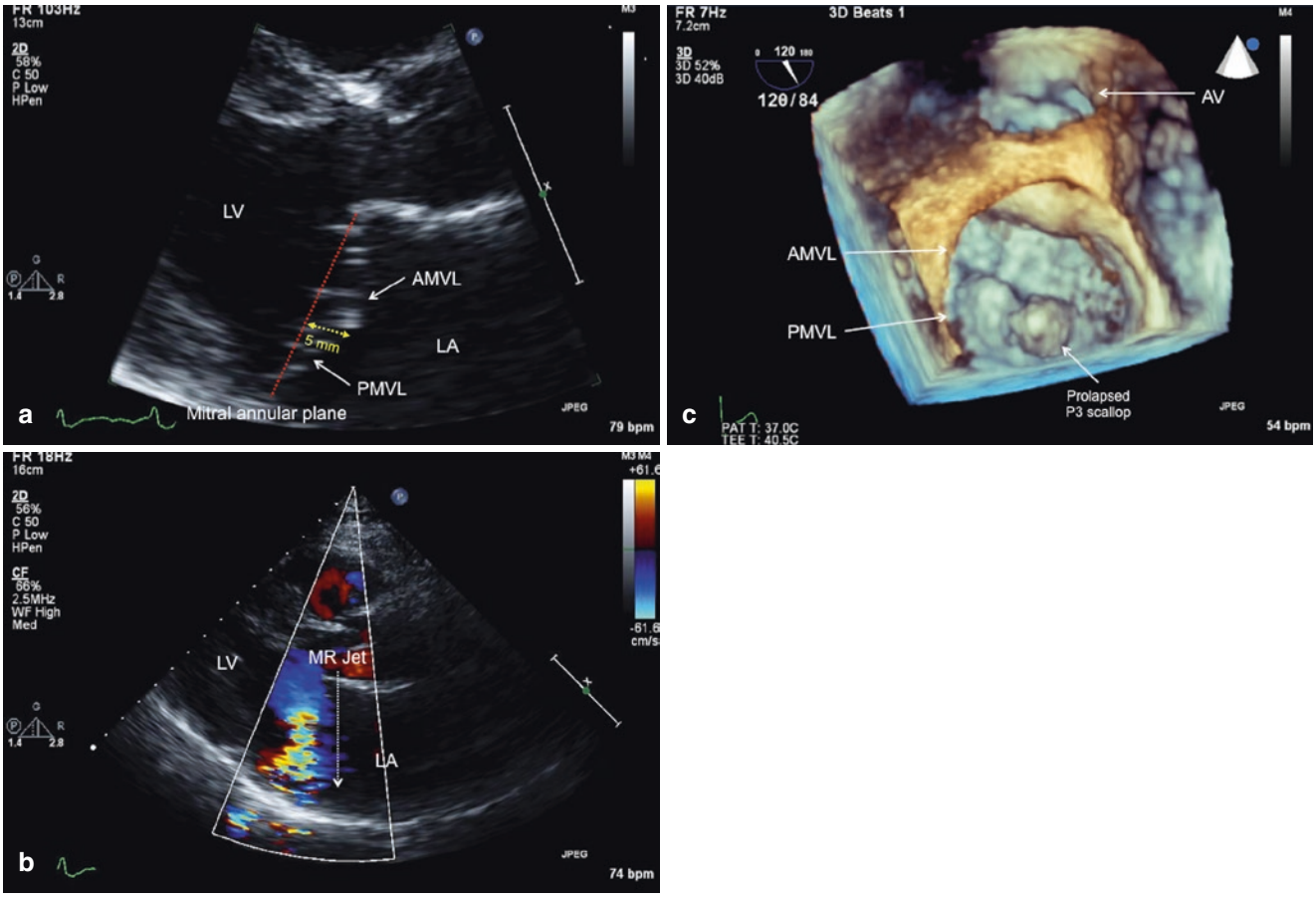

Fig. 21.9 Echocardiographic appearance of mitral valve prolapse. In a normal functioning mitral valve, the leaflets meet in the left ventricle during systolic to prevent significant regurgitation. In mitral valve prolapse, there is redundant leaflet tissue. As a result of this redundant leaflet tissue, during systole, one or both mitral leaflets billow back into the left atrium. Panel A is a parasternal long-axis view of a patient with myxomatous mitral valve disease with prolapse. Both leaflets are seen to cross the mitral annual plane (denoted by the dotted red line) into the left atrium with the anterior leaflet prolapsing more than the posterior leaflet, ~5 mm (shown in yellow) beyond the mitral annular plane. Because of the redundant tissue, the leaflets coapt poorly, and significant regurgitation can occur. Panel B is a color Doppler assessment of this same patient demonstrating significant eccentric posteriorly directed mitral regurgitation (represented by the dotted white line). There exist multiple qualitative, semiquantitative, and quantitative parameters for the assessment of mitral regurgitation severity. An integrative approach combining all these different parameters is utilized to accurately grade mitral regurgitation severity. While transthoracic echocardiography is often the initial diagnostic test of choice, transesophageal echocardiography is often necessary to further characterize the anatomic abnormality and severity of mitral regurgitation. Due to improved image resolution, three-dimensional (3D) imaging is possible. Shown in Panel C is a 3D image of a patient with posterior mitral valve prolapse. In this view, the valve is viewed from above in the left atrium with the aortic valve oriented at ~12:00 (termed the "surgical view"). Identification of the specific prolapsing segment was challenging on 2D, but 3D imaging clearly demonstrates an isolated posterior prolapsing segment. AMVL, anterior mitral valve leaflet; AV, aortic valve; LA, left atrium; LV, left ventricle; MR, mitral regurgitation; PMVL, posterior mitral valve leaflet

MVP is defined on echocardiography by systolic displacement of the mitral valve leaflets >2 mm into the left atrium above the plane of the mitral annulus (Fig. 21.9). Color flow and Doppler are useful in quantifying the degree of MR. Predictors of adverse outcome with MVP include older age, severe MR, thickened valve leaflets, and a dilated LV or LA. If the MR is only mild or moderate, patients can be provided with reassurance and have serial echocardiography every 3–5 years. Screening echocardiography is recommended for first-degree relatives of patients with MVP. Infective endocarditis prophylaxis is only indicated for patients with a prior history of endocarditis. Beta-blockers may be helpful in relieving symptoms of chest pain or palpitations.

21.5 Mitral Stenosis

Rheumatic fever is the leading cause of mitral stenosis (MS). Widespread use of programs for the detection and treatment of Group A streptococcal pharyngitis has reduced the incidence of rheumatic fever in the developed world. As a result,

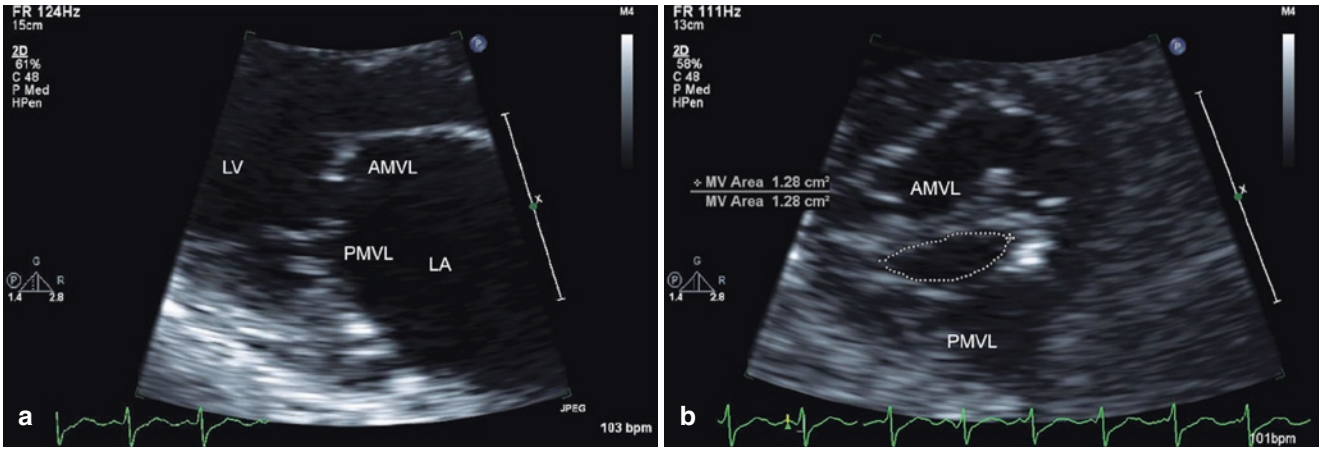

Fig. 21.10 Severe rheumatic mitral stenosis. Rheumatic mitral valve disease is characterized by fusion of the mitral commissures as well as thickening of the mitral leaflets and/or subvalvular apparatus. Panel A shows a parasternal long-axis view of a rheumatic mitral valve. Fusion of the mitral commissures results in restriction of the leaflet tips with the basal and midportions of the leaflets moving more normally. This bowing in the mid-leaflet results in a characteristic "hockey stick" deformity of the anterior mitral leaflet shown here. Panel B shows a parasternal short-axis view at the level of the mitral valve leaflet tips in the same patient. Due to commissural fusion, the mitral valve orifice is stenotic with a classic "fish mouth" appearance. Direct planimetry of this valve shows a mitral valve area of 1.3 cm^2, consistent with severe mitral stenosis. AMVL, anterior mitral valve leaflet; LA, left atrium; LV, left ventricle; PMVL, posterior mitral valve leaflet

the incidence of rheumatic MS has declined considerably in recent decades. Rheumatic heart disease remains the dominant cause of valvular disease in developing countries. In patients with rheumatic heart disease, 28% have pure MS, 40% have mixed MS/MR, and 28% have mixed valve disease (e.g., MS and AR). Two-thirds of patients with MS are female. Rheumatic fever leads to inflammation and scarring of the mitral valve, with fusion of the valve commissures and subvalvular apparatus. Although the initial insult is rheumatic, altered flow patterns may lead to calcification and further valve deformity. Taken together, these changes lead to a narrowing at the apex of a funnel-shaped ("fish mouth") valve (Fig. 21.10).

In normal adults, the mitral valve orifice is 4–6 cm^2, and MS develops when the area is reduced to <2 cm^2, and an elevated left atrioventricular pressure gradient is required to propel blood across the mitral valve. Severe MS is present when the valve area is <1.5 cm^2. The elevated left atrial pressures lead to pulmonary hypertension, exercise intolerance, and eventually right-sided heart failure. Adequate transit time is required to allow blood to flow across the stenotic mitral valve during diastole. As a consequence, the first symptoms are often precipitated by conditions resulting in tachycardia, such as fevers, anemia, hyperthyroidism, pregnancy, sexual intercourse, infection, or atrial fibrillation (AF). Chronically elevated LA pressures in MS contribute to the development of AF, which may in turn put patients at risk for thrombus formation and arterial embolization.

MS is a slowly progressive disease with a latent period of up to two decades between the episode of rheumatic carditis and symptom onset. The disease led to death within 2–5 years in the era before the development of mitral commissurotomy. As symptoms progress, lesser stresses precipitate symptoms, and the patient becomes limited in her daily activities; orthopnea and paroxysmal nocturnal dyspnea develop. Development of permanent AF marks a turning point in the patient's course, with an accelerated rate of symptom progression. Systemic embolization may be the first clue to the presence of MS, both from AF as well as the calcified mitral valve itself, with up to 20% of embolic events occurring during normal sinus rhythm. Patients may also suffer from hemoptysis due to shunting between the bronchial and pulmonary veins, leading to rupture. Rarely patients with MS may present with hoarseness due to compression of the recurrent laryngeal nerve due to severe left atrial enlargement (Ortner's syndrome).

21.5.1 Physical Findings

Patients with MS may have signs of heart failure, including pulmonary rales or pleural effusion, peripheral edema, ascites, an elevated jugular venous pressure, and congestive hepatomegaly. In severe mitral stenosis, patients may also have a malar flush with pinched and blue facies. The first heart sound (S1) is usually accentuated and slightly delayed. The opening snap (OS) of MS is best appreciated in early diastole during expiration with the diaphragm near the cardiac apex. The time interval between aortic valve closure (A2) and OS varies inversely with the severity of MS and the height of the left atrial pressures. The OS is followed by a low-pitched rumbling diastolic murmur best heard at the apex with the

patient in the left lateral decubitus position. It is accentuated by mild exercise (e.g., a few sit-ups) performed just before auscultation. In general the duration of the murmur corresponds to the severity of stenosis. Associated valvular lesions, including the murmurs of pulmonic valve regurgitation and tricuspid regurgitation, may be present, along with a loud P2 from pulmonary hypertension.

The murmur of MS must be distinguished from several other conditions. A diastolic flow murmur may be present in severe MR but commences later than the murmur of MS and is associated with signs of LV enlargement. Similarly, the apical diastolic murmur of severe AR (Austin Flint murmur) may be mistaken for MS but can be differentiated because it is not intensified following atrial presystole in patients in sinus rhythm. The murmur of an atrial septal defect or that of a left atrial myxoma may also be confused with MS. An ASD, however, usually is associated with fixed splitting of S2. Patients with left atrial myxoma often have signs of systemic illness, such as weight loss, and marked change in their exam based on body position. If there is doubt, echocardiography is invaluable in distinguishing among these conditions.

21.5.2 Diagnostic Testing

In patients with MS in sinus rhythm, left atrial enlargement is present. The QRS complex is usually normal. In severe pulmonary hypertension from MS, there may be right axis deviation and right ventricular (RV) hypertrophy. Chest x-ray may reveal signs of left atrial enlargement including upward displacement of the left main bronchus. Kerley B lines along the periphery of the mid and low lung fields may be present. Echocardiography with both two-dimensional imaging and color flow Doppler can estimate transmitral gradients and orifice size. Echocardiography is important for determining the presence and severity of accompanying MR, along with rheumatic involvement of the other valves and the degree of pulmonary hypertension. If there is a discrepancy between the clinical findings and echocardiography, either cardiac catheterization or cardiac magnetic resonance imaging may be indicated. All patients should be referred for further evaluation if the estimated mitral valve area is <1.5 cm^2, if they are symptomatic or develop atrial fibrillation, or if there is evidence of pulmonary hypertension on clinical exam or Doppler interrogation.

21.5.3 Treatment

21.5.3.1 Medical Therapy

Priorities of management are prevention of recurrent rheumatic carditis, treating the consequences of MS, and monitoring for its progression. Appropriate patients with MS should receive penicillin prophylaxis against recurrent Group A beta-hemolytic streptococcal infections [19]. No treatment is required for asymptomatic patients in sinus rhythm. Diuretic therapy along with dietary salt restriction is the mainstay for treating symptoms of pulmonary congestion. If AF develops, rate control with beta-blockers or nondihydropyridine calcium channel blockers (e.g., diltiazem or verapamil) is crucial because a rapid heart rate reduces mitral inflow time, thereby increasing LA pressure and reducing cardiac output. Warfarin to an INR of 2–3 should be administered to all patients with MS with either AF or history of thromboembolism. Direct oral anticoagulants have not been approved for use in patients with rheumatic MS. Once the ventricular rate has been slowed in AF, chemical or electrical cardioversion is indicated to restore sinus rhythm once the patient has been therapeutically anticoagulated for 4 weeks. If more urgent cardioversion is required, transesophageal echocardiography may be required to exclude left atrial thrombus. Patients with MS should be followed by clinical examination and echocardiography until symptoms limit lifestyle and AF or pulmonary hypertension develops at which time they should be referred for mechanical correction of the stenosis.

21.5.3.2 Mitral Valvotomy and Replacement

In the absence of contraindication, mitral valvotomy is indicated in symptomatic (New York Heart Association Class II-IV) patients with isolated severe MS (valve area is <1 cm^2). Percutaneous mitral balloon commissurotomy (PMBC) can achieve durable results in appropriately selected patients. PMBC is performed by transseptal puncture, passing a guidewire across the mitral valve, and inflating a balloon (Inoue balloon) across the mitral orifice to split the commissures and widen the stenotic valve. Ideal patients for PMBC are younger (<45 years old) and have pliable mitral leaflets with little calcification. They can be identified by careful echocardiographic study. Such patients have excellent event-free survival after PMBC with rates of 80–90% over 3–7 years when performed by a skilled operator in a high-volume center. Successful PMBC doubles the mitral valve area, reduces transmitral gradient, and improves symptoms. If anatomy is unfavorable for PMBC or the procedure is unsuccessful, open surgical valvotomy may be performed, which requires cardiopulmonary bypass. Persistence of symptoms after commissurotomy suggests that it induced MR or that underlying LV dysfunction or associated subvalvular disease was present. There is a moderate rate of restenosis after both percutaneous and surgical commissurotomies with most patients requiring a repeat procedure within one to two decades.

Mitral valve replacement (MVR) is necessary in patients with MS and significant MR and those in whom valve anatomy is too distorted to respond to commissurotomy alone.

MVR is performed with preservation of the chordal attachments to facilitate LV recovery. Given the long-term complications of MVR, it should be considered in those patients with a valve area <1.5 cm^2 and NYHA III–IV symptoms. The average operative risk for MVR is 5%, with an overall 10-year survival of 70%. Long-term prognosis is influenced by patient age, comorbid conditions, and the presence of pulmonary hypertension and RV dysfunction.

21.6 Tricuspid Regurgitation

Tricuspid regurgitation (TR) is most commonly secondary (functional) and related to dilatation of the tricuspid annulus due to RV infarction, severe pulmonary hypertension, or dilated cardiomyopathy. The most important causes of primary valvular tricuspid regurgitation are trauma and infective endocarditis, particularly in patients who abuse injected intravenous drugs. Carcinoid is another cause, as is Ebstein's anomaly, a congenital heart defect in which the annulus of the tricuspid valve is displaced apically into the right ventricle. TR is often first identified in patients with evidence of a holosystolic murmur along the left sternal border. When severe, TR may contribute to symptoms of right heart failure, including fatigue, edema, and ascites. The murmur of TR usually increases in intensity with inspiration (Carvallo's sign) since inspiration augments RV filling. Examination of the neck veins reveals large V-waves. A pulsatile liver edge may also be felt in the right upper quadrant.

ECG often reveals right axis deviation and RV hypertrophy. Chest radiography may show an enlarged right heart border and obliteration of the retrosternal window. Echocardiography is valuable for identifying the cause of TR and estimating its severity. Primary valvular disease, such as vegetations with endocarditis, may be noticed, and pulmonary pressures can be estimated to determine if underlying pulmonary hypertension is present. There is almost universal right ventricular and atrial enlargement. Severe TR may be accompanied by hepatic vein systolic flow reversal.

Despite the significant volume load, in general, the RV tolerates severe TR remarkably well, and operation is rarely indicated. Therapy for secondary TR is targeted at the underlying disease process. For example, if there is LV failure, appropriate management with diuresis and afterload reduction may reduce the degree of functional TR. Similarly treatment of pulmonary hypertension may reduce the degree of TR. In severe TR, chronic diuretics are the mainstay of therapy to reduce symptoms, RV volume overload, and systemic venous hypertension. Tricuspid annuloplasty or replacement may be required for severe TR causing refractory symptoms of right heart failure or worsening RV systolic dysfunction.

21.7 Prosthetic Heart Valves

Valve replacement surgery has been a major breakthrough allowing patients with severe VHD to have better quality and length of life. Successful valve replacement surgery is dependent on the patient's myocardial function and general medical condition, as well as careful intra- and postoperative care. Durability and anticoagulation are the two most important long-term considerations. All valve prostheses have drawbacks, including the risk of thromboembolism, infective endocarditis, and mechanical failure. As a consequence, there has been an increasing emphasis on valve repair rather than replacement in recent years, particularly for primary MR.

Prosthetic valves may be either mechanical or bioprosthetic. Bioprosthetic valves are usually xenografts (porcine or bovine pericardium), but homografts from human cadavers may be used in complicated aortic valve endocarditis. All transcatheter valve replacements are bioprosthetic. In choosing an appropriate valve prosthesis, the need for anticoagulation, hemodynamic profile, durability, and patient preference must be considered. In general, considerations for choice of valve are similar for the aortic and mitral positions.

Mechanical valves have excellent durability and hemodynamic performance. However, all patients who have undergone valve replacement with a mechanical prosthesis are at risk for thromboembolic complications and must be maintained on systemic anticoagulation with warfarin, which in turn increases the risk of bleeding. The target INR level for a mechanical valve in the mitral position is higher (2.5–3.5) than the aortic position (2.0–3.0). Patients with an aortic mechanical valve at high risk for thrombotic events, including those with AF, LV dysfunction, previous thromboembolic event, or hypercoagulable state, should have a target INR of 2.5–3.5. High-risk patients with a bioprosthetic valve should have INR targets of 2.0–3.0. Low-dose aspirin therapy is recommended for all patients with a prosthetic valve [4]. Direct oral anticoagulants are not recommended for use in patients with mechanical heart valves owing to concerns about increased risk of thromboembolic and bleeding events [20]. They appear to be as effective and safe as warfarin for stroke prevention in the setting of AF with a bioprosthetic heart valve.

The principal advantage of bioprosthetic valves is the significantly reduced risk of thrombotic complication after 3 months, such that long-term anticoagulation is not indicated [21]. Recently, however, a small incidence (~5%) of surgical bioprosthetic leaflet thrombosis has been reported. It appears to respond to anticoagulation with either warfarin or a direct oral anticoagulant. The incidence of leaflet thrombosis is about twofold higher, however, with TAVR valves [13]. Bioprostheses are also at increased risk for structural deterioration. This deterioration requires repeat

valve surgery in up to 30% of patients by 10 years and in 50% by 15 years. Bioprosthetic valves remain the preferred choice for patients >65 years old. They are also indicated for women who expect to become pregnant, as well as in others who have a contraindication to or refuse to take anticoagulation. In patients without contraindication to anticoagulation who are <65 years old, a mechanical prosthesis is reasonable, but most patients opt for a tissue valve, and the decision must be individualized. There has been a trend to using bioprosthetic valves in younger patients given the increased durability of the new-generation bioprosthetic valves, decreased risk at reoperation, and aggregate risks of long-term anticoagulation. Valve-in-valve TAVR is now approved for treatment of high-risk patients with failed bioprostheses [22].

21.8 Preventing Infective Endocarditis

Emerging data on the lifetime risk of infective endocarditis, as well as trends in antibiotic resistance and antibiotic-associated adverse events, have led to changes in guideline recommendations for antibiotic prophylaxis [19]. Infective endocarditis is much more likely to occur from frequent exposure to random bacteremias associated with daily activities than with medical or dental procedures. Antibiotic prophylaxis for infective endocarditis should be provided to patients at greatest risk for complication from endocarditis. They include patients with prosthetic valves, previous endocarditis, complex congenital heart disease, or cardiac transplantation. There is ongoing research into trends in the incidence of endocarditis among moderate-risk patients (e.g., those with bicuspid aortic valves or MVP) since the 2007 change in recommendations. Prophylaxis in these high-risk populations is recommended for all dental procedures involving manipulation of gingival tissue or perforation of oral mucosa. Antibiotic prophylaxis may also be reasonable for procedures involving the respiratory tract, infected skin, or the musculoskeletal system. Antibiotic therapy solely to prevent endocarditis is no longer recommended for genitourinary or gastrointestinal procedures. Antibiotic prophylaxis is targeted to gram-positive oral and skin flora. Standard prophylaxis regimens in adults include amoxicillin (2 g 1 h before procedure) or if penicillin-allergic then clindamycin (600 mg 1 h before procedure) or azithromycin (500 mg 1 h before procedure).

Case Vignette 1

Mrs. C. H. is a 77-year-old woman with a history of controlled hypertension, type 2 diabetes mellitus, and hypercholesterolemia who was noted to have a 2/6 systolic ejection murmur after hospitalization for total hip arthroplasty 5 years previously. She had no difficulty rehabilitating from her surgery and resumed her normal activities, including walking the two flights of stairs in her house and doing her own grocery shopping. She returns to the clinic for her semiannual checkup and is now noted to have a late-peaking 3/6 systolic ejection murmur loudest at the base and radiating to the carotids with a diminished aortic component of the second heart sound. She has an apical S4 gallop, clear lungs, and no ankle edema. ECG reveals sinus rhythm and left ventricular hypertrophy. Echocardiography reveals a thickened and calcified aortic valve with reduced leaflet excursion. Her ejection fraction is 60%, and her peak transaortic velocity is 4.5 m/s with a peak gradient of 81 mmHg and an aortic valve area of 0.7 cm^2, findings consistent with severe aortic stenosis (Fig. 21.2). She is referred to a cardiologist for further evaluation.

Age-related calcific degeneration of the aortic valve with stenosis is associated with traditional coronary risk factors, including hypertension, diabetes mellitus, and dyslipidemia. Calcific AS is a progressive disease, though it may have a long latent phase during which mortality may be similar to that of similar patients without AS. Exercise testing fails to uncover any symptoms attributable to her aortic valve disease. Because of the importance of symptoms in determining the timing of referral for aortic valve surgery, Mrs. C.H. is told to seek medical attention immediately if she develops chest pain, shortness of breath, light-headedness, or any reduction in exercise capacity (Fig. 21.3). Given her severe AS, serial echocardiography and clinical follow-up every 6 months is arranged to monitor left ventricular function and progression of her already severe valve disease. In the meantime, she will be maintained on an antihypertensive regimen featuring an ACE inhibitor for hypertension, insulin therapy for diabetes, as well as HMG-CoA reductase inhibitor (statin) therapy for her hypercholesterolemia.

Case Vignette 2

Mr. J.M. is an 82-year-old man with history of coronary artery disease, history of myocardial infarction, coronary artery bypass surgery 12 years ago, mild systolic dysfunction with left ventricular ejection fraction 45%, stage 2 chronic kidney disease, hypertension, and diabetes on insulin therapy. He presents to your office complaining of progressive shortness of breath over several months, which has been limiting his ability to play double tennis. During the previous 6 months, he has also lost 5 pounds and has had a declining appetite. On physical exam, his jugular veins are distended to 12 cm, he has a 3/6 late-peaking systolic ejection murmur at the right upper sternal border with pulsus parvus et tardus, and 1+ lower extremity edema is present. Compared to his last visit, he appears frail and has evidence of evolving loss of skeletal muscle (sarcopenia). Resting ECG shows sinus rhythm and left ventricular hypertrophy, unchanged from his prior tracings, while serum laboratories reveal stable renal function.

He is referred for transthoracic echocardiography, which confirms ejection fraction 45% and severe valvular aortic stenosis with peak velocity 4.0 m/s and an aortic valve area estimated to be 0.6 cm^2. Because he has symptomatic severe aortic stenosis (stage D), he is referred to a multidisciplinary heart valve team for consideration of aortic valve replacement (Fig. 21.4). He is deemed to be a high-risk candidate for surgical AVR based on the Society of Thoracic Surgeons Risk Calculator due to his age, diabetes, reduced ejection fraction, and re-operative status. Instead he undergoes evaluation for transcatheter AVR (TAVR) (Fig. 21.5). Coronary catheterization shows no progression of his chronic coronary artery disease that would explain his worsening symptoms, while CT angiography confirms patent, large caliber peripheral arterial vasculature.

After a brief period of medical optimization with low-dose diuretics, the patient undergoes an uncomplicated transfemoral TAVR and is discharged from the hospital 3 days later. Follow-up echocardiography confirmed dramatic improvement in his transaortic gradient (Fig. 21.6). Following initial post-procedure recovery, the patient enrolls and completes a 12-week cardiac rehabilitation program including nutritional support. Six months after TAVR, he is back playing double tennis.

Case Vignette 3

Mr. C.D. is a 49-year-old man who was found to have a systolic ejection click and murmur 13 years ago during a routine health maintenance physical. He underwent echocardiography, which revealed myxomatous degeneration of the mitral valve with prolapse of the posterior mitral valve leaflet and moderate, anteriorly directed mitral regurgitation. He remained asymptomatic working as an investment banker. While walking to work one day, he developed palpitations and visited his primary care physician. Physical examination revealed a regular rhythm, with a 3/6 holosystolic murmur radiating throughout the precordium, accompanied by an enlarged, laterally displaced point of maximal impulse. He was referred to a cardiologist for further evaluation given his mitral regurgitation with palpitations and evidence of left ventricular enlargement on exam.

Resting ECG showed normal sinus rhythm with left atrial enlargement, and Holter monitoring revealed paroxysms of atrial tachycardia. Echocardiography demonstrated mitral valve prolapse with severe mitral regurgitation, moderate left atrial enlargement, and a left ventricular ejection fraction of 65%. (Fig. 21.5). Given the absence of myocardial dysfunction, he was provided reassurance that asymptomatic severe mitral regurgitation can be well tolerated for many years. However, he has been carefully followed every 6 months with serial echocardiography and clinical evaluations to determine when mitral valve repair would be indicated. (Fig. 21.6)

Mr. C.D. continues to work and has no exertional dyspnea in his daily activities or with light aerobic exercise but has been counseled against performing strenuous isometric exercise such as weight lifting. He does not require routine antibiotic prophylaxis for dental procedures since he is not at high risk for complication from endocarditis. He has been told to seek medical attention if symptoms of exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and fatigue develop, at which point mitral valve repair will be recommended. Mitral valve prolapse is the most common cause of severe mitral regurgitation in North America requiring surgical therapy.

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Pericardial Diseases

22

Fidencio Saldana and Leonard S. Lilly

22.1 Introduction

Pericardial disease may present as an isolated condition or as a manifestation of systemic illness. Recognition of the clinical signs and symptoms of pericardial disorders in the primary care setting is critical for appropriate, and potentially lifesaving, triage and management. This chapter considers acute pericarditis and its potential complications relevant to the primary care provider: recurrent pericarditis, pericardial effusion, and constrictive pericarditis.

22.2 Anatomy/Physiology

The pericardium is a fibroserous sac that consists of two layers. The outer fibrous layer (the *parietal pericardium*) is composed of collagen and elastic fibers, which allow the pericardium to gradually expand if subjected to chronic stretch. The internal portion of the fibrous pericardium is composed of a serous layer, which reflects onto the epicardial surface of the heart, forming the *visceral pericardium* [1]. The space between the parietal and visceral layers normally contains 15–35 mL of serous fluid, providing lubrication to the heart's movements. The pericardium is well innervated with nerve afferents so that acute inflammation produces pain and vagal reflexes [2].

The pericardium attaches to the diaphragm, sternum, and neighboring structures in the anterior mediastinum and, in this manner, serves to anchor the heart within the thorax. Additionally, the pericardium is thought to limit acute dilatation of the heart [3]. The ability to restrain myocardial expansion is likely one of the most important functions of the pericardium. Despite these presumed actions, the complete absence of the pericardium (e.g., congenitally) is generally without clinical consequence [4].

The fibrous pericardium has the tensile strength of rubber [5]. As such, a sudden increase in volume within the pericardial space results in an equal external pressure against each of the cardiac chambers, which can lead to hemodynamic instability, as described below. Conversely, a slow increase in volume, over weeks to months, allows gradual stretching and accommodation of greater volume before chamber compression occurs.

22.3 Acute Pericarditis

22.3.1 Case Study 1

A 51-year-old woman with a history of Hodgkin lymphoma presents to the outpatient office with the gradual onset of left anterior pleuritic chest pain and mild dyspnea. The chest pain is non-radiating, dull, and worse with chest and arm movements and is relieved by sitting forward. She also reports 2 weeks of malaise and fatigue accompanied by low-grade fever. On physical examination, she appears uncomfortable and anxious. The temperature is 99 °F, pulse rate 120 bpm, and blood pressure 125/70 mmHg, with pulsus paradoxus of 6 mmHg. The jugular venous pressure is 7 cm water. Her chest is clear to percussion and auscultation. On cardiac examination there is no retrosternal dullness. No murmurs, gallops, or rubs are auscultated. The electrocardiogram (Fig. 22.1) demonstrates ST-segment elevation in most of the ECG leads. A transthoracic echocardiogram (Fig. 22.2) obtained at the outpatient center reveals a small circumferential pericardial effusion with no signs of cardiac tamponade physiology.

22.3.1.1 Epidemiology and Etiology

Case Study 1 depicts the classic presentation of acute pericarditis, an inflammatory condition of the pericardial sac,

F. Saldana · L. S. Lilly (✉)
Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
e-mail: llilly@bwh.harvard.edu

P. P. Toth, C. P. Cannon (eds.), *Comprehensive Cardiovascular Medicine in the Primary Care Setting*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-319-97622-8_22

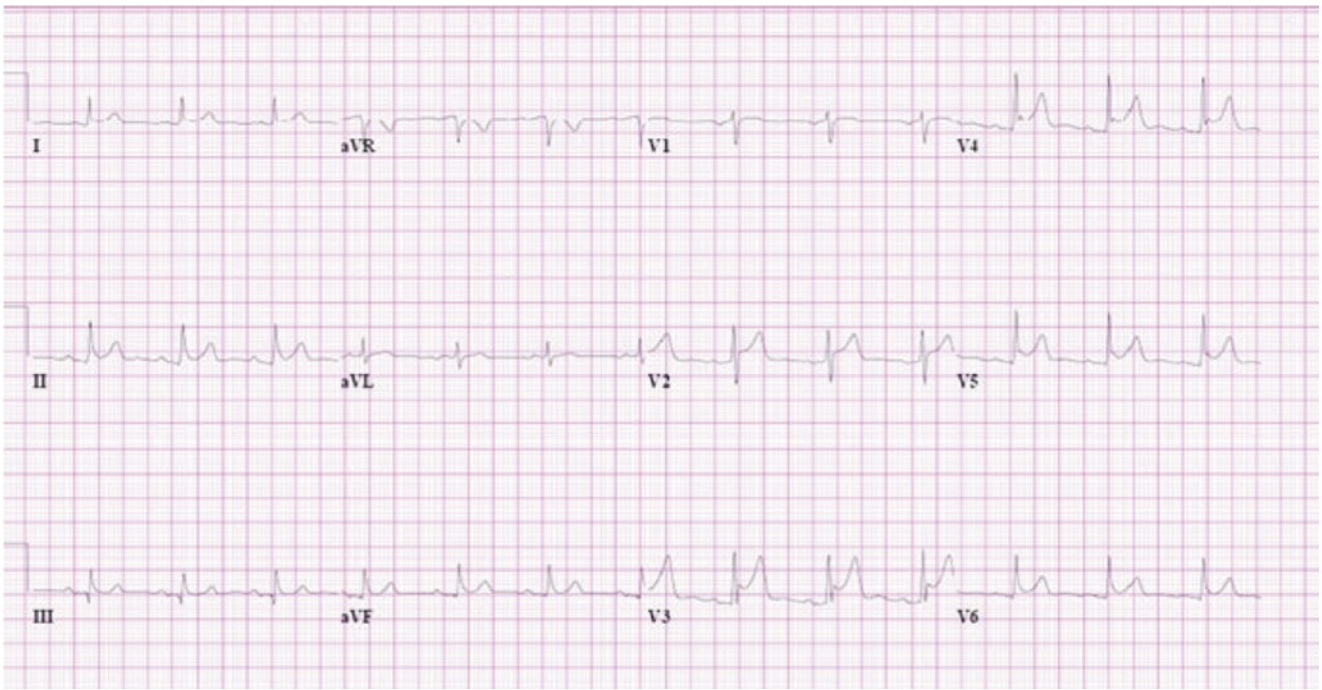

Fig. 22.1 Twelve-lead electrocardiogram of acute pericarditis, Stage 1. Diffuse concave upward ST-segment elevation is present

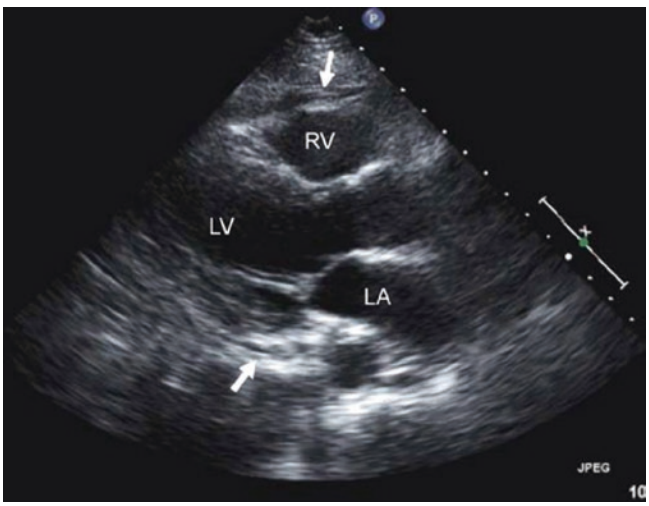

Fig. 22.2 Case Study 1. Two-dimensional echocardiogram, parasternal long-axis view, demonstrating a small pericardial effusion (*black arrows*). *LA* left atrium, *LV* left ventricle, *RV* right ventricle

Table 22.1 Causes of acute pericarditis

Infectious
Viral
Bacterial and mycobacterial
Fungal and protozoal
Autoimmune disorders
Systemic lupus erythematosus
Rheumatoid arthritis
Scleroderma
Malignancy
Breast and lung carcinoma
Lymphoma
Metabolic disorders
Uremia
Hypothyroidism
Drugs
Hydralazine
Procainamide
Diphenylhydantoin
Isoniazid
Following mediastinal irradiation
Following cardiothoracic surgery
Following myocardial infarction

the differential diagnosis of which is broad (Table 22.1). As many as 90% of cases of acute pericarditis are considered to be post-viral or of unknown ("idiopathic") origin [6]. The majority of idiopathic cases are actually likely due to undetected viral infection, often with enteroviruses (e.g., coxsackievirus, echovirus) [7]. Less common viral causes of acute pericarditis include herpesviruses (CMV, Epstein–Barr virus, HHV-6), adenovirus, and parvovirus B19. Acute pericarditis can also result from non-viral infections, autoimmune disorders, malignancy (most commonly lung or breast carcinoma or lymphoma), and uremia, following transmural myocardial infarction, cardiac surgery, or chest irradiation therapy or as a result of specific medications such as isoniazid and hydralazine [5, 7, 8].

Tuberculosis (TB) is only rarely encountered as a cause of pericarditis in industrialized countries. However, it is an

important etiology in immunocompromised patients and in less developed regions of the world. In Africa, TB is the most common source of pericardial disease in patients with HIV infection [8].

Echocardiographic or postmortem evidence of pericardial inflammation is very common in autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis with reported prevalences of 40–80%. However, symptomatic manifestations of acute pericarditis occur in <30% of patients with these conditions [9, 10].

A form of post-MI pericarditis that may be encountered in the primary care office is *Dressler syndrome*, which can arise weeks or months following an acute myocardial infarction and is thought to be of autoimmune origin, resulting from exposure to antigens released from necrotic myocardial cells. This form of pericarditis has become rare in the era of acute reperfusion therapies for acute ST-segment elevation myocardial infarction. A more common similar syndrome, *post-pericardiotomy pericarditis*, may present weeks following cardiac surgical procedures [7].

22.3.1.2 Clinical Presentation

Patients with acute pericarditis typically present with chest discomfort that may mimic more serious conditions such as myocardial infarction or pulmonary embolism [6]. However, the pain is typically pleuritic and positional in nature, worsening with recumbency and improving when the patient sits and leans forward. The discomfort can radiate widely; however, localization to the trapezius ridge is highly suggestive of pericardial irritation, as the phrenic nerve innervates both the pericardium and the trapezius muscle [2]. The discomfort tends to be rapid in onset and can last for hours to days [11].

Symptoms of a viral syndrome, including low-grade fever and malaise, may precede post-viral pericarditis. In cases of pericarditis that develop more gradually (e.g., uremia, collagen vascular conditions, tuberculosis, neoplastic disease), the patient may not describe any chest pain at all. *High* fever and more severe symptomatology are typical of bacterial (purulent) pericarditis.

A thorough review of systems and past history can help identify specific etiologies of acute pericarditis. For example, drug-induced pericarditis should be considered in a patient taking isoniazid, diphenylhydantoin, or hydralazine. A history of HIV or mycobacterium infection should lead to consideration of those pathogens or associated complications. A prior malignancy may raise the concern of recurrence manifesting as pericardial involvement.

22.3.1.3 Physical Examination

Approximately one-third of patients with acute pericarditis manifest a pericardial friction rub [8]. It is best auscultated over the left mid-to-lower sternal border, while the patient leans forward [12]. The character of the rub can be scratchy, leathery, or the crunchy sound of walking in snow and can be distinguished from a pleural rub by a breath hold, which extinguishes the latter [7, 12]. It is most often triphasic, representing the phases of rapidly changing cardiac volumes: ventricular ejection, rapid ventricular filling in early diastole, and atrial systole [5, 12]. The mechanism that produces the rub may not solely be the interaction between the inflamed pericardial layers as the finding can be detected even in patients with large pericardial effusions, in whom the layers are widely separated from one another [12]. In any patient with acute pericarditis, it is important to inspect for potential signs of cardiac tamponade described in more detail below: hypotension, distended neck veins, and distant heart sounds.

22.3.1.4 Electrocardiogram

The electrocardiogram can help distinguish pericarditis from other forms of chest discomfort. There are usually diffuse ST-segment elevations in the limb and precordial leads, typically with the exception of lead aVR. This is commonly accompanied by PR-segment deviation opposite to the direction of the P-wave. These findings reflect epicardial irritation of both the ventricles and the atria [13]. The electrocardiographic abnormalities typically evolve in four stages [2, 14, 15]:

Stage 1—Diffuse ST-segment elevations and PR-segment deviations (see Fig. 22.1)
Stage 2—Normalization of the ST- and PR-segments
Stage 3—Diffuse T-wave inversions (often weeks later)
Stage 4—Complete resolution

More than 60% of patients with acute pericarditis present with Stage 1 electrocardiographic findings [8]. Anti-inflammatory treatment has been shown to prevent further progression of the ECG abnormalities [16].

There are several characteristics that distinguish the ECG findings of pericarditis from those of acute myocardial infarction. In patients with acute ST-segment elevation myocardial infarction (STEMI), the ST-segment elevation is localized to the region of the involved myocardium and is accompanied by ST depression in the opposite leads. The direction of the ST-segment elevation is typically concave upward in pericarditis but convex upward in STEMI. In addition, in infarction, T-wave inversions develop, while the ST-segments are still elevated, whereas this occurs many days later in pericarditis, after the ST-segments have returned to baseline (Stage 3). Finally, acute myocardial infarction does not cause deviations of the PR-segment.

Individuals with the common ECG variant known as *early repolarization* display baseline ST elevations that can mimic Stage 1 pericarditis. However, in distinction to those with early repolarization, the height of the ST-segment in acute pericarditis tends to be >25% of the height of the T-wave.

22.3.1.5 Chest X-Ray

The chest radiograph may be normal in uncomplicated pericarditis. However, the presence of a large effusion (>250–300 mL) is manifest as a symmetrically enlarged cardiac silhouette [7].

22.3.1.6 Blood Studies

Measurement of acute and convalescent serum viral titers, or virus identification by polymerase chain reaction (PCR) testing, is not of practical value in the diagnosis of pericarditis as most patients will have recovered before such results are available. Indicators of systemic inflammation are often elevated in acute pericarditis, and while there is no consensus on the utility of measuring markers, such as C-reactive protein or erythrocyte sedimentation rate (ESR), they can be helpful in establishing the diagnosis or following the course of disease [7]. In general, a modestly elevated ESR is consistent with idiopathic or post-viral pericarditis, while higher levels are suggestive of underlying inflammatory states such as rheumatoid arthritis, systemic lupus erythematosus, or tuberculosis. Similarly, a mild leukocytosis is typical of viral or idiopathic pericarditis, whereas a markedly elevated white blood cell count is more consistent with purulent pericarditis. In 35–50% of patients with pericarditis, troponin levels are increased due to extension of inflammation to the adjacent myocardium [17–19]. However, elevation of cardiac-specific troponins is not a negative prognostic marker in acute pericarditis [20–22].

22.3.1.7 Echocardiogram

Current guidelines recommend that a transthoracic echocardiogram be obtained in patients with suspected pericardial disease to assess for effusion, contributing pathology, and evidence of impending hemodynamic compromise [7]. In patients with uncomplicated pericarditis, the echocardiogram may be completely normal. If a pericardial effusion has formed, it is visualized as an echo-free space external to the cardiac chambers, as in Fig. 22.2 [6]. The smallest effusions appear posterior to the left ventricle because of the effect of gravity. Larger effusions wrap around the sides of the heart and, if more than approximately 250 mL has accumulated, appear anterior to the right ventricle as well.

22.3.1.8 Treatment

Idiopathic or post-viral pericarditis is a self-limited condition that tends to improve spontaneously within 1–3 weeks. Drug therapies are employed for earlier symptomatic relief. The European Society of Cardiology has published guidelines with management strategies [7]. The mainstay of acute treatment is oral nonsteroidal anti-inflammatory agent (NSAIA) therapy such as aspirin (2–4 g daily), ibuprofen (1600–3200 mg daily), or indomethacin (75–225 mg daily) [7]. No one NSAIA appears to be more effective than others; ibuprofen is used frequently in North America, and aspirin tends to be preferred in Europe. For individuals who have sustained a recent myocardial infarction, aspirin is the drug of choice given a concern of impairment of healing of infarcted tissue by other NSAIAs in animal models [6]. In addition to oral NSAIAs, parenteral ketorolac has been shown to be effective at resolving symptomatic acute pericarditis [23].

Colchicine, in combination with an NSAIA, has been shown to shorten initial symptoms and reduce the recurrence rate of acute pericarditis. The prospective ICAP trial randomized patients with a first episode of acute pericarditis to colchicine (0.5 mg twice daily or 0.5 mg once daily for weight ≤70 kg for 3 months) or placebo in addition to NSAIA therapy. Colchicine reduced the rate of recurrent pericarditis (16.7% compared to 37.5% in the placebo-treated patients) and shortened the duration of initial symptoms [24]. Conversely, corticosteroids are not recommended as first-line agents in uncomplicated pericarditis as their use predisposes to relapses [7, 25, 26].

Symptoms typically resolve within days of treatment, often after the first few doses. NSAIAs are usually continued for 7–14 days followed by gradual reduction in dosage over 1–2 weeks for a total treatment time of 3–4 weeks. If colchicine is used, it should be continued for 3 months, as was the protocol in clinical trials. Acute pericarditis is not an absolute contraindication to concurrent anticoagulation therapy in patients with atrial fibrillation or intracardiac thrombus. However, the risks and benefits of continued anticoagulation must be evaluated on a patient-by-patient basis.

22.3.1.9 Triage

Identification of high-risk features is important in the triage of patients with acute pericarditis. Findings that warrant hospitalization and close observation include a large circumferential pericardial effusion, cardiac tamponade, patients who are on anticoagulation therapy, high fever, underlying immunosuppressed state, evidence of accompanying myocarditis, or trauma-associated pericarditis (Fig. 22.3) [21, 27]. There is no consensus on triage of patients who do not exhibit such high-risk features. In general, patients with uncomplicated idiopathic/post-viral pericarditis can be safely treated in an observation setting for several hours, have an echocardiogram performed, and, if stable, return home [21].

22.4 Recurrent Pericarditis

Between 15% and 30% of patients treated for acute pericarditis experience relapses after a symptom-free interval [11, 24]. Symptoms are similar to the initial episode, characterized by fever, pleuritic chest pain, pericardial rub, and elevation of inflammatory markers [28]. Recurrences may relate to an immune-mediated reaction following the initial episode or may be the manifestation of a previously undiagnosed and

ongoing inflammatory condition such as an autoimmune disorder [6, 11].

Relapses can be challenging to suppress. The first defense is prevention of recurrent episodes by optimizing treatment of the index presentation. As noted above, the ICAP trial demonstrated a decreased recurrence rate in patients with acute pericarditis treated with NSAIA therapy plus colchicine compared with an NSAIA alone [24]. Once a recurrence develops, symptoms often respond to renewed therapy with an NSAIA agent plus colchicine. In the prospective Colchicine for Recurrent Pericarditis (CORE) trial, 84 patients with a first bout of recurrent pericarditis were randomized to aspirin alone versus aspirin in addition to colchicine (1.0–2.0 mg on the first day and then 0.5–1.0 mg daily for 6 months). Compared with aspirin alone, the combination reduced further recurrences by 50%, and symptom persistence at 72 h fell by approximately 33% [29]. Recurrent episodes with refractory symptoms may require the addition of a corticosteroid [7]. Of note, a retrospective review of 100 patients with recurrent pericarditis concluded that lower steroid doses (prednisone 0.2–0.5 mg/kg/day) were better tolerated and were associated with fewer subsequent recurrences than historically used higher dosages [7, 30]. Patients with persistent symptoms or recurrent episodes that fail to cease with these measures should be referred to a specialist for consideration of advanced approaches, such as more powerful immunosuppressive regimens or pericardiectomy [7].

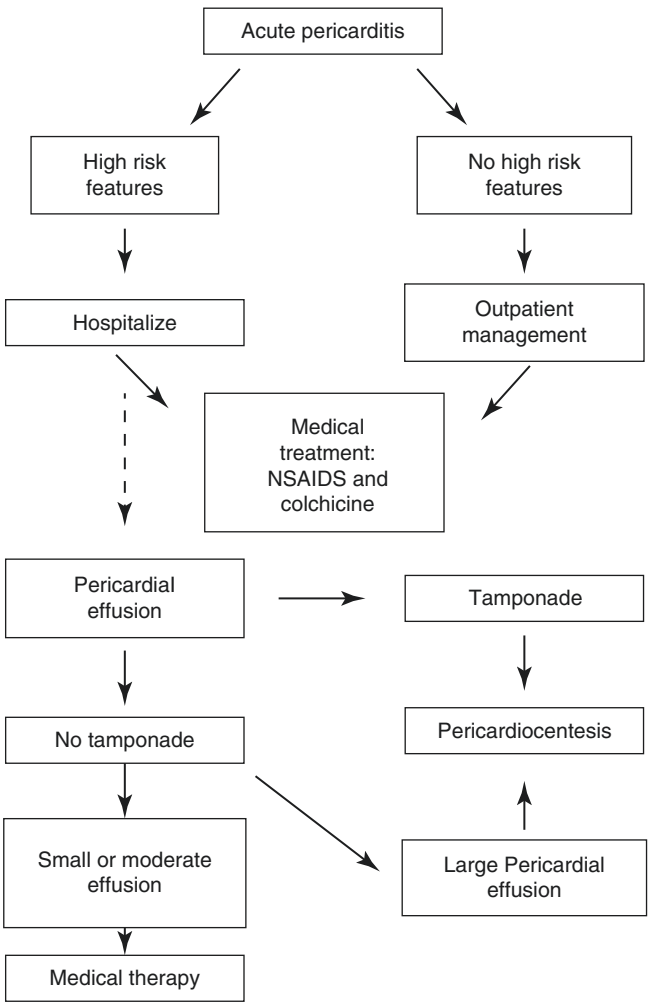

Fig. 22.3 Approach to the management of acute pericarditis and pericardial effusion. *NSAIDs* nonsteroidal anti-inflammatory drugs

22.5 Pericardial Effusion

22.5.1 Case Study 2

The 51-year-old woman from Case Study 1 returns to her primary care doctor 2 weeks after her initial presentation. Her symptoms had responded initially to a course of ibuprofen plus colchicine. The colchicine was discontinued after a few days due to diarrhea. Her current symptoms are increasing dyspnea on exertion and chest fullness when she leans toward her left side. She denies fevers, sweats, or chills.

On physical examination, the temperature is 98 °F, heart rate 115 bpm, and blood pressure 112/70 mmHg with a pulsus paradoxus of 15 mmHg. The jugular venous pressure is 12 cm water. The chest is clear to auscultation. On cardiac exam, there is retrosternal dullness, and a pericardial friction rub is auscultated. There is no abdominal distension, hepatomegaly, or peripheral edema. The patient undergoes an urgent echocardiogram (Fig. 22.4), which demonstrates a large circumferential pericardial effusion with right atrial and right ventricular diastolic collapse.

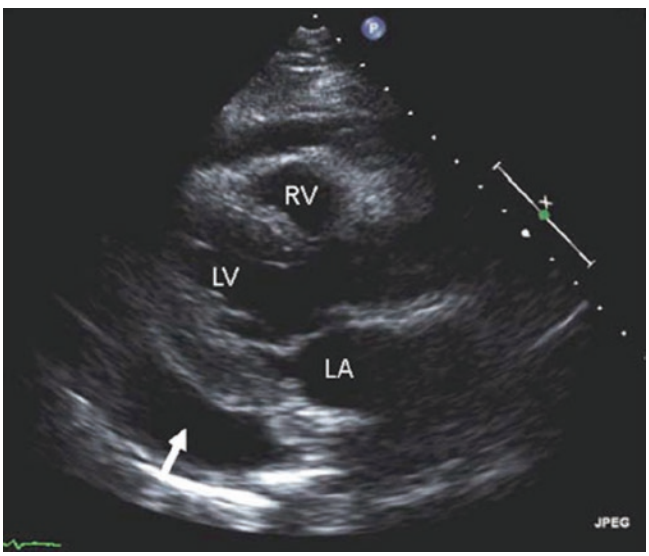

Fig. 22.4 Case Study 2. Echocardiogram demonstrating a large pericardial effusion (*white arrow*). *LA* left atrium, *LV* left ventricle, *RV* right ventricle

22.5.1.1 Etiology

A pericardial effusion results from the accumulation of fluid within the potential space between the visceral and parietal pericardial layers. Fluid accumulation can result from an inflammatory reaction, direct trauma, or obstruction of lymphatic drainage [11]. The etiologies of acute pericardial disease in Table 22.1 are all potential causes of pericardial effusion accumulation. Large effusions are most commonly idiopathic, neoplastic, or uremic in origin [29, 31]. As many as 15% of patients with idiopathic pericarditis and 60% of patients with purulent or malignant disease present with an effusion [32].

Effusions that are most likely to progress to tamponade are those caused by trauma, non-viral infections (bacterial, fungal), and malignancy. It is unusual for idiopathic/post-viral pericarditis to lead to tamponade.

22.5.1.2 Pathophysiology

The pericardium has only a limited potential for expansion. A sudden increase in pericardial volume, even of small quantity, can lead to hemodynamic instability due to external compression of the cardiac chambers, resulting in diminished cardiac output and possible cardiogenic shock. Conversely, a slowly accumulating effusion (over weeks or months) can stretch the pericardium and accommodate a much larger volume (e.g., >1 L) before tamponade physiology develops [5].

22.5.1.3 Clinical Presentation

In the primary care setting, a pericardial effusion may come to light in the setting of known pericarditis, as an incidental finding on an imaging study, or in an individual who presents with symptoms of tamponade [2, 33]. In the absence of tamponade physiology, a patient with a pericardial effusion may not have symptoms attributable to it. Conversely, patients with tamponade typically manifest dyspnea, chest discomfort, cough, and evidence of decreased cardiac output [11, 33].

22.5.1.4 Physical Examination

Patients with a small pericardial effusion may not have any abnormal findings on exam. The only clue to its presence may be distant heart sounds on auscultation and retrosternal dullness to percussion. A pericardial rub may be present [12]. Conversely, in patients who have developed tamponade, the triad of hypotension, distant heart sounds, and elevated jugular venous pressure is expected [34]. Furthermore, tamponade physiology produces pulsus paradoxus, an abnormal decline in blood pressure with normal inspiration (see Section 22.6) [2, 34]. One review analyzed five features observed in patients with tamponade: dyspnea, tachycardia, pulsus paradoxus, elevated jugular venous pressure, and cardiomegaly on chest radiography. Of these features a pulsus paradoxus >10 mmHg identified the presence of tamponade with a sensitivity of 98% and specificity of 70% [34, 35]. Of note, pulsus paradoxus may not appear in tamponade when coexisting conditions impede respiratory alterations in left ventricular filling, including left ventricular dysfunction, aortic regurgitation, and atrial septal defects. Conversely, conditions that cause large alterations in intrathoracic pressure (e.g., advanced obstructive airway disease or pulmonary embolism) can produce pulsus paradoxus in the absence of tamponade.

22.6 Pulsus Paradoxus

Measurement of pulsus paradoxus at the bedside is of great value in assessing the hemodynamic significance of a pericardial effusion. During the respiratory cycle in healthy patients, inspiration draws blood from the systemic veins into the thorax and the right side of the heart, causing the interventricular septum to bow toward the left, which transiently reduces LV filling. As a result, LV stroke volume declines, and systolic blood pressure normally falls slightly (<10 mmHg) with inspiration. In tamponade, this mechanism is exaggerated by the presence of high-pressure pericardial effusion compressing the cardiac chambers. The more marked inspiratory decline in LV filling in tamponade reduces the LV stroke volume to a greater extent, and the systolic blood pressure falls >10 mmHg.

22.6.1 Procedure to Measure Pulsus Paradoxus

The arm sphygmomanometer is inflated to a level greater than the systolic pressure. As the cuff is slowly deflated, note the pressure at which the first Korotkoff sound is heard. Next listen as the Korotkoff sound at that level disappears with inspiration. Then continue to deflate the cuff slowly until the Korotkoff sounds stop drifting in and out, i.e., they are heard during both inspiration and expiration. The difference in pressure between the first Korotkoff sound and when the Korotkoff sounds are heard during both inspiration and expiration is the pulsus measurement.

22.6.2 Electrocardiogram

A large pericardial effusion decreases transmission of electrical forces from the myocardium resulting in decreased voltage on the ECG [34]. In addition, a sufficiently large effusion allows the heart to swing back and forth within the pericardial sac. This is manifest as beat-to-beat variation in the axis of the QRS complex on the ECG, causing *electrical alternans* (Fig. 22.5) [36].

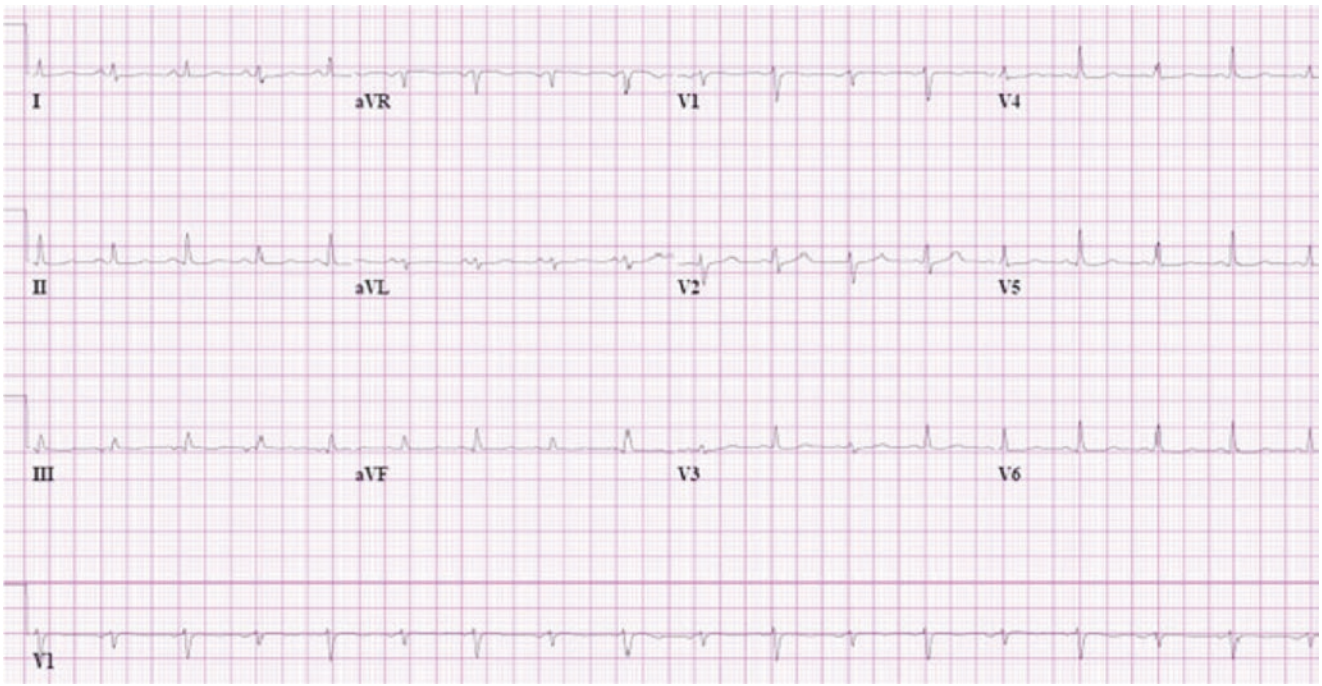

Fig. 22.5 Twelve-lead electrocardiogram and V1 rhythm strip demonstrating electrical alternans

22.6.3 Chest X-Ray

If a pericardial effusion is greater than ~250–300 mL in volume, the cardiac silhouette enlarges, typically in a symmetrical fashion.

22.6.4 Echocardiogram

Echocardiography is the most useful noninvasive modality in the diagnosis of pericardial effusion and cardiac tamponade [37, 38]. The location and size of the pericardial effusion as well as its hemodynamic impact can be readily assessed. Important signs of tamponade include diastolic collapse of the right ventricle and the right atrium, distention of the inferior vena cava, and exaggerated reciprocal respiratory variations in mitral and tricuspid diastolic Doppler velocities. Magnetic resonance imaging and computed tomography can also help localize and characterize pericardial effusions but rarely add to the clinical information afforded by echocardiography in the evaluation of tamponade physiology [39].

22.6.5 Treatment of Pericardial Effusion with Cardiac Tamponade

Cardiac tamponade is a medical emergency requiring rapid recognition and management. Patients who present in the primary care setting with findings consistent with this diagnosis should be immediately triaged to the hospital for consideration of urgent pericardiocentesis. When performed, pericardial fluid analysis for diagnostic purposes should include cytology and bacterial, fungal, and mycobacterial cultures [8, 40]. However, the diagnostic yield of pericardial fluid culture for *M. tuberculosis* is low. If TB is suspected, a more rapid diagnosis from the pericardial fluid can be accomplished by polymerase chain reaction or by the finding of an elevated level of adenosine deaminase [41].

22.6.6 Management of Pericardial Effusion Without Tamponade

Asymptomatic patients with small- to moderate-sized effusions can be followed with serial echocardiograms to ensure ultimate resolution. Pharmacologic treatment aimed at decreasing pericardial inflammation should be considered (e.g., NSAIA and/or colchicine; see Section 22.3) [7]. When the cause of effusion is not clear from the clinical presentation, investigating for specific etiologies should be undertaken, such as testing for tuberculosis; serologic evaluation (e.g., antinuclear antibodies) for collagen vascular diseases; mammography and chest CT for screening of breast and lung cancers, respectively; and, in the appropriate clinical contexts, assessing for Lyme disease or hypothyroidism.

Patients with asymptomatic large chronic pericardial effusions who are being followed in the outpatient setting may occasionally develop tamponade unexpectedly [42].

Reassuringly, in one series of 45 patients with large pericardial effusions managed conservatively, no progression to tamponade was demonstrated [40].

22.7 Constrictive Pericarditis

22.7.1 Etiology and Pathophysiology

Constrictive pericarditis is characterized by a thickened and/or scarred pericardium with abnormal rigidity that impairs filling of the cardiac chambers [7, 43]. Any of the etiologies of acute pericarditis listed in Table 22.1 can result in constrictive pericarditis. The most common causes are idiopathic pericarditis, post-cardiac surgery, and prior mediastinal radiation therapy [44]. Tuberculous pericarditis, no longer a common cause of constrictive pericarditis in the developed world, remains an important etiology in developing countries [7].

In constriction, pericardial compliance becomes the limiting factor of ventricular filling leading to elevation and equalization of diastolic intracardiac pressures [5]. In early diastole (just after the mitral and tricuspid valves open), the ventricles actually begin to fill quite briskly because atrial pressures are typically elevated. However, as soon as the ventricles fill to the limit imposed on them by the surrounding rigid pericardium, filling abruptly ceases. Venous congestion results from the elevated diastolic pressures, and the reduced LV filling impairs ventricular stroke volume and forward cardiac output.

22.7.2 Clinical Presentation

Clinical findings in constrictive pericarditis develop insidiously over a period of months to years. Patients typically present with systemic congestion out of proportion to pulmonary congestion. Symptoms of right-sided heart failure in constriction include elevated jugular venous pressure, hepatic congestion, early satiety, ascites, and peripheral edema. Dyspnea in the absence of pulmonary congestion is also common [7]. Late in the disease, signs of reduced cardiac output become manifest including cachexia and muscle wasting.

22.7.3 Physical Exam

The jugular venous pressure is markedly elevated with two prominent descents during each cardiac cycle (*x* and *y* descents), creating a distinctive filling and collapsing pattern that is often evident from across the room. In distinction to normal individuals, the degree of jugular venous distention fails to decrease, or may increase further, with inspiration (*Kussmaul sign*). In normal individuals, inspiration decreases intrathoracic pressure resulting in increased venous return to the heart and a decline in jugular venous pressure. Conversely, in pericardial constriction the inspiratory decrease in intrathoracic pressure is not transmitted through the rigid pericardium to the cardiac chambers, resulting in an increased jugular venous pressure instead. On cardiac auscultation there may be a *pericardial knock*. This is a high-pitch sound that is best heard at the left sternal border or the apex in early diastole. It corresponds to the abrupt cessation of ventricular filling in early diastole. Additional physical findings include abdominal distension, ascites, and peripheral edema.

22.7.4 Laboratory Studies

There are no specific findings of constrictive pericarditis on the electrocardiogram, usually simply nonspecific ST- and T-wave abnormalities. However, atrial arrhythmias such as atrial fibrillation are common, and about one-third of patients manifest low QRS voltage. The chest radiograph may show a rim of pericardial calcification, particularly in those with chronic tuberculous pericarditis, best observed at the right heart border on a lateral projection. Echocardiography may demonstrate a thickened pericardium, but this is often difficult to visualize by a standard transthoracic study. Doppler analysis reveals a characteristic pattern that can be differentiated from other causes of diastolic dysfunction such as restrictive cardiomyopathy (see Table 22.2) [45, 46]. Cardiac magnetic resonance imaging and computed tomography are superior to echocardiography in visualizing pericardial anatomy. Pericardial thickness is usually increased at >2 mm in patients with constrictive pericarditis, though nearly 20% of patients with proven constriction have normal thickness [47]. Cardiac catheterization demonstrates elevation and equalization of right and left ventricular diastolic pressures with abrupt cessation of diastolic filling as ventricular volumes reach the limit imposed by the constricting pericardium.

22.7.5 Treatment

Complete surgical pericardiectomy is the mainstay of treatment in patients with advanced constrictive pericarditis [7]. Pericardiectomy results in symptomatic improvement rapidly in many patients, but recovery may be more gradual in those with associated myocardial stiffness or fibrosis. Patients with constriction due to viral/idiopathic pericarditis have the best outcomes after surgery, while results are less favorable in those with radiation-associated constriction [44].

Table 22.2 Findings that differentiate constrictive pericarditis from restrictive cardiomyopathy

	Constrictive pericarditis	Restrictive cardiomyopathy
Physical examination		
Kussmaul sign Pericardial knock	Common May be present	Uncommon Absent
Chest X-ray		
Pericardial calcification	May be present	Absent
Echocardiography		
Thickened pericardium	Present	Absent
Thickened myocardium	Absent	Common (may be "speckled" in infiltrative disease)
Exaggerated variation in transvalvular velocities	Present	Absent
Doppler tissue imaging at mitral annulus (represents LV relaxation rate at earliest phase of diastole)	Normal (>8 cm/s)	Reduced (<8 cm/s)
CT or MRI		
Thickened pericardium	Usually	Absent
Cardiac catheterization		
Equalized RV and LV diastolic pressures	Yes	LV often > RV by more than 3–5 mmHg
Endomyocardial biopsy	Normal	Usually abnormal (e.g., amyloid)

LV left ventricle, *PA* pulmonary artery, *RV* right ventricle

22.7.6 Constrictive Pericarditis Versus Restrictive Cardiomyopathy

The clinical findings of constrictive pericarditis can closely resemble those of restrictive cardiomyopathy (e.g., cardiac amyloidosis). Both of these pathologies result in impaired diastolic ventricular filling. The distinction is important as constrictive pericarditis is treatable with surgical resection, while options for restrictive cardiomyopathies are much more limited. Table 22.2 lists common features that cardiologists consider in differentiating these entities.

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Common Atrial and Ventricular Arrhythmias

23

Blair Foreman

Key Points

- Appropriate history taking facilitates arrhythmia diagnosis.
- A systematic approach to ECG interpretation helps avoid diagnostic pitfalls.
- Many clinical syndromes are due to a continuum of cardiovascular disease.
- Atrial fibrillation and atrial flutter are often grouped together but comprise distinct clinical entities.
- Genetic cardiac diseases and their evaluation are growing in today's clinical practice.
- Guidelines have been published on the evaluation and treatment of a myriad of cardiac arrhythmic syndromes.
- Antiarrhythmic drug therapy is often giving way to aggressive therapy with pacemaker, implantable cardioverter-defibrillators, and invasive arrhythmia ablation.

23.1 Introduction

Cardiac arrhythmias and their clinical correlates form the basis for some of the most intriguing aspects of cardiac care. During training, however, emphasis is often placed on care related to congestive heart failure, myocardial infarction, and the treatment of dyslipidemias. Unfortunately, patient complaints related to cardiac arrhythmias are often a common reason for a patient's presentation to emergency rooms, for office visits, and for referrals to subspecialists.

B. Foreman (✉)
Cardiovascular Medicine, Midwest Cardiovascular Research Foundation, Davenport, IA, USA

One must develop a basic understanding of cardiac anatomy, cardiac pharmacology, and basic electrocardiogram (ECG) interpretation to accurately evaluate and treat cardiac arrhythmias. Combining the patient's history with knowledge of expected arrhythmias associated with a variety of disease states, the ECG can then be used as a tool to verify a patient's specific arrhythmic complaint. In certain circumstances, while the clinical complaints suggest an arrhythmic component, one may often find through thorough evaluation that indeed no arrhythmia exists. Only through a systematic approach to evaluation can one make the correct diagnosis.

Clinical manifestations of cardiac arrhythmias include symptoms of irregular heart beating or awareness of heart beating (palpitations), altered consciousness, lightheadedness, chest fullness, chest pain, heart failure, and syncope and may include sudden cardiac death. Recurrent symptoms may also be a clue to the arrhythmia.

Inherent in the identification of common and less common arrhythmias is the importance of timing in evaluation and treatment. Multiple guidelines and consensus statements have been published over the last several years to help guide the evaluation and treatment of arrhythmic abnormalities. Throughout the chapter, use of these guidelines that may aid in the prompt diagnosis of the majority of the arrhythmias will be presented. Treatment strategies will also be discussed.

The surface ECG is a culmination of cardiac cellular depolarization and repolarization within the atria and ventricles. Changes in the normal pattern of cellular electrophysiologic events result in pattern changes at the macroscopic level. To better understand cardiac arrhythmias, a basic understanding of these events is helpful. Due to special conduction tissue within the heart, sinus node and atrioventricular (AV) node tissue are distinctly different than atrial tissue, Purkinje tissue, or ventricular myocardium. In Fig. 23.1, generalized cellular activation is shown for both tissue groups. Features of the sinus and AV node tissue

P. P. Toth, C. P. Cannon (eds.), *Comprehensive Cardiovascular Medicine in the Primary Care Setting*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-319-97622-8_23

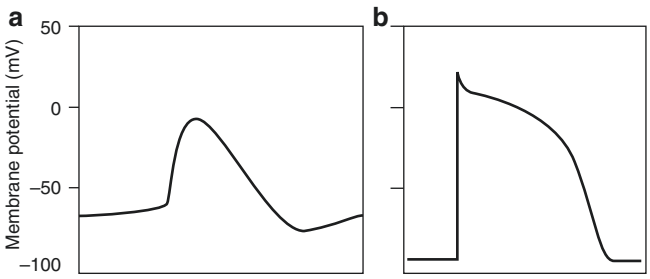

Fig. 23.1 Stylized representation of the action potential in predominantly calcium-dependent cardiac tissues and sodium-dependent cardiac tissues. (**a**) Sinoatrial node and AV node tissue rely on a slower, calcium-dependent phase 0 depolarization. (**b**) Nonspecialized atrial and ventricular tissue, typical accessory pathways, and His-Purkinje tissue rely on rapid phase 0 depolarization

include a calcium-dependent upstroke of phase 0 of the action potential and prolonged action potential duration and refractory period at more rapid rates. This results in slower propagation through the tissue at faster intrinsic heart rates. At faster rates, early coupled extrasystoles are less likely to be propagated.

In contrast, atrial, His-Purkinje, and ventricular tissue have a rapid, sodium-dependent upstroke in phase 0. At faster rates, action potential duration shortens resulting in a shorter refractory period, and conduction rates through tissue are unchanged or slightly improved [1]. Early coupled extrasystoles are, thus, more likely to be propagated at faster baseline heart rates.

The surface ECG is a culmination of multiple cellular events throughout the cardiac chambers. As shown in Fig. 23.2, normal cardiac activation arises from the sinus node complex located in the superior-medial aspect of the right atrium. Atrial activation proceeds across the right atrium and into the left atrium and from a superior to inferior direction resulting in the normal P-wave on the surface ECG [2]. Atrial activation typically takes less than 100 ms. Atrial enlargement or atrial disease processes may significantly increase the magnitude or duration of the P-wave on the ECG. As the wave front enters into the AV node, additional delay is encountered prior to activation of the His-Purkinje system. The resultant PR interval is considered normal if its duration is between 120 and 200 ms. Rapid activation of the myocardium through the Purkinje network results in a QRS complex duration between 80 and 120 ms in normal myocardium. Delay through the right bundle or the left bundle fascicles results in prolongation of the QRS. Activation of the myocardium without utilizing the His-Purkinje tissue (via a premature ventricular contraction, a paced complex, or an accessory pathway) also results in abnormally slow activation of the ventricles and, thus, prolonged QRS duration. As the ventricular myocardium repolarizes, the QT interval occurs [3]. Repolarization of atrial tissue also occurs after the P-wave, but it is not detectable on the surface ECG due to its small magnitude and frequency compared to ventricular activation occurring simultaneously.

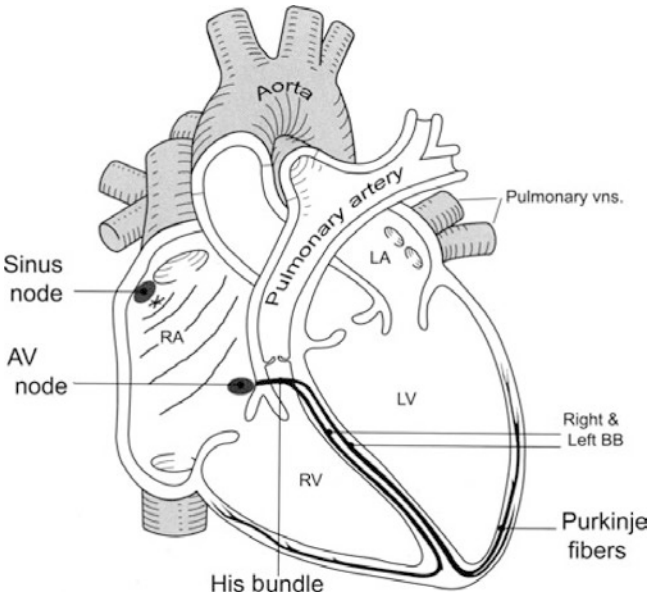

Fig. 23.2 Schematic representation of cardiac activation originating in the sinus node and penetrating the AV node. Conduction delay occurs in the AV node and then rapidly traverses the His bundle and into the right and left bundle branches to depolarize ventricular myocardium. RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; AV, atrioventricular; vns., veins

Drugs, aging, ischemia, and metabolic derangements can affect myocardial cells. These changes can lead to alterations in excitability resulting in increased or decreased automaticity. Additionally, spontaneous or drug-associated atrial or ventricular activation may occur due to triggered activity. The resultant atrial or ventricular ectopy or sustained arrhythmia would be the surface ECG correlate. Alterations in conduction due to changes at the level of the sinus node or AV node can result in sinus exit block, sinus pauses, AV node Wenckebach, or higher-grade AV block. Changes in conduction at the Purkinje level can lead to left or right bundle branch block and even reentrant ventricular arrhythmias. Alterations in myocardial propagation, often in the setting of scar, can lead to functional or anatomic block resulting in reentrant atrial or ventricular arrhythmias [4].

23.2 Clinical Arrhythmias

One can organize arrhythmias based on their mechanism, origin, or clinical scenario with which they are associated. In daily practice, utilizing a clinical approach based on arrhythmia origin is often useful. The approach outlined here is anatomy-based, beginning with the atrium and progressing through the AV or accessory pathway and then into the His-Purkinje system and onward into the ventricle. Additional

delineation based on a bradycardic or tachycardic rhythm or isolated event versus sustained arrhythmia is also proposed.

23.2.1 Supraventricular Arrhythmias

23.2.1.1 Atrial-Based Arrhythmias

Sinus Arrhythmia

Under normal physiologic conditions, the sinus rate at rest is considered normal between the rates of 60 and 100 beats/min (bpm). During regular rhythm, variations in rate occur, usually in a rhythmic pattern. Under autonomic control, sinus rhythm is influenced by variations in sympathetic and parasympathetic input [5–8]. Usually varying by only a few beats per minute under normal circumstances and nearly imperceptible, sinus arrhythmia can be more pronounced, at other times. More noticeable changes often occur during sleep when the influences of vagal tone may dominate [9]. Variations in sinus rate and the concomitant sinus arrhythmia are normal (Fig. 23.3). No therapy is needed or recommended. Absence of some degree of heart rate (HR) variation over the course of evaluation would be considered abnormal and may occur in some dysautonomias, most commonly advanced diabetes and heart failure [10–13]. Excessive variation and noticeable pauses during sleep may suggest medical conditions such as central or obstructive sleep apnea that may require treatment of the underlying condition [14].

23.2.1.2 Bradyarrhythmias

Sinus Bradycardia, the Sinus Pause, and Sinus Arrest

Sinus bradycardia is by definition a regular atrial rhythm less than 60 bpm with a P-wave morphology similar to that of normal sinus rhythm (Fig. 23.4). In today's world of polypharmacy and increase in the average age of patients, drugs are a common cause of sinus bradycardia not associated with sleep. Most beta-blockers and calcium channel blockers have a direct effect on sinus rates. Even agents once thought to exhibit little sinus slowing, such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, have slowing effects in vitro and in vivo [15]. Not all sinus bradycardia should be considered abnormal. Some individuals will exhibit sinus bradycardia due to rigorous physical aerobic training or may have a more unusual finding of familial bradycardia [16, 17]. Unfortunately, no widely accepted pharmacologic therapy for symptomatic sinus bradycardia exists despite data to suggest some benefit. Theophylline compounds have been studied and are occasionally tolerated and may be effective in patients with sinus node dysfunction [18]. There are unfortunately, no safe, long-term beta-agonists available in oral form. Acute increases in heart rate may be accomplished with direct or indirect beta-agonists such as Isuprel, dopamine, and dobutamine. Parasympathetic blockade with atropine may also be helpful acutely in certain cases [19, 20].

Patients with asymptomatic awake heart rates above 40 bpm do not usually require additional therapy, most notably atrial pacing. Symptomatic patients and minimally symptomatic patients with resting bradycardia less than 40 bpm may benefit from pacing [21]. Consideration of dual chamber pacing in certain patients should be considered given the tendency to go on to symptomatic AV block in a notable proportion. Again, evaluation for an underlying cause should be considered as hypertension, coronary disease, sleep apnea, and infiltrative diseases such as sarcoidosis, hemosiderosis, or amyloidosis may cause sinus bradycardia.

As atrial disease progresses, sinus node automaticity may decline erratically resulting in pauses that may become more symptomatic [22]. This is often due to simple aging, the use of drug therapy, or advancing cardiopulmonary disease. While variations in heart rate are certainly common, and vagally mediated slowing is noticed frequently at night, pauses in excess of second are abnormal (Fig. 23.5). In the absence of other reversible causes, pauses in excess of 5 s

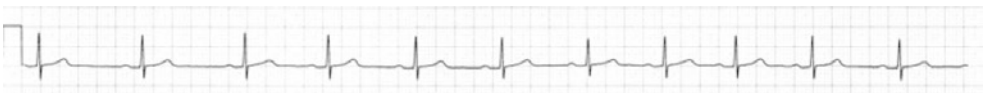

Fig. 23.3 Sinus arrhythmia. Rhythmic variation in the sinus rate is noted across the rhythm strip. P-wave morphology and PR intervals remain essentially unchanged

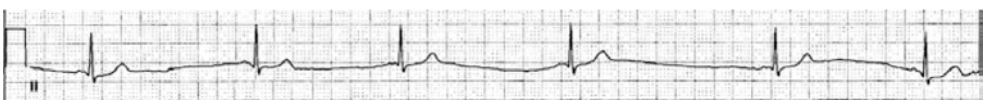

Fig. 23.4 Marked sinus bradycardia at a rate of approximately 30–40 bpm. Competing junctional beats are noted in the third and fourth beats with a PR interval shorter than expected

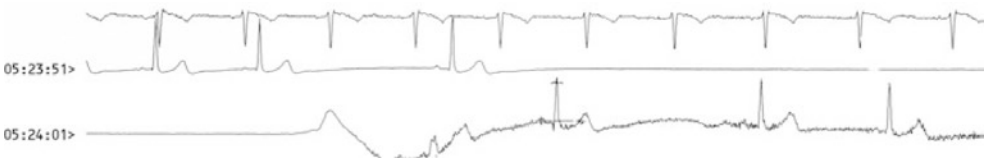

Fig. 23.5 Sinus slowing and sinus arrest. Early morning monitoring reveals a sudden slowing and then a nearly 10-s episode of sinus arrest. Return rate is slow initially and then increases

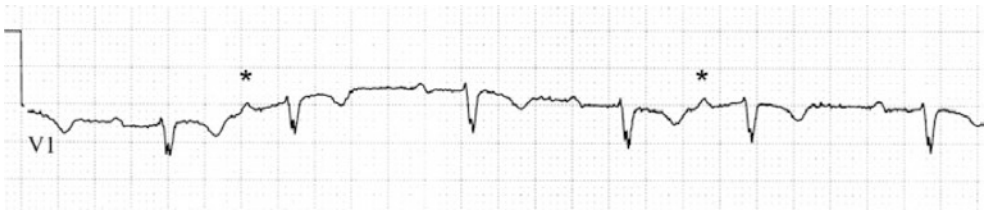

Fig. 23.6 Sinus rhythm with first-degree AV block and occasional premature atrial complexes. Noted on the second and fifth beat (*), early atrial complexes with a different morphology are noted giving rises to an irregular rhythm

suggest significant sinus node disease and may warrant pacing to prevent symptomatic postural events that may result in injury [21]. Vagally mediated pauses of greater than 20–30 s are not uncommon during tilt table tests or with carotid sinus massage in susceptible patients. Again, drug therapy is often insufficient, and pacing may be required in certain circumstances [23].

23.2.1.3 Wandering Atrial Pacemaker, Premature Atrial Contractions, and Ectopic Atrial Rhythm

Related to sinus arrhythmia and resulting in heart rate variation at physiologic rates, a wandering atrial pacemaker rhythm represents a change in the origin of the atrial activation periodically outside the normal sinus complex and into adjacent atrial tissue and sometimes into AV junctional tissue [24]. The morphology of the P-wave changes shape and often direction, and the changes in rate are typically more abrupt than with sinus arrhythmia. Due to changes in atrial origin, the resultant atrial conduction time to the AV node and changes in the degree of prematurity and changes in the PR interval are often seen [25]. As the changes become even more noticeable and less regular, sinus rhythm with premature atrial contractions (PACs) becomes the rhythm designation. Wandering atrial pacemaker rhythm is a less commonly used term but typically reflects a physiologic rhythm. This is found more commonly in the setting of normal hearts, but altered autonomic tone may influence arrhythmogenesis in the setting of atrial disease and intrinsic sinus node disease.

Premature atrial contractions arise from abrupt, early activation of the atria and may arise from either the right or the left atrium. Newer evidence suggests atrial ectopy may frequently arise from electrically active tissue within the pulmonary veins and may be the trigger for atrial fibrillation [26]. Usually a benign rhythm, PACs may be quite bothersome with symptoms of palpitations or tachypalpitations. Premature atrial contractions may reflect underlying atrial disease either intrinsic in nature or associated with a pulmonary process, hypertension, valvular heart disease, ischemic cardiac disease, or even infiltrative heart disease [27]. Consideration of patient age, associated medical problems, and underlying cardiac disease should be made when determining the clinical ramifications of symptomatic or asymptomatic PACs (Fig. 23.6).

A regular, persistent atrial rhythm originating outside the sinus node gives rise to a P-wave morphology distinct from the typical sinus P-wave. Termed ectopic atrial rhythm, patients are usually asymptomatic, and the rhythm is benign (Fig. 23.7). An ectopic atrial rhythm is not infrequently seen in the setting of concurrent medical or metabolic derangement such as acute or chronic pulmonary disease or alcohol excess or ischemia. These slower rhythms may also be a clinical sign of advancing sinus node or atrial tissue disease [4].

The clinical term sick sinus syndrome (SSS) is applied when a variety of atrial bradycardias and tachycardias are noted. It encompasses clinical palpitations associated with sinus pauses, sinus bradycardia, premature atrial complexes, a variety of atrial dysrhythmias, atrial fibrillation, and atrial flutter [28, 29]. Sick sinus syndrome is reflective of advanced sinus node and atrial disease and is typically progressive. Treatment to reduce rapidly conducted atrial tachycardias is complicated by intrinsic sinus node dysfunction often giving rise to excessive resting bradycardia, and frequently concurrent therapy with pacing is required [21].

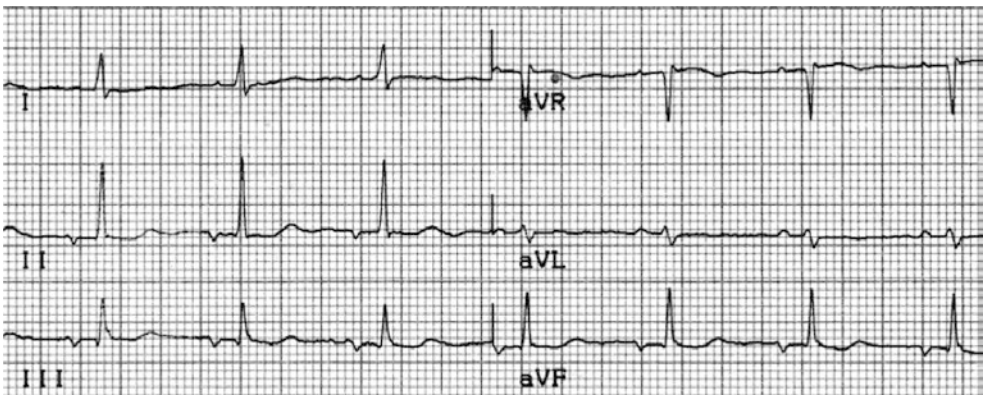

Fig. 23.7 Ectopic atrial rhythm. A regular rhythm at approximately 85 beats is noted with inverted P-waves in the inferior leads and upright in AVR suggesting an origin in the low septal right or left atrium

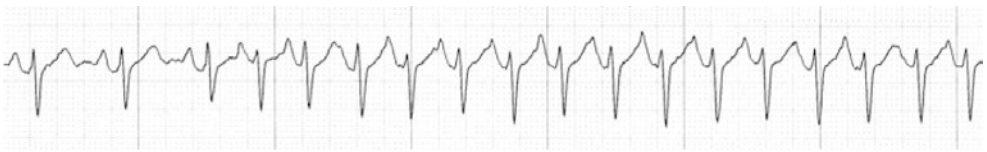

Fig. 23.8 Ectopic atrial tachycardia. Sinus rhythm with peaked P-waves suggestive of atrial overload is replaced by a sudden onset of regular atrial tachycardia at a rate of 160 bpm. The new P-wave morphology is noticeably different beginning with the first early beat (fourth P-wave)

23.2.1.4 Tachyarrhythmias

Sinus Tachycardia

As atrial rates increase, additional rhythm disorders come into play. The simplest tachyarrhythmia arising from the atria is sinus tachycardia. While one could dismiss this as just a normal sinus mechanism at a faster rate, one has to remember that sinus tachycardia occurring in patients that are supine, resting in an office, or in a hospital bed is usually inappropriate and may point to conditions that may have been overlooked. Metabolic derangements may manifest early as sinus tachycardia. Thyrotoxicosis, sepsis syndrome, shock, hypovolemia, pheochromocytoma, diabetes-associated autonomic dysfunction, substance abuse, malignant hyperthermia, myocardial infarction, drug toxicity, and pain are just a few clinical scenarios that may predispose a patient to sinus tachycardia [30]. Additionally, clinical tachyarrhythmias may also arise in or around the sinus node unrelated to clinical or metabolic disorders and are discussed below.

Ectopic Atrial Tachycardia

Atrial tachyarrhythmias arising from a single region also include ectopic atrial tachycardias (EAT). These arrhythmias often have abrupt onset of a regular tachycardia with P-waves that are distinctly different from the typical sinus P-wave (Fig. 23.8) [31]. Abrupt onset and offset often occur, but a mild warm-up at initiation and a mild slowing prior to termination also suggest a certain degree of autonomic modulation. Additionally, the arrhythmia rates appear to be under the control of autonomic input as assessed by heart rate variability obtained by time- and frequency-domain methods. However, short R-R changes may result from an intrinsic abnormality of the ectopic rhythm or possibly from a specific autonomic difference [32].

Most atrial tachycardias. are non-sustained and asymptomatic found during routine ambulatory monitoring. However, they can become incessant resulting in a rate-related cardiomyopathy [33]. The origin of the ectopic atrial arrhythmia may be throughout either the right or left atria. Hot spots within atrial appendages, along the cristae terminalis, and around the pulmonary veins have been described [34–38]. Drug therapy in patients with atrial tachyarrhythmias such as ectopic atrial tachycardia may include beta-blockers, calcium channel blockers, and Vaughan Williams class Ic and III drugs [30]. Radio-frequency ablation has been used in patients with symptomatic ectopic atrial rhythms in which type Ic or III agents fail or are not preferred. Unfortunately, many of these arrhythmias are often difficult to initiate with programmed stimulation in the electrophysiology. lab [38].

Multifocal Atrial Tachycardia

An atrial tachyarrhythmia warranting mention is multifocal atrial tachycardia (MAT). Characterized by heart rates greater than 100 bpm and an irregular rhythm with greater than two atrial P-wave morphologies, MAT often arises in the setting of metabolic or respiratory distress. Treatment of the underlying medical illness is the treatment of choice. Verapamil has been shown to help to a limited degree.

Digoxin use is discouraged due to limited value and concerns over digoxin toxicity-associated atrial tachycardia with block going unrecognized in the setting of MAT. There is no role for direct current cardioversion (DCC), ablation, or antiarrhythmic drugs [30].

Sinus Node Reentry Tachycardia, Positional Orthostatic Tachycardia Syndrome, Inappropriate Sinus Tachycardia, and Neurocardiogenic Syncope

Similar to the ectopic atrial tachycardias, atrial tachycardias associated with or originating in the sinus node may occur. Sinus node reentrant tachycardia (SNRT) arises from the sinus node complex and is associated with an abrupt change in heart rate with a P-wave morphology similar to the sinus P-wave. The reentrant mechanism may be entirely within the sinus node or involve nearby transitional atrial myocardium. Treatment of SNRT involves similar drug therapy to EAT [39]. However, due to extensive autonomic innervation of the sinus node complex, treatment may be more difficult to manage. Ablation therapy may be appropriate in many cases [40]. Sinus node reentry may occur as an isolated finding or may be associated with occult or overt cardiac disease. Automatic or triggered atrial tachycardias can also arise within the sinus node complex and may be treated similarly.

Additional clinical syndromes may also result in sinus tachycardia. Patients suffering from postural orthostatic tachycardia syndrome (POTS) will manifest abrupt increases in heart rate, usually sustained, with upright posture. Volume expansion and re-evaluation to exclude hypovolemia as a cause of tachycardia is necessary. Clinical elimination of other dysautonomic syndromes is also necessary to make the diagnosis. POTS likely involves a cardiac sympathetic dysautonomia mediated by increased norepinephrine release from intact cardiac sympathetic nerves. This is not associated with fixed abnormalities in cell activity or sympathetic innervation density [41]. Treatment with a beta-blocker may control postural changes in heart rate, often with good success [42–45].

Over a decade ago, Lee and colleagues described a group of patients with inappropriate sinus tachycardia (IST) [46]. Inappropriate sinus tachycardia is a syndrome affecting young women almost exclusively. Patients have consistently higher heart rates for a given activity or even at rest. P-wave morphology is identical or similar to sinus rhythm, and there is not another identifiable cause for the sinus tachycardia. It has a gradual onset and offset in contrast to paroxysmal atrial tachycardias. In these patients, symptoms of palpitations and heart racing are difficult to control with beta-blockers, calcium channel blockers, volume expansion, or antiarrhythmic drugs. In one series, patients were treated with invasive ablation of their sinus node complex resulting in resting bradycardia [46]. Extensive destruction of the sinus node may result in bradycardia severe enough to warrant pacing to restore appropriate quality of life. Interestingly, many of the patients in this study were health-care personnel. Additional studies have since demonstrated efficacy of ablation in the management of this disorder [47–49].

Vasovagal syncope (VVS) or neurocardiogenic syncope (NCS) may also be preceded by dramatic increases in heart rate just prior to abrupt decline in heart rate and vasodilation resulting in loss of consciousness. Situational events such as public speaking, a sudden frightening event, external or internal painful stimuli, and hypovolemia may be the precipitating factor for the initial increase in heart rate. Studies have demonstrated that both sympathetic activation just prior to syncope and sympathetic withdrawal may occur, resulting in initial tachycardia [50–52].

Atrial Fibrillation and Atrial Flutter

No other arrhythmias have been more thoroughly studied, evaluated, and written about than atrial fibrillation (AF) and atrial flutter (AFL). Despite this, atrial fibrillation remains the number one cause for hospital admissions among arrhythmias. Atrial fibrillation affects nearly 2.2 million people in America and 4.5 million people in the European Union. The incidence of AF continues to grow due to the aging population, obesity, hypertension, and better screening techniques. By the year 2050, atrial fibrillation is expected to affect nearly 5.6 million individuals in the USA [53].

Atrial fibrillation and atrial flutter are often grouped together as a single entity. This tendency by practitioners occurs due to nearly identical symptoms, treatment, and clinical outcomes with respect to stroke and stroke prevention. However, mechanistically, atrial fibrillation and flutter are distinct entities and should be understood as such.

Atrial fibrillation is characterized by the absence of organized atrial electrical activity resulting in the loss of mechanical function. On the surface ECG, no discernable P-waves are seen but are replaced by multiform oscillations in the baseline. The ventricular response is typically irregular and rapid, as disorganized atrial activity is conducted through the AV node. The ventricular response in patients with normal AV node physiology is usually rapid. Heart block with a junctional or ventricular escape rhythm may also be seen. This is most common in older patients, those with advanced AV node disease, or individuals undergoing pharmacologic treatment with beta-blockers, calcium channel antagonists, or digoxin (Fig. 23.9) [54].

In contrast, typical atrial flutter is a macro-reentrant arrhythmia occupying nearly the entire right atrium. Impulses travel up the interatrial septum, across the roof of the atrium

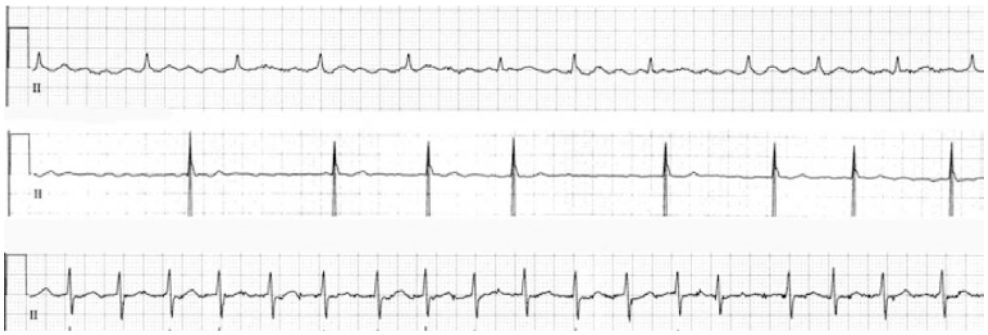

Fig. 23.9 Variably conducted atrial fibrillation. In panel 1, coarse atrial fibrillation is conducted at a normal, variable rate between 55 and 80 bpm. In panel 2, AF is conducted slowly at a rate of between 32 and 70 bpm. In panel 3, AF is conducted rapidly at around 120 bpm. In each case R-R intervals are variable demonstrating absence of heart block

superiorly and laterally, and traverse inferiorly along the lateral wall along the crista. Propagation progresses medially along the cavotricuspid isthmus and then back up the interatrial septum. Left atrial activation occurs with each rotation, while conduction down to the ventricle typically occurs in a 2:1, 3:1, or 4:1 atrial to ventricular activation pattern (Fig. 23.10). Cavotricuspid isthmus atrial flutter has a rate around 240–300 bpm with conducted ventricular rates an integer of that or around 150, 100, 75, or 60 bpm. Typical AFL on the surface ECG is seen as a regular sawtooth pattern of atrial activity most easily discerned in the inferior leads with negative flutter waves and a positive flutter wave in V1 [37, 55]. The majority of atrial flutter is of a counterclockwise rotation. Ten percent of the time this atrial flutter wave rotates clockwise, and in some patients, both can be seen at different times (Fig. 23.11). Macro-reentrant left-sided atrial flutter or macro-reentrant atypical atrial flutter around the right atrial cristae are beyond the scope of this chapter. However, evaluation and possible treatment considerations are similar as described below.

Atrial fibrillation is now classified in a scheme that provides a framework for appropriate evaluation and treatment regimens. The ACC/AHA/ESC 2006 Practice Guidelines on Atrial Fibrillation outline the current system. First-detected atrial fibrillation is simply when AF is originally diagnosed, recognizing that prior asymptomatic or symptomatic episodes may have already occurred. When two or more episodes have occurred, AF is considered recurrent. Episodes of self-terminating AF of less than 7 days are considered paroxysmal, while those lasting greater than 7 days are considered persistent. Persistent atrial fibrillation also includes long-standing AF (very long duration), which usually results in permanent AF. Permanent AF also includes atrial fibrillation in which pharmacologic or electrical cardioversion has not been tried or has failed [55].

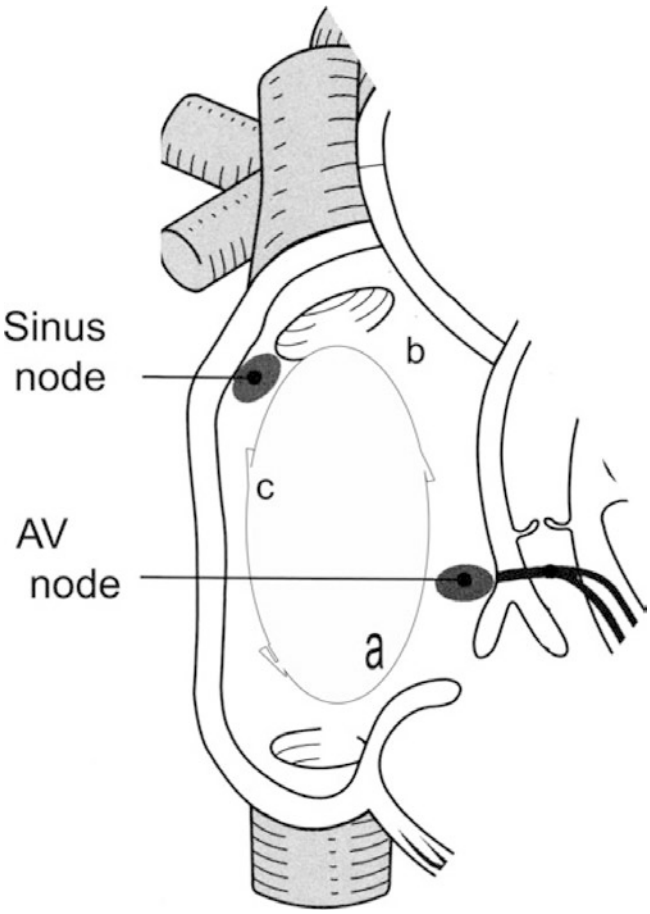

Fig. 23.10 Typical counterclockwise cavotricuspid isthmus atrial flutter. The wave front at (**a**) moves laterally to medial across the isthmus between the inferior vena cava and the tricuspid annulus. It propagates superiorly up the interatrial septum (**b**) and traverses the roof medial to lateral and down the lateral wall along the cristae (**c**) to propagate another cycle. Typical conduction slowing is often found along the isthmus

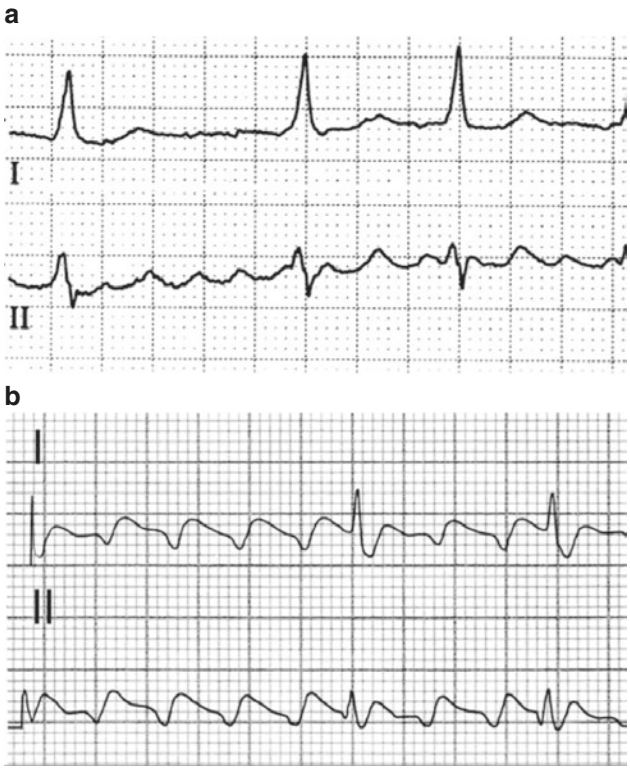

Fig. 23.11 Typical clockwise (**a**) and counterclockwise (**b**) atrial flutter with variable conduction to the ventricle

Risk factors for the development of atrial fibrillation include progressive myocardial fibrosis, surgical manipulation, pressure and volume overload with atrial stretch and enlargement, genetic predisposition related to sodium and potassium channelopathies, and possible abnormalities in intercellular gap junctions, alterations in the renin-angiotensin-aldosterone system, and inflammatory and infiltrative changes. Clinical syndromes of valvular heart disease, obesity, hypertension, sleep apnea, thyroid disease, acute pulmonary embolism or pneumonia, heart failure, and ischemic heart disease are associated with increased rates of atrial fibrillation [56–69]. When a patient presents with atrial fibrillation, one should consider these disease states in their evaluation as a potential treatment mechanism both to prevent future AF breakthrough and to affect the long-term outcome of a patient's non-arrhythmic health.

The clinical symptoms of AF are often protean with little or no symptoms in some individuals, while others may suffer an advanced heart failure exacerbation, severe palpitations, chest pain, syncope, or even catastrophic stroke. An individual may have a clinical course that varies depending on volume status, age, heart rate, and changes in underlying health status [70–74]. In patients with paroxysmal AF of short duration, the diagnosis is often delayed. Patients presenting to the office or emergency room for evaluation are often in sinus rhythm on evaluation, delaying the correct diagnosis. Symptoms may also predominantly occur with resolution of AF, culminating in long pauses and syncope with ECG evaluation at follow-up being normal (Fig. 23.12) [75]. Ambulatory short-term (24–48 h) or long-term (30 days) monitoring may demonstrate episodes of asymptomatic AF or symptomatic aspects of associated tachycardia or bradycardia [76]. Associated signs of sinus node or atrial disease, such as moderate frequency atrial ectopy, bursts of ectopic atrial tachycardia, or asymptomatic pauses, may also raise the suspicion of AF for a patient's tachypalpitations.

Advancements in the treatment strategies for atrial fibrillation are ongoing. In the past, most clinicians concentrated on restoring sinus rhythm as the primary therapy for atrial fibrillation. Short-term anticoagulation drug therapy with AV nodal blocking agents and antiarrhythmic drugs were utilized, and cardioversion is performed. More recently a paradigm shift has occurred as a result of two large trials that looked at event rates in warfarin anticoagulated patients who were randomized to either rate control or maintenance of sinus rhythm. The AFFIRM trial studied patients that were an average age of 69 years old with a high incidence of hypertension and coronary artery disease. Structural heart disease with left atrial enlargement was noted in 67% and left ventricular (LV) dysfunction in 26%. Patients were followed for 5 years. This large trial of 4060 patients demonstrated that restoration of sinus rhythm offered no survival advantage over the rate-control strategy. In addition, it affirmed the continued role of warfarin even after restoration of sinus rhythm in prevention of stroke [77]. This trial and earlier smaller trials [78–81] have led to appropriate chronic anticoagulation and rate control as first-line therapy in many patients with AF. Considerable debate has been raised with respect to the advanced age in the patient populations studied, the moderate crossover from rate to rhythm control arms, low beta-blocker use in the rhythm strategy arm, and a lower incidence of heart failure in both groups [82]. Despite these shortcomings, evidence suggests that many typical AF patients can be treated with simple rate-control and chronic warfarin anticoagulation.

In a second major trial reported in 2008, the AF-CHF trial studied patients with atrial fibrillation and a history of left ventricular ejection fraction of 35% or less and symptoms of heart failure. Time to death from cardiovascular causes was the primary endpoint. In this trial of 1376 patients followed for a mean of 37 months, no difference in CV death rate was seen (27% versus 25% for the rhythm-control versus rate-control group). Secondary endpoints were also similar including all-cause mortality, stroke, worsening heart failure, and composites of the same. In summary, even in patients with depressed LV function and heart failure, AF may be reasonably treated with a rate-control and anticoagulation strategy [82].

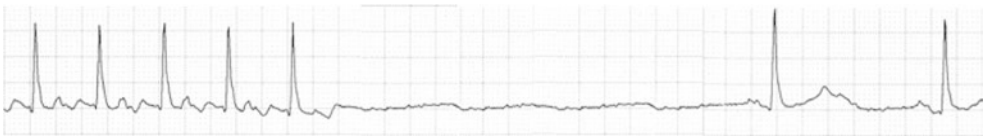

Fig. 23.12 Pause associated with termination of atrial flutter with restoration of sinus bradycardia in a patient with episodes of intermittent transient light-headedness and syncope

Table 23.1 Common drugs, drug dosing, and route for rate control in atrial fibrillation

Drug	Dose	Frequency	Route	Comments
Digoxin	0.125–0.25 mg	Daily	i.v. or p.o	0.25–1.0 mg load, drug levels available (inc. mortality above 1.0 in HF) usually inadequate as a single agent
Nonselective beta-blockers				
Inderal	10–30 mg	t.i.d.	p.o.	Nonselective beta-blocker (parent compound)
Inderal LA	30–60 mg	Daily–b.i.d.	p.o.	Long acting
Pindolol	5–30 mg	b.i.d.	p.o.	Intrinsic sympathomimetic action
Beta-1 selective				
Acebutolol	200–600 mg	b.i.d.	p.o.	Lower doses may be effective once daily
Bisoprolol	2.5–20 mg	Daily	p.o.	Mild intrinsic sympathomimetic action
Esmolol	500 mcg/kg over 1 min	Load	i.v.	Ultrashort acting, acute onset
	50–200 mcg/kg	Continuous	i.v.	
Metoprolol tartrate	5 mg	b.i.d.–q.i.d.	i.v.	Short onset, medium duration
	25–100 mg	b.i.d–t.i.d	p.o.	
Metoprolol succinate	25–100 mg	Daily–b.i.d	p.o.	Slow onset, long acting
Mixed alpha/beta				
Labetalol	100–400 mg	b.i.d.	p.o.	Predominantly used for hypertension
Carvedilol	3.125–50 mg	b.i.d.	p.o.	Used extensively in heart failure therapy
Calcium channel blockers				
Diltiazem	5–15 mg/h		i.v.	(0.25–0.35 mg/kg initial bolus)
Diltiazem	30–120 mg	t.i.d.	p.o.	Quick onset, short duration
Diltiazem extended	120–540 mg daily	Daily	p.o.	
Verapamil	2.5–10 mg	Bolus	i.v.	Short acting, acute onset
Verapamil	40–12 mg	t.i.d.	p.o.	Potent AV node blocker, negative inotropic effect in HF
Verapamil extended	180–480 mg	Daily	p.o.	

To achieve clinical results with a rate-control and anticoagulation strategy, appropriate use of pharmacotherapy and patient follow-up is needed. Anticoagulation with either aspirin or warfarin should be initiated in the appropriate patients [83]. Warfarin dosing is recommended to be followed at weekly intervals until a stable international normalized ratio (INR) value is reached. At a minimum, monthly INR evaluation should be obtained in stable patients thereafter [55]. Unfortunately, many drugs may interfere with warfarin, and more frequent evaluation may be warranted in those circumstances [84, 85].

In many trials, beta-blockers were utilized as the primary AV node blocking agent. Concurrent digoxin and non-dihydropyridine agents may also be useful. Long-acting metoprolol succinate or twice daily metoprolol tartrate are often used due to ease of use and being beta-1 adrenergic receptor selective. In addition, these drugs have a positive mortality benefit in patients with depressed LV systolic function and heart failure symptoms [86]. Other beta-blockers may also be used to affect AV node blockade. When additional rate control is needed, the addition of digoxin to this regimen after up-titration of the beta-blocker to maximal tolerated dose can prove useful. In patients with normal LV systolic function or isolated diastolic dysfunction, diltiazem or verapamil may be added to control the rate (Table 23.1). In some individuals, rate control may require polypharmacy and may still not be achieved. More invasive methods may be required such as AV junctional ablation and pacing in these patients [55]. AV junction ablation and biventricular pacing have been proposed to potentially reduce the risk of pacing-associated cardiomyopathy. This approach has not been fully validated in a prospective, randomized clinical trial.

The evaluation of heart rate control is not solely based on the resting pulse or ECG. Heart rate may appear controlled at rest yet inappropriately increase with even minimal activity. In the AFFIRM trial, a resting HR of less than 80 bpm was required as well as an average heart rate of less than 100 bpm

over 18 h of ambulatory monitoring. Heart rates could not exceed the 100% age-predicted maximum heart rate during rest or activity [77]. In common practice, hourly average heart rates of less than 100 bpm are expected. Variability in the conducted HR also provides some insight into the status of autonomic control and may have some prognostic implications [87–90].

While rate control as an alternative to rhythm control has gained popularity, electrophysiologists continue to find ways to restore sinus rhythm. Two major strategies for rhythm control include antiarrhythmic drug use or invasive techniques of either pulmonary vein isolation or surgical atrial reduction and isolation. Antiarrhythmic drug use since the mid-1980s has been relegated mostly to cardiologists and electrophysiologists due to the recognition of potentially significant proarrhythmic properties of some drugs and increased risk for mortality associated with their use. However, identification of patients at low risk for iatrogenic arrhythmogenesis can be undertaken and antiarrhythmic drugs initiated in a monitored setting appropriately by nearly all practitioners.

In patients considered for antiarrhythmic drug use, identification of structural heart disease through echocardiography, electrocardiography, and evaluation of ischemic heart disease through history, exercise testing, or angiography should be performed. In addition, evaluation of renal function, hepatic function, and pulmonary and thyroid function may be necessary in certain cases. Evaluation of patient compliance and dosing schedules are also important.

In the 2006 ACC/AHA/ESC Guidelines for the Treatment of Atrial Fibrillation, high-risk features for proarrhythmia for class Ia, Ic, and III drugs are presented. In patients being considered for class Ia or III agents, underlying prolonged QT or concurrent use of agents that can prolong the QT interval, female gender, bradycardia, structural heart disease, high dose or rapid increase in dosing, as well as renal dysfunction and depressed LV function all increase the chance of proarrhythmia. In patients being considered for type Ic drugs, a prolonged QRS duration, structural heart disease with or without LV dysfunction, rapid heart rates, and high drug dose or rapid dose acceleration can all increase proarrhythmia [55].

For acute conversion of atrial fibrillation, the class Ic agents propafenone and flecainide can be used in patients without significant structural heart disease [91–95]. The class III, short-acting i.v. ibutilide can also be used with high efficacy [96–98]. In patients with structural heart disease such as left ventricular hypertrophy (LVH) or with coronary artery disease with preserved ejection fraction, the class III agents dofetilide [99–103] and amiodarone can be used [91, 104–106]. These agents may also be helpful in patients with normal hearts in which earlier agents have been ineffective. Finally, in patients with heart failure or LV dysfunction, dofetilide and amiodarone may be used [105, 106]. Again, consideration of drug clearance and other factors that may affect drug choice should be made [55].

Other antiarrhythmic drugs may also be efficacious but are being replaced. For acute conversion of atrial fibrillation, quinidine, procainamide, and disopyramide have fallen out of favor due to lack of efficacy compared to other agents or increased risk for adverse effects. Digoxin and verapamil or diltiazem may be helpful in slowing conducted atrial rates but are not effective in converting AF to sinus rhythm [55].

Compared to acute conversion of AF to sinus, the maintenance of sinus rhythm in patients is very similar. The major difference is that sotalol plays a role in patients with normal hearts as well as in patients with hypertension without left ventricular hypertrophy (LVH) and patients with revascularized coronary artery disease with preserved ejection fraction. Beta-blockers and disopyramide also may play a role in selected patient groups [107–111]. In addition, amiodarone has taken on a large role due to the safety and efficacy of outpatient initiation and reduction in recurrence rate and duration of atrial fibrillation in relation to other antiarrhythmic drugs [112–116].

Restoration of sinus rhythm by pharmacologic therapy alone is often not enough. Direct current cardioversion is often necessary either with or without the use of antiarrhythmic treatment. In patients with highly symptomatic paroxysmal or persistent AF or permanent AF, an appropriate anticoagulation regimen is utilized, and cardioversion can be effective with a low risk for thromboembolism. Efficacy of direct current cardioversion utilizing a biphasic rectilinear waveform defibrillator was greater than 99% in 1877 procedures [117]. Atrial fibrillation of prolonged duration (greater than 1 year) has a significantly lower rate of conversion and maintenance of sinus rhythm.

More recently completed trials and registries have looked at the role of various forms of invasive treatment of atrial fibrillation. Pioneering surgical therapies in which surgical cutting and resewing the atrium into multiple sections to effectively produce conduction block and atrial size reduction accomplished the elimination of atrial fibrillation through a surgical technique [118–124]. Swartz and associates demonstrated that AF could be eliminated through endocardial radio-frequency ablation using similar ablation lines [125]. Over the next one and one-half decades, various techniques have been advanced to reduce procedure times, decrease complications, and still yield effective therapy.

Limited single-center and multicenter trials and surveys form the bulk of literature to assess the efficacy of AF suppression after radio-frequency ablation, quality of life, and

the morphologic changes in atrial and ventricular myocardium. In the 2007 Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation, indications for ablation, anticoagulation, surgical approaches, and outcomes were summarized. Patients were considered appropriate candidates for AF ablation if they continue to have highly symptomatic atrial fibrillation despite at least one antiarrhythmic drug trial in the setting of appropriate rate control and anticoagulation. Individuals that were younger in age, had smaller atria, absence of significant valvular disease, and preserved LV function were considered more ideal candidates. Currently, a patient's desire alone to eliminate anticoagulation should not be considered an appropriate indication for AF ablation, as long-term stroke risk after successful ablation of anticoagulation has not been studied [126].

Table 23.2 outlines the results of non-randomized and randomized trials as well as that of a large ablation survey including 9000 patients. Generalization of the trials suggests success rates are higher for patients with paroxysmal rather than persistent AF and multiple procedures are required to affect a success with or without suppressive antiarrhythmic drugs. In addition, major complications of ablation in the survey were relatively high at 6%.

Table 23.2 Summary of clinical trials evaluating the role of radio-frequency ablation and drugs on the treatment of atrial fibrillation. Recurrence rates for isolated and multiple procedures are summarized for the non-randomized trials. In the survey, results are grouped

Non-randomized clinical trials		
	Single procedure success	*Multiple procedure success*
Paroxysmal AF	38–78% (most >60%)	54–80% (most >70%)
Persistent AF	22–45% (most <30%)	37–88% (most >50%)
Mixed AF	16–84%	30–81%
Randomized clinical trials		
	Recurrence	*Comments*
Wazni et al. [127] ($n = 70$)	Drug: 63% ≥1	(Paroxysmal AF, flecainide, or sotalol, 1 year f/u)
	RFA: 13% ≥1	
Oral et al. [128] ($n = 168$)	DCC: 42%	(Persistent AF, DCC vs. RFA 1 year f/u)
	RFA: 26%	
Stabile et al. [129] ($n = 137$)	Drug: 91%	(PAF and persistent AF, drug vs. RFA)
	RFA: 44%	
Pappone et al. [130] ($n = 199$)	Drug: 78%	(Paroxysmal AF, drug vs. RFA)
	RFA: 14%	
Jais et al. [131] ($n = 53$)	Drug: 93%	(Drug vs. RFA)
	RFA: 25%	
Survey [132] ($n = 9000$)	RFA: 48%	(Includes single and multiple procedures and paroxysmal and persistent AF)
	RFA + Drug: 24%	

The impetus to pursue maintenance of sinus rhythm without pharmacotherapy continues as several trials have demonstrated significant improvements in objective cardiac parameters including a reduction in left atrial size and function and improvements in LV ejection fraction [128, 133–139]. Quality of life indicators have also been shown to improve in many trials. However, many were unblinded or non-randomized, and the role of a placebo effect may be difficult to exclude [98, 99].

Supporting the growing role of AF ablation, a recent trial by Khan and colleagues randomized patients with heart failure and an ejection fraction of 40% or less to either a pulmonary vein isolation ablation procedure or to AV junctional ablation and biventricular pacing for rate control. The composite score of ejection fraction, distance on 6-min walk test, and Minnesota Living with Heart Failure (MLWHF) score was the primary endpoint. In this small trial, success rates for freedom from AF in the ablation arm were 88% with or without antiarrhythmic drug use. Quality of life, improvement in LV systolic function, and 6-min walk test all statistically improved. In patients randomized to AV junctional ablation and biventricular ablation, ejection fraction remained unchanged, and quality of life and 6-min walk test improved only modestly. Of note, 30% of patients in the pacing arm had progression of their atrial fibrillation. Larger trials are needed to validate these findings. A standard rate-control arm may also help elucidate the functional changes in myocardial structure and function [140].

Additional ongoing trials are likely to further demonstrate the importance of atrial fibrillation ablation procedures in selected groups. However, the economic impact of the procedure and the potential complications should not be understated [126]. In addition, standard surgical and minimally invasive surgical techniques have also been developed over the last 20 years, and procedure rates are growing in specialty centers with good results [141–147]. Clearly the future of atrial fibrillation management is a moving target. A proposed algorithm for the treatment of atrial fibrillation is shown in Fig. 23.13.

In contrast to atrial fibrillation, typical cavotricuspid isthmus-dependent atrial flutter ablation has a high success rate and is less complex to perform. Linear lesions, typically utilizing radio-frequency current or cryoablation, are delivered between the tricuspid annulus toward the inferior vena cava. This isthmus is a critical portion of the macro-reentrant rhythm of atrial flutter. As the wave front collides into the ablation line, the atrial flutter terminates and sinus rhythm is restored (Fig. 23.14). Following ablation, pacing the right atrium from the coronary sinus activates the atrium superi-

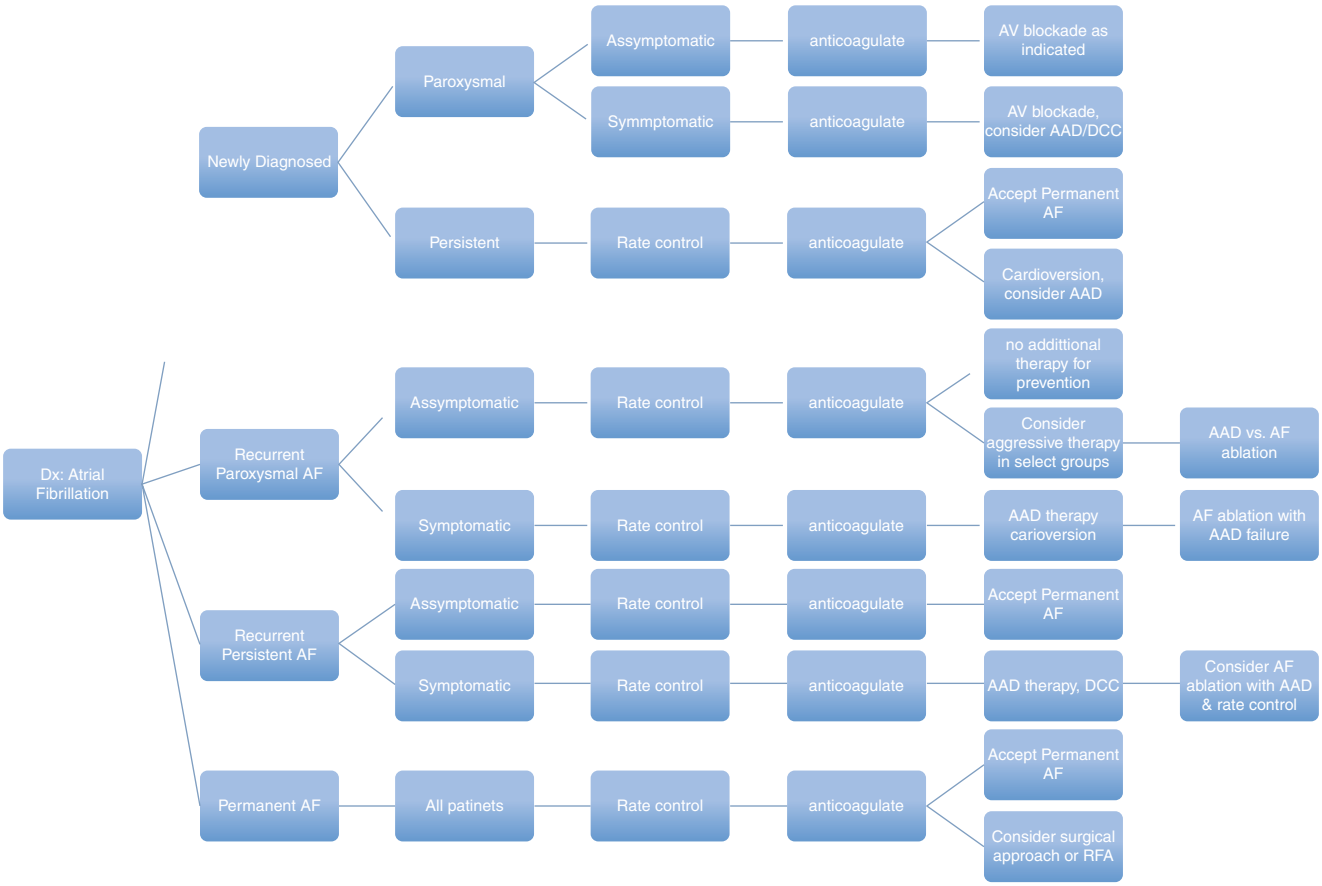

Fig. 23.13 Algorithm for the treatment of newly diagnosed AF, recurrent paroxysmal AF, recurrent persistent AF, and permanent AF. Treatment with warfarin is generally indicated in most groups unless specifically contraindicated. AAD, antiarrhythmic drug; DCC, direct current cardioversion

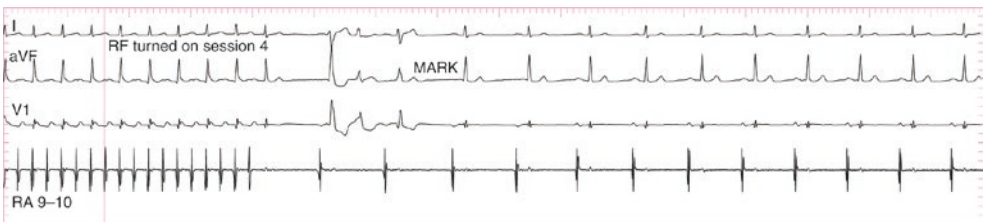

Fig. 23.14 Termination of atrial flutter during radio-frequency ablation along the venocaval-tricuspid isthmus. Rapid intracardiac depolarizations during atrial flutter are replaced by slower sinus depolarizations noted in lead RA 9–10. Surface leads II, aVF, V1, and intracardiac atrial recording from the high right atrium (RA 9–10) are shown

orly and also infero-laterally along the isthmus. Wave front collision with the ablation line laterally in the isthmus results in activation of the lateral wall in a superior to inferior direction. This is in contrast to the activation pattern prior to ablation where lateral wall activation from coronary sinus pacing typically occurs in an inferior to superior manner (Fig. 23.15). Success rates are often as high as 90% with very low complication rates, making cure through ablation the treatment of choice for many individuals [148, 149]. Unfortunately, patients may have intermittent atrial fibrillation, and long-term anticoagulation may need to be continued.

23.2.2 Atrioventricular Chamber-Associated Arrhythmias

23.2.2.1 Bradycardic Arrhythmias

Atrioventricular Block

Changes in atrioventricular (AV) node and His-Purkinje physiology over time or as a consequence of drugs or disease states are common. Progressive AV block is demonstrated in Fig. 23.16. The simplest form of abnormal AV association is first-degree AV block and is seen as a prolongation of the AV

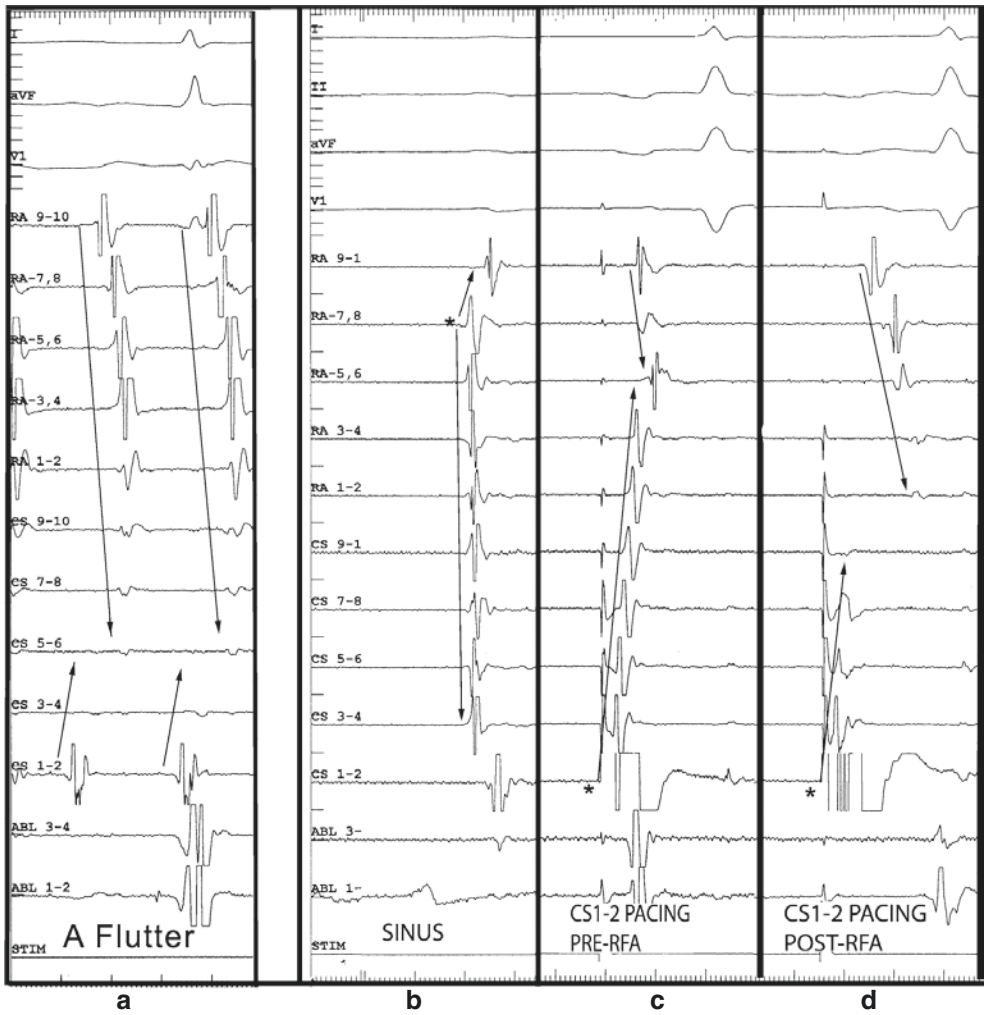

Fig. 23.15 Intracardiac recordings of atrial flutter during AFL, sinus rhythm, and during coronary sinus pacing prior to ablation and following isthmus ablation demonstrating medial to lateral block along the cavotricuspid isthmus at intracardiac recording (CS 9–10). (**a**) The AFL wave front travels counterclockwise from RA 9–10 laterally along the cristae eventually reaching csv5–6. Conduction delay is noted to CS 3–4 and CS 1–2 and then rapidly ascends up the interatrial septum back to RA 9–10. (**b**) During sinus, RA 7–8 near the sinus node is earliest with activation down the crista and superior medially toward RA 9–10. CS 1–2 representing low LA activation is also late. (**c**) Pacing in the CS (at CS 1–2) propagates laterally along the isthmus and then up the lateral wall toward RA 3–4. A simultaneous wave front reaches the superior-medial electrode at CS 9–10 and then laterally toward the opposing wave front to collide at or near RA 3–4. Finally, in (**d**) following isthmus ablation, pacing from the CS (at CS 1–2) results in propagation across only part of the isthmus with termination of the wave front at CS 9–10. A simultaneous wave front from the CS 1–2 pacing propagates up the interatrial septum to the RA 9–10 electrode and then laterally along the crista toward the RA 1–2 electrode

interval over 200 ms (Fig. 23.16a). It is usually not a clinically important ECG finding and rarely progresses to complete heart block [150]. Conduction delay in first-degree AV block is usually at the AV node level but in rare circumstances can also occur in His-Purkinje tissue [151, 152]. An electrophysiology study is necessary to confirm the level of conduction delay and is rarely indicated for first-degree AV block. However, very long AV intervals in which atrial activation occurs prior to opening of the tricuspid and mitral valve from the prior ventricular depolarization can give rise to atrial stretch and loss of effective atrial contribution to cardiac output and resultant symptoms.

As AV conduction becomes more affected, type I second-degree AV block can be seen. With this, there is progressive prolongation of conduction time of each atrial depolarization through the AV node and His-Purkinje tissue with PR prolongation until conduction fails and no intrinsic QRS is seen. The PR interval on the first conducted beat after the dropped QRS is shorter than the last conducted PR interval prior to the dropped beat, confirming the diagnosis (Fig. 23.16b) [153].

Asymptomatic type I AV block is commonly seen during sleep and in trained athletes [154]. In patients without structural heart disease, type I AV block is usually benign.

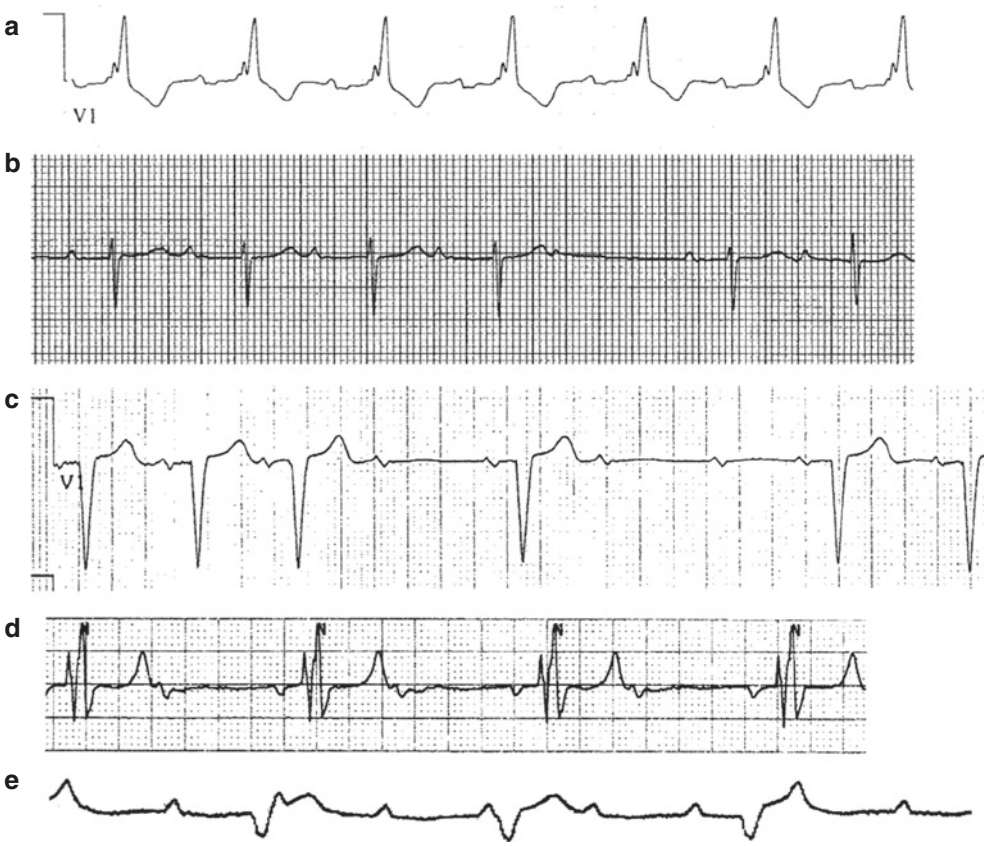

Fig. 23.16 Varying degrees of AV block. (**a**) Sinus rhythm with first-degree AV block with prolonged PR interval. (**b**) Type I, second-degree AV block (Wenckebach) with progressive PR prolongation followed by non-conducted P-wave and then a shorter PR interval on the next conducted P-wave. (**c**) Type II second-degree and higher-grade AV block. The third QRS complex is followed by a non-conducted P-wave without PR prolongation. The fourth QRS is followed by two consecutive non-conducted P-waves followed by two normally conducted beats. (**d**) 2:1 AV block is noted with every other P-wave being conducted. (**e**) Complete heart block with wide QRS escape rhythm. Atrial and ventricular depolarizations are independent

However, in patients with structural heart disease, its importance is dictated by the severity of the underlying heart disease and symptoms [155]. Like first-degree AV block, type I AV block is usually a product of AV nodal tissue delay but can occur in the His-Purkinje tissue and is usually seen in patients with significant bundle branch block on surface ECG as well [156, 157].

As AV association becomes even more strained, type II second-degree AV block is noted during regular sinus rhythm with a fixed AV interval followed by failure to conduct to the ventricle with a dropped QRS (Fig. 23.16c). The PR interval on the return beat is the same as that just prior to the dropped beat. Higher degrees of AV block are seen such as 2:1 AV block where every other QRS is dropped (Fig. 23.16c, d). Type II AV block is usually associated with underlying bundle branch block and delay within or below the His bundle [158, 159]. Pacing is typically indicated, as it is not uncommon for patients with underlying bundle branch block to progress to paroxysmal heart block or suffer Stokes-Adams-type syncopal spells [132, 160, 161].

Complete heart block is seen when no atrial conduction to the ventricle occurs. Non-conducted P-waves are seen with a junctional or ventricular escape rhythm eventually seen (Fig. 23.16e). Complete heart block may also occur as a congenital disorder with treatment concentrating on pacing in bradycardic patients with low cardiac output and those with a wide QRS escape rhythm where heart block is presumed to occur below the level of the His bundle [162].

In general, acquired heart block is usually associated with drugs, ischemic heart disease, or degenerative processes. Beta-blockers, non-dihydropyridine calcium antagonists, and membrane active antiarrhythmic drugs such as amiodarone, procainamide, propafenone, and flecainide are just a few drugs responsible for alterations in AV conduction at the level of the AV node or His-Purkinje system. Degenerative diseases such as Lenegre or Lev's disease or infectious etiologies such as rheumatic fever, Chagas disease, and rheumatic diseases including ankylosing spondylitis and rheumatoid arthritis, and infiltrative processes (amyloidosis, sarcoid, or Hodgkin's disease) are less common [4].

23.2.2.2 Tachyarrhythmias

Junctional Rhythm, AV Nodal Reentrant Tachycardia, and AV Reciprocating Tachycardia

Junctional rhythm occurs when the automaticity of the AV node is faster than that of the sinus node and typically a regular narrow QRS rhythm is noted. Retrograde activation of the atrium may result in an inverted P-wave immediately following the QRS or there may be ventriculoatrial dissociation.

Occasionally, antegrade conduction from a spontaneous atrial depolarization through the AVN may occur, advancing the next QRS and confirming the absence of complete heart block. At rates greater than 60 beats/min, junctional rhythm is considered to be abnormal and termed accelerated junctional rhythm. Junctional rhythm often occurs during times of heightened vagal tone such as sleep or rest but may also be seen with digoxin toxicity [163, 164]. Junctional and accelerated junctional rhythm may also be seen frequently after valvular surgery or after major cardiac surgery where sinus node function may be transiently impaired or the AV node is mechanically irritated.

Atrioventricular nodal (junctional) reentrant tachycardia (AVNRT) is the most common form of sustained supraventricular tachycardia excluding atrial fibrillation and flutter [165, 166]. In this arrhythmia, the AV node has functionally two pathways termed slow and fast pathways. Reentrant tachycardia occurs when an impulse travels down one of the pathways and backs up the other. Perpetuation of the tachycardia occurs when the impulse again travels down the initial pathway and around again. Retrograde activation of the atrium occurs, and inverted P-waves are often seen in the terminal portion of the QRS in the most common form (Figs. 23.17 and 23.18). Due to autonomic input into the AV node, maneuvers to enhance vagal tone such as Valsalva maneuvers or carotid sinus massage can often terminate the arrhythmia [165, 167]. Drugs affecting the AV node including beta-blockers, non-dihydropyridine calcium antagonists, and digoxin are used to suppress recurrence. Adenosine injected rapidly intravenously is often used to terminate the arrhythmias in emergency rooms with high success rates [168–170].

An important tachycardia that should not be missed by the practicing physician is a bypass tract-mediated tachycardia. Commonly referred to as Wolff-Parkinson-White syndrome, clinical tachypalpitations and the presence of a delta wave in sinus rhythm are clues to the possible mechanism of a patient's clinical arrhythmia. In the setting of manifest or overt preexcitation during sinus rhythm, a narrow QRS tachycardia with retrograde P-waves distinct from the terminal portion of the QRS strongly suggests orthodromic atrioventricular tachycardia. The arrhythmia in this setting utilizes the AV node, His-Purkinje tissue, and ventricle in an antegrade limb. The ventricular myocardium is thus acti-

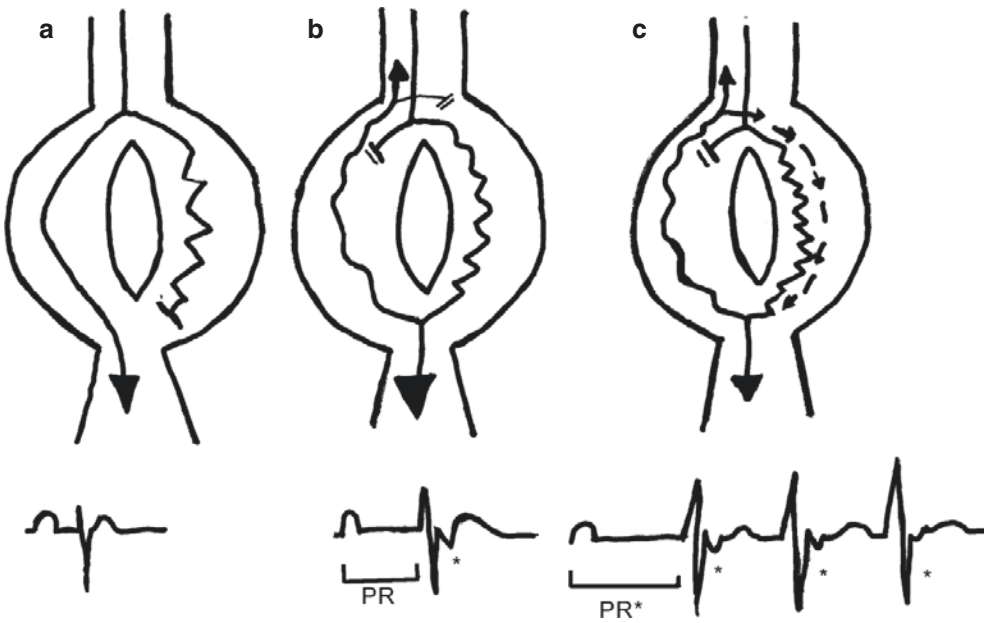

Fig. 23.17 Initiation of typical AV nodal reentry tachycardia (AVNRT). (**a**) Normal activation sequence. An impulse travels through the AV node then travels down two simultaneous pathways. Ventricular activation under normal circumstances occurs rapidly through the fast pathway and results in a normal PR interval. Conduction block occurs in the slower pathway as the impulse collides with the depolarized shared tissue. (**b**) Isolated reentry echo beat. An atrial impulse or premature beat initially travels down the faster pathway but encounters block. Conduction then travels along the slower pathway activating the ventricle resulting in a longer PR interval. The impulse then travels retrograde up the fast pathway that either has not been depolarized or is no longer refractory and activates the atrium (*). The slow pathway is refractory to activation and antegrade conduction is blocked. (**c**) Initiation and perpetuation of tachycardia. An atrial beat or premature atrial beat again blocks in the fast pathway. Activation proceeds along the slow pathway giving rise to an even longer PR interval. Retrograde fast pathway activation occurs, and the atrium is activated giving rise to the inverted P-wave (*). Due to the additional recovery time, the previously refractory antegrade slow pathway is now excitable, and the wave front progresses to activate the ventricle. The circuit repeats giving rise to the tachycardia

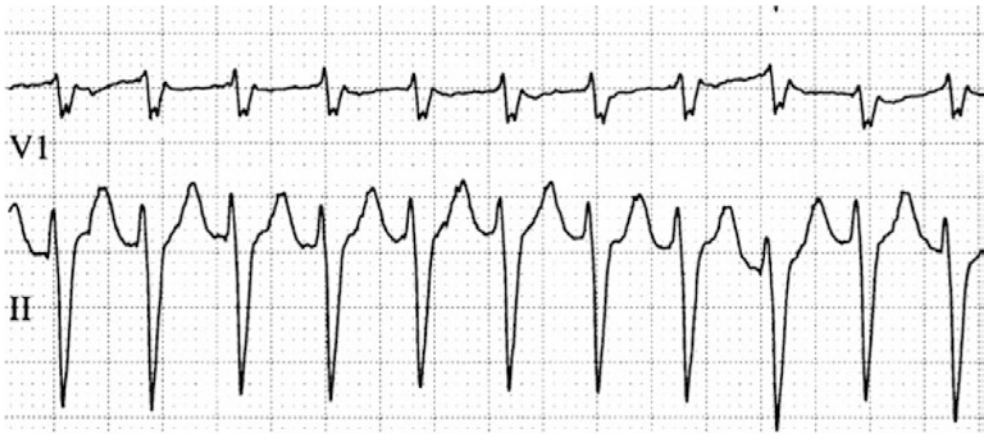

Fig. 23.18 Typical atrioventricular tachycardia (AVNRT). Lead V1 and lead II show a narrow complex tachycardia with no discernible retrograde P-waves during the tachycardia

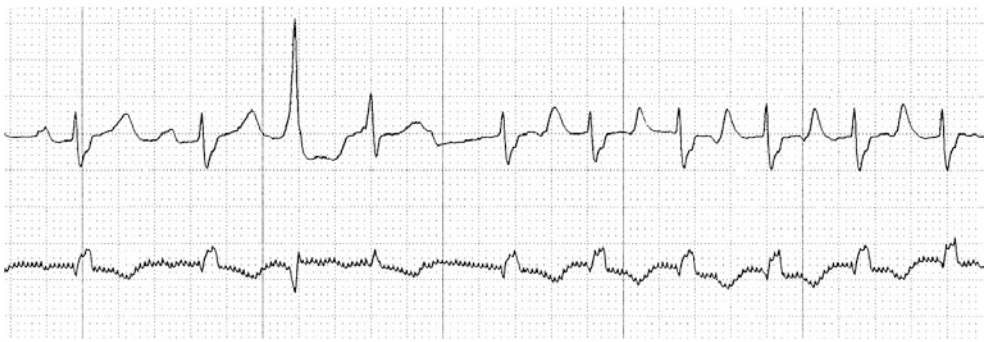

Fig. 23.19 Initiation of orthodromic AV reciprocating tachycardia. A P-wave arrives early resulting in a prolonged PR interval. Normal ventricular activation occurs through the AV node. Retrograde atrial activation occurs over the bypass tract giving rise to a long VA time. Perpetuation of reentry then occurs

vated normally and results in a narrow QRS. Retrograde atrial activation occurs when the bypass tract is activated from ventricular depolarization. Atrial activation then perpetuates antegrade ventricular activation and the circuit perpetuates (Fig. 23.19).

In antidromic AV reentrant tachycardia (AVRT) or circus movement tachycardia, the bypass tract is utilized antegrade, and the tachycardia is a wide complex tachycardia as a result of slower cell-to-cell ventricular myocardial activation, not His-Purkinje-based activation (Fig. 23.20) [1]. Retrograde activation of the atrium occurs usually through the His-Purkinje-AV node axis but may rarely utilize a second bypass tract in the retrograde direction. Antidromic AV reciprocating tachycardia may mimic ventricular tachycardia and is suggested when preexcitation of the QRS is noted after restoration of sinus rhythm. Agents such as verapamil or diltiazem that may enhance antegrade AV conduction over the bypass tract in the setting of atrial fibrillation may result in ventricular fibrillation and are contraindicated.

23.2.2.3 Ventricular Origin-Associated Arrhythmias

Premature Ventricular Contractions

The most common type of ventricular arrhythmia is that of the simple premature ventricular contraction (PVC). An early ventricular depolarization occurs prior to the normal antegrade activation from the atrium or the normal AV node-His-Purkinje axis. Occurring in normal and abnormal myocardium, PVCs may be asymptomatic but also may give rise to the sensation of palpitations and on occasion lightheadedness. In very high frequency, ventricular ectopy may be entirely asymptomatic but may also give rise to decreased cardiac output states in patients with both normal and abnormal systolic function. The morphology of the PVCs and sequential PVCs can give clues to their ventricular location and may suggest a certain type of pathophysiology or syndrome [171, 172].

Premature ventricular contractions that are of a single morphology are termed monomorphic or uniform and those that have multiple morphologies, polymorphic or polyform [173]. In the setting of no significant structural heart disease, monomorphic PVCs with a left bundle branch block, normal axis frequently arises from the pulmonary outflow tract region and are usually thought to be benign (Fig. 23.21a) [174]. Termed RV outflow tract PVCs (RVOT PVCs), these beats may be suppressed with beta-blockers, calcium antagonists, and Vaughan Williams class I and class III drugs. In the asymptomatic patient, no therapy is generally needed. In cases of drug failure or intolerance in the symptomatic patient or in individuals with greater than 20% ectopy with decreased LV systolic function, ablation therapy is utilized

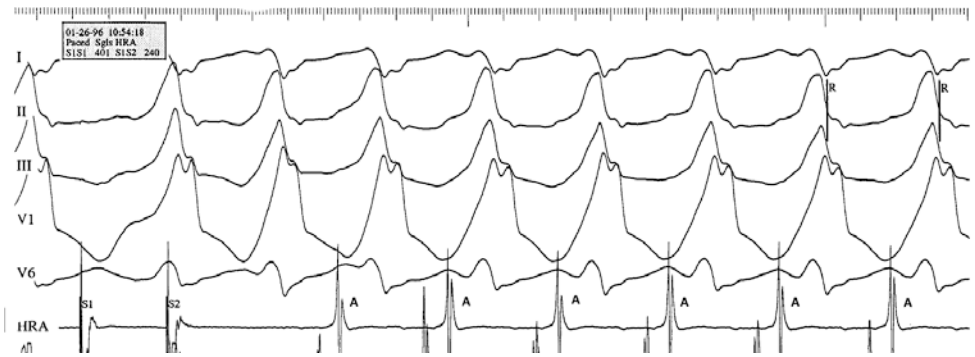

Fig. 23.20 Imitation and perpetuation of antidromic AV reciprocating tachycardia. An atrial premature is delivered (S2) during antegrade pacing with manifest preexcitation (wide QRS and short AV time). Retrograde atrial activation is noted in the HRA channel followed by a regular wide complex tachycardia with a right bundle branch block/right axis tachycardia consistent with a left lateral bypass tract

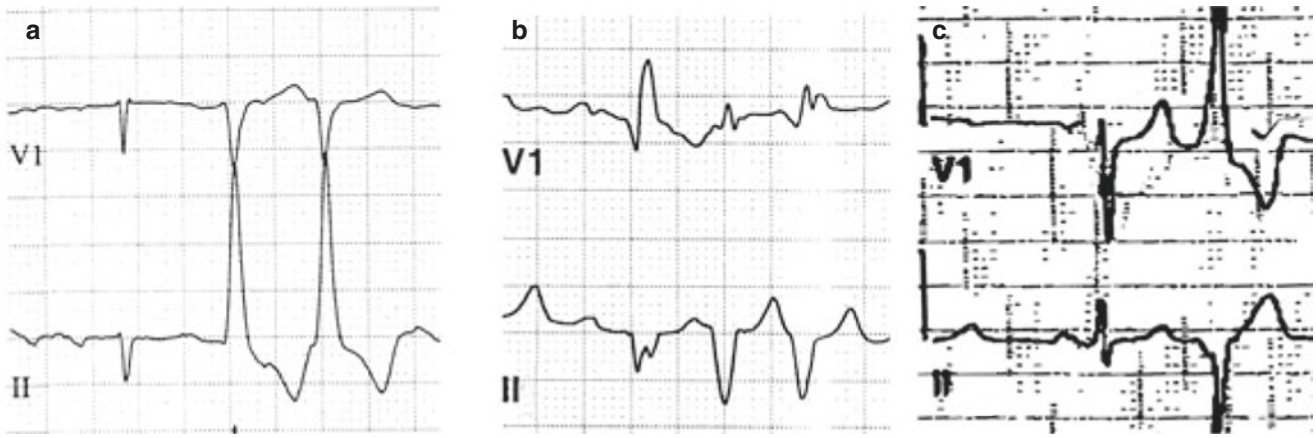

Fig. 23.21 Premature ventricular contraction (PVC) variability. (**a**) Left bundle/normal axis PVCs arising from the right ventricular outflow tract. (**b**) Right bundle branch/superior axis PVC arising from left ventricular inferior scar. (**c**) A right bundle branch/superior axis PVC with a narrower QRS consistent with fascicular PVCs arising from the left posterior fascicle

with typically good success [174–176]. In making the diagnosis of benign RVOT PVCs, one first needs to confirm the absence of ischemia, as anterior wall distribution ischemia may also give rise to frequent asymptomatic and symptomatic PVCs.

Right bundle branch block (RBBB) superior axis monomorphic PVCs suggest an inferior origin of the left ventricle (Fig. 23.21b). Careful inspection of the resting ECG may reveal a prior inferior infarct suggesting that the ventricular ectopy is arising in the setting of myocardial scar or ischemia and may not be benign [177–181]. Patients with left ventricular dysfunction (ejection fraction less than 40%), prior myocardial infarction, and high-frequency ventricular ectopy have a high incidence of sudden cardiac death [182–186]. These individuals have been the subject of many drug and device trials over the last two decades as well as those with non-sustained ventricular tachycardia [187–190].

In other patients, uniform ectopy arising from the inferior base of the left ventricle may also appear as RBBB, superior axis PVCs in the absence of structural heart disease (Fig. 23.21c). These may arise from the posterior fascicles of the left bundle and may be associated with a typically benign form of normal heart ectopy or ventricular tachycardia, albeit often symptomatic [191]. The PVC and ventricular tachycardia-associated QRS morphology is often subtlety narrower than scar-related or ischemia-related ventricular tachycardia and may help in the diagnosis [192–195]. This verapamil or adenosine-sensitive rhythm is typically benign but may require treatment in symptomatic patients.

When reviewing an ECG or rhythm strip, attention to the variable morphologies of ventricular ectopy is equally important. Individuals with polyform ventricular ectopy with left bundle branch block (LBBB)/superior axis and LBBB/normal axis or moderate variability of the LBBB-type QRS morphology in the setting of normal, nonischemic left ventricular function may be found to have arrhythmogenic right ventricular cardiomyopathy (ARVC). This is a progressive disease of the right ventricular myocardium with premature

cellular apoptosis and replacement with fatty tissue [196]. Associated with palpitations, syncope, and sudden cardiac death thought secondary to malignant ventricular tachycardia or ventricular fibrillation, ARVC may be detected with ECG-gated computed tomography, MRI, or occasionally endomyocardial biopsy [197–200]. The high suspicion and early referral to a specialist is often necessary to prevent untoward events. Drug therapies with sotalol, beta-blockers, and implantable defibrillators have been used. Ablation therapy may be used to reduce episodes of sustained ventricular tachycardia (VT). New origins for VT arise as the disease progresses, however, making ventricular tachycardia ablation alone less reliable [201].

Multiform or polyform PVCs also occur in the setting of ongoing or prior ischemic heart disease. Symptoms of heart failure exacerbation, new chest pain, or prior infarct increases suspicion that the ventricular ectopy is an indicator of unstable myocardium. Evaluation of left ventricular function and noninvasive or invasive ischemic evaluation is warranted [201]. Depressed LV systolic function coupled with a high level of ventricular ectopy foreshadows a poor prognosis. In the GISSI-2 study, patients with normal and depressed left ventricular function and with varying degrees of ventricular ectopy were evaluated. Patients with depressed LV function and high degrees of ventricular ectopy had significantly higher mortality than those with low-frequency ectopy and normal LV function [202].

Nonischemic Ventricular Tachycardia

Ventricular ectopy associated with nonischemic entities such as right ventricular outflow tract PVCs, arrhythmogenic right ventricular cardiomyopathy, and verapamil-sensitive tachycardia may all be associated with sustained ventricular tachycardia. Management and treatment of these arrhythmias is similar to treatment of the asymptomatic patient with PVCs alone. In symptomatic patients, however, specific drug therapy, ablation therapy, and implantable defibrillator placement may take on a greater role.

An additional ventricular tachycardia associated with nonischemic cardiomyopathy is bundle branch reentry tachycardia. In this tachycardia, the reentrant circuit involves antegrade conduction down the right bundle branch and retrograde conduction up the left bundle branch, turning around at the His bundle. The tachycardia has a LBBB/normal axis morphology and should be considered in patients with nonischemic cardiomyopathy. Elimination of the tachycardia is accomplished through ablation at the right bundle [203]. Unfortunately, many patients may have additional ventricular tachyarrhythmias in the setting of nonischemic cardiomyopathy and may still warrant treatment with implantable defibrillators.

Ventricular tachycardia may occur in the setting of surgical scar, sarcoidosis, scleroderma, Chagas disease, and after treatment of complex congenital heart disease repair. Long-term follow-up of many of these entities is limited with respect to ablation therapy. The role of implantable cardioverter-defibrillators (ICDs) has expanded to include many of these disease states as pacing indications are also met. Ventricular tachycardia ablation may be used to reduce the frequency of VT and ICD discharge in these patients [204, 205].

Ischemic Ventricular Tachycardia

As ventricular ectopy becomes more frequent and runs or short salvos of non-sustained ventricular tachycardia occur, risk of sudden cardiac death (SCD) increases [178–181, 183–185]. Greater than 3 consecutive beats at a rate of more than 100 bpm is termed non-sustained ventricular tachycardia (NSVT). Greater than 30 s of VT would be considered sustained VT even if it terminates spontaneously [201]. A regular slower ventricular rhythm less than 100 bpm is termed accelerated idioventricular rhythm (AIVR). While abnormal, this rhythm has not been used as a criterion for SCD risk management in modern day trials.

Several large trials of high-risk patients with prior cardiac arrest or who are thought to be at high risk for sudden cardiac death have utilized ventricular tachycardia, either spontaneous or induced as a risk stratifier, for evaluation and treatment. In the secondary prevention AVID trial [206], patients with prior cardiac arrest without reversible cause and unexplained syncope with inducible ventricular tachycardia in the setting of LV dysfunction and individuals with sustained, symptomatic ventricular tachycardia were evaluated and treated either with drug therapy (predominantly amiodarone) or implantable cardioverter-defibrillator (ICD) therapy. This trial and others have demonstrated the superior effectiveness of device therapy to drug therapy for the secondary prevention of SCD in high-risk patients [207, 208].

Patients with underlying ischemic heart disease with prior infarct and non-sustained VT by ambulatory holter monitoring were evaluated by invasive electrophysiology study in the MADIT and MUSST trials [209, 210]. Individuals with inducible ventricular tachycardia through programmed stimulation that was not suppressible with drug therapy were deemed to be at high risk and were treated with conventional antiarrhythmic drug therapy or implantable defibrillators. In these landmark trials, implantable defibrillators were shown to be superior to drug therapy in this high-risk group for the primary prevention of SCD. In addition, antiarrhythmic drug use was associated with event rates greater than that of patients treated with placebo [210]. Over the last 10 years, several additional trials have been completed that emphasize the importance of left ventricular ejection fraction as an inde-

pendent risk factor for SCD and the importance of standard drug therapy for the treatment of left ventricular dysfunction and device therapy in the reduction of premature death [211, 212].

23.2.2.4 Special Considerations in Evaluation of Arrhythmias

Ventricular Tachycardia: Identification by Surface ECG

A difficult problem that often occurs in clinical practice is distinguishing ventricular tachycardia from supraventricular tachycardia with aberrancy or pacing. At rapid rates or in the setting of an abnormal QRS during intrinsic ventricular activation, QRS morphology can become wide and resemble ventricular tachycardia. Several papers have been written over the last 30 years to help the clinician distinguish between these two entities. Important in the evaluation of the rhythm strip or ECG is the baseline QRS and clinical history of prior infarct and drug therapy. As with most tests, clinical information can greatly enhance the specificity of test findings [213].

Inherent in the evaluation of the wide complex rhythm are certain features of the QRS complex including duration, axis, precordial concordance, and Q-wave morphology. Additional information including AV dissociation, presence of fusion beats, and QRS alternans can be used. In 1978, Wellens and colleagues characterized QRS morphology and duration in RBBB wide complex tachycardias as well as presence of AV dissociation to distinguish ventricular tachycardia and supraventricular tachycardia [214]. In 1988, Josephson and colleagues characterized QRS morphologies in LBBB wide complex tachycardias [215]. Separate papers published in 1991 characterized most wide complex tachycardias based on a hierarchical evaluation of the QRS morphology and AV association [216, 217]. In 1997, additional evaluation of patients with intraventricular conduction disease was reported [218]. Newer criteria by Vereckei and associates utilized additional criteria of the QRS complex during tachycardia to improve specificity over prior algorithms. While potentially useful, these criteria too have shortcomings in certain patient populations including patients with prior infarction, preexcited tachycardias, and those on medications [219]. Inherent in all the algorithms is the importance of the patients' clinical history. Patients with prior myocardial infarction with or without left ventricular dysfunction are much more likely to have ventricular tachycardia compared to aberrant supraventricular tachycardia (SVT) as the correct diagnosis during wide complex tachycardias [220]. Detailed evaluation of these algorithms is beyond the scope of this text, and the reader is referred to the cited articles.

Arrhythmias Associated with Genetic Disorders

Abnormalities of cardiac depolarization and repolarization occur in patients with genetic disorders typically involving sodium and potassium channels. Table 23.3 lists common and some uncommon arrhythmic syndromes and their presumed genetic mutations [221–223]. In many circumstances, genetic miscoding is not readily apparent on surface ECG, and provocative measures may be required to elucidate them. In patients with familial hypertrophic cardiomyopathy, the electrocardiogram may be normal despite the fact that this mutation can result in adverse clinical events [224, 225]. Abnormalities in sodium and potassium channels and their subunits as well as regulatory proteins have been implicated in Brugadas syndrome and long QT syndrome. In the Brugada syndrome, an atypical RBBB with persistent ST elevation and frequently associated T-wave inversion is noted on the surface ECG and is most notable in leads V1–3 (Fig. 23.22). Subsequent evaluation has linked this syndrome to *SCN5A*, the gene responsible for the alpha subunit of the sodium channel and is inherited in an autosomal-dominant pattern with variable penetrance. Electrical abnormalities of right ventricular epicardium appear to be responsible for the abnormal ECG pattern [226–228].

Genetic polymorphisms in the sodium and potassium channels and their subunits have been demonstrated for a variety of individuals with long QT syndrome. Prolongation of ventricular myocardial repolarization due to genetic errors or drugs is manifested on the ECG by a long QT interval. A table of normal values for men and women is shown (Table 23.4) [229]. Individuals with prolongation of the QT interval with unexplained syncope, light-headedness, or a family history of sudden cardiac death warrant further evaluation. Asymptomatic patients may also warrant further evaluation, as sudden cardiac death may be the first presenting sign of patients at risk.

Polymorphous ventricular tachycardia with acquired long QT in the setting of drugs or pause-dependent QT prolongation may be seen. In Fig. 23.23, frequent PVCs result in bradycardia-dependent QT prolongation, and a second PVC produces an R-on-T phenomenon resulting in non-sustained polymorphous ventricular tachycardia that appears to twist about a point termed torsades de pointes. Temporary pacing, Isuprel infusion to increase intrinsic heart rate, beta-blockers, and lidocaine may be useful in reducing these events. Removing offending QT prolonging drugs is necessary.

Ventricular fibrillation may also occur in the setting of inherited channelopathies and in familial and sporadic hypertrophic cardiomyopathies [221, 222, 224]. Ventricular fibrillation is also frequently seen associated with acute ischemic events and may follow prolonged sustained monomorphic ventricular tachycardia as the myocardial substrate changes. Prompt treatment with advanced cardiopulmonary resuscitation and direct current cardioversion is required.

Table 23.3 Gene, gene locus, protein, physiologic effect, and associated clinical syndromes associated with several common and less common cardiac arrhythmias

Gene	Locus	Protein	Effect	Syndrome
SCN5A	3p24–p21	Sodium channel (hH1)	Repolarization (I_{Na} current)	Long QT 3, Brugada syndrome, progressive cardiac conduction disease, AV block, atrial standstill
SCN4B	11q23	Sodium channel subunit $Na_V\beta4$	Repolarization	Long QT 10
CAV3	3p25	Caveolin-3 protein	Repolarization (alters sodium channel current)	Long QT 9
KCNQI	11p15.5	Potassium channel-alpha subunit (K_vLQT1)	Repolarization (I_{Ks} current)	Long QT 1, short QT syndrome, chronic AF, sudden infant death
KCNH2 (HERG)	7q35–q36	Potassium channel-alpha subunit	Repolarization (I_{Kr} current)	Long QT 2, short QT syndrome, AF
KCNE1	21q22	Potassium channel-beta subunit (mink)	Repolarization (I_{Ks} current)	Long QT 5
KCNE2	21q22	Potassium channel-beta subunit (MirP)	Repolarization (I_{Kr} current)	Long QT 6, paroxysmal AF
KCNJ2	17q23	Potassium channel	Resting membrane potential maintenance (I_{Kr} current)	Long QT 7
CACNA1c	12p13.3	Calcium channel Cav1.2		Long QT 8, congenital heart disease, Brugadas syndrome-3
AnkB	4q25–q27	Anchoring protein	Altered Ca^{2+}, cellular disruption/ organization, reduced protein levels	Long QT 4, AF
Ryr2	1q42.1–q43	Cardiac ryanodine receptor	Ca^{2+} release channel of endoplasmic reticulum (ER)	Catecholaminergic polymorphic ventricular tachycardia
CASQ2	1p13–p11	Calsequestrin	Ca^{2+} storage of ER	Catecholaminergic polymorphic ventricular tachycardia
HCN4	15q24–q25	Cation channel	Spontaneous diastolic depolarization (I_f current)	Sinus bradycardia
PRKAG2	7q36	cAMP-activated protein kinase	Glycogen metabolism	WPW, hypertrophic cardiomyopathy (HCM)
CSX	5q34	Transcription factor	Heart chamber growth/formation	AV block, congenital heart disease
TNNT2	1q32	Troponin T	Sarcomere contractile protein	Idiopathic ventricular tachycardia, HCM
GJA5	1q21.1	Connexin-40	Cell signaling-gap junctions	AF
Unknown	10q22–24	Possible alpha-, beta, receptor, or G-protein receptor kinase	Unknown	Familial paroxysmal and chronic AF
Unknown	6q14–16	Unknown	Unknown	Familial PAF progressing to chronic AF
Unknown	5p13	Unknown	Unknown	Chronic AF young associated with neonatal death, VF

AV atrioventricular, *AF* atrial fibrillation, *WPW* Wolf-Parkinson-White

Paced Rhythms

An important rhythm seen commonly during ambulatory ECG monitoring and routine ECG is the paced atrial and ventricular complex. Many modern-day pacemakers and pacemaker defibrillators are designed not only to sense normal intrinsic atrial and ventricular depolarization but also to distinguish the onset and offset of various atrial and ventricular arrhythmias. In certain modes, devices may be programmed to identify the rhythm and attempt to pace faster than the tachycardia in an effort to terminate it. Implantable cardioverter-defibrillators are designed to also deliver a high-voltage shock to terminate the arrhythmia automatically (Fig. 23.24). Complex algorithms within the device's program help prevent unwarranted shocks for rapidly conducted atrial fibrillation or sustained supraventricular tachycardia.

Basic components of the pacemaker include the pace generator, the battery and computer, and the lead. The pacing wire is typically placed endovascularly and traverses the subclavian vein, into the superior vena cava, and is delivered to the right atrium, right ventricle, or, in certain circumstances, within the coronary sinus. These soft, flexible wires are design to affix to the endomyocardium in a variety of techniques, including passive adherence and screws. The pacing wire is able to carry electrical signals from the heart to the pacemaker generator where timing circuits analyze whether an impulse is to be delivered to the myocardium. As indicated impulse travels from the generator to the myocardium via the lead, activating the endomyocardium directly and initiating a wave front across the affected chamber.

Inherently slower than specialized atrial tissue or the Purkinje system of the ventricular myocardium, activation

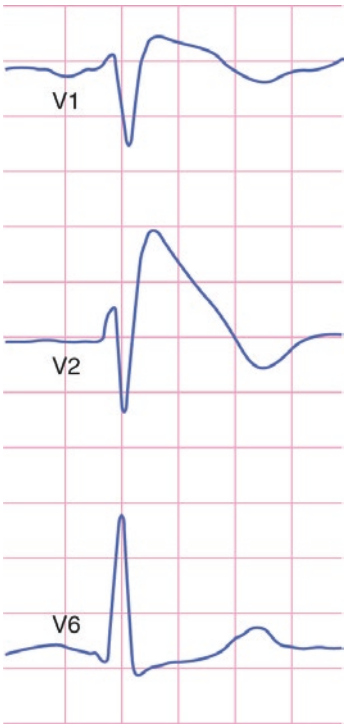

Fig. 23.22 Atypical right bundle branch block. QRS activation is noted in precordial leads V1, V2, and V6. The slurred, downsloping ST segment is most notable in V2 in this example

Table 23.4 Normal QT intervals for individuals under the age of 15 and for adult men and women

Rating	1–15 years (ms)	Adult male (ms)	Adult female (ms)>
Normal	<440	<430	<450
Borderline	440–460	430–450	450–470
Prolonged	>460	>450	>470

ms milliseconds

is typically prolonged resulting in prolonged P-wave duration when pacing in the atrium or a bundle branch block appearance of the QRS during ventricular stimulation. Activation of the right ventricle with pacing results in a left bundle branch block pattern, while activation of the left ventricle results in a RBBB pattern. Apical activation results in a superior axis, while right ventricular outflow position results in a normal axis. Pacing in the coronary sinus typically results in a right bundle branch block pattern (Fig. 23.25). However, inadvertent delivery of a lead across a patent foramen ovale, ventricular septal defect, or perforation of the right ventricle with pacing of the left ventricular epicardium can also occur. Knowledge of the lead delivery technique in patients with RBBB paced QRS configuration is important in avoiding embolic phenomenon from left ventricular endocardial placement or other serious complications such as tamponade from erroneous lead perforation.

23.3 Conclusion

Through careful attention to the clinical history, association of atrial and ventricular impulses, and morphology of atrial and ventricular depolarization on the surface ECG, most common clinical arrhythmias can be accurately diagnosed. In many instances, treatment of an arrhythmia can be straightforward and handled without referral or consultation. However, new and expanding treatment options including device therapy and ablation as well as specific antiarrhythmic drug management may often require additional expertise. Cardiac arrhythmias associated with genetic mutations are becoming more recognized. While gene therapy is not currently available, genetic identification of many disorders is available, and characterization in certain groups may aid in diagnosis of asymptomatic or high-risk patients and lead to pharmacologic or invasive procedures.

23.4 Case Studies

23.4.1 Case Study 1

GB was a 52-year-old professional truck driver that presented to the emergency room following a single vehicle accident while driving across the state. The patient does not recall the accident and had eaten lunch about an hour earlier. He is diabetic, obese; he smokes one and a half packs of cigarettes per day; and he has a history of dyslipidemia. He takes a diuretic for mild hypertension but frequently does not use it due to his occupation. His wife reports he snores. He reports frequent morning headaches and when not working complains of fatigue, lack of energy, and falls asleep easily while watching TV. He reports occasional heart racing that usually lasts only a few minutes but can last up to an hour. He denies angina, orthopnea or paroxysmal nocturnal dyspnea, stroke-like symptoms, episodes of hypoglycemia, or syncope. His HgbA1c is 9.0%.

Initial evaluation demonstrates a 5′10″ male with a BMI of 42.3. Blood pressure was 148/84, and his serum glucose in the office is 186 mg/dL. Oxygen saturation was 94%. Potassium was 3.8, blood urea nitrogen 31, and creatinine 1.3 with a bicarbonate of 31. His cardiac exam is normal except for jugular venous distention, decreased heart sounds, and moderate lower extremity edema.

23.4.1.1 Clinical Testing

Initial ECG demonstrated sinus arrhythmia with an incomplete right bundle branch block. Chest X-ray reveals moderate changes consistent with chronic obstructive lung disease. Cardiac size was upper limits of normal. Hemoglobin was 17.2 mg/dL. A head CT demonstrated no hemorrhage or mass.

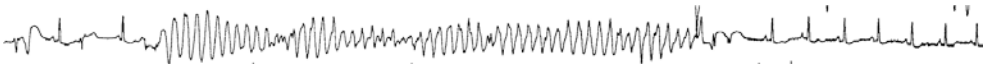

Fig. 23.23 Initiation and spontaneous termination of polymorphous ventricular tachycardia (PMVT). Variation in the RR interval results in pause-dependent QT prolongation. A PVC then initiates a PMVT that appears to twist about a point termed torsades de pointes. The arrhythmia terminates and sinus rhythm results

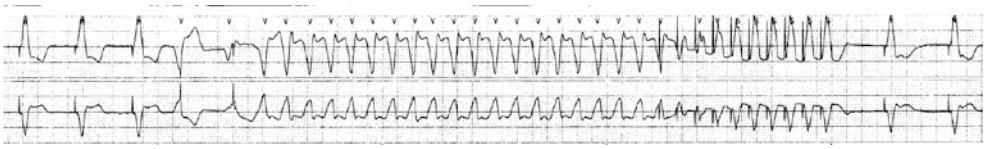

Fig. 23.24 Pace termination of ventricular tachycardia (VT). A paced rhythm is followed by a premature ventricular contraction and rapid VT. Ten rapid pulses delivered from an implantable defibrillator are delivered automatically and terminate the tachycardia

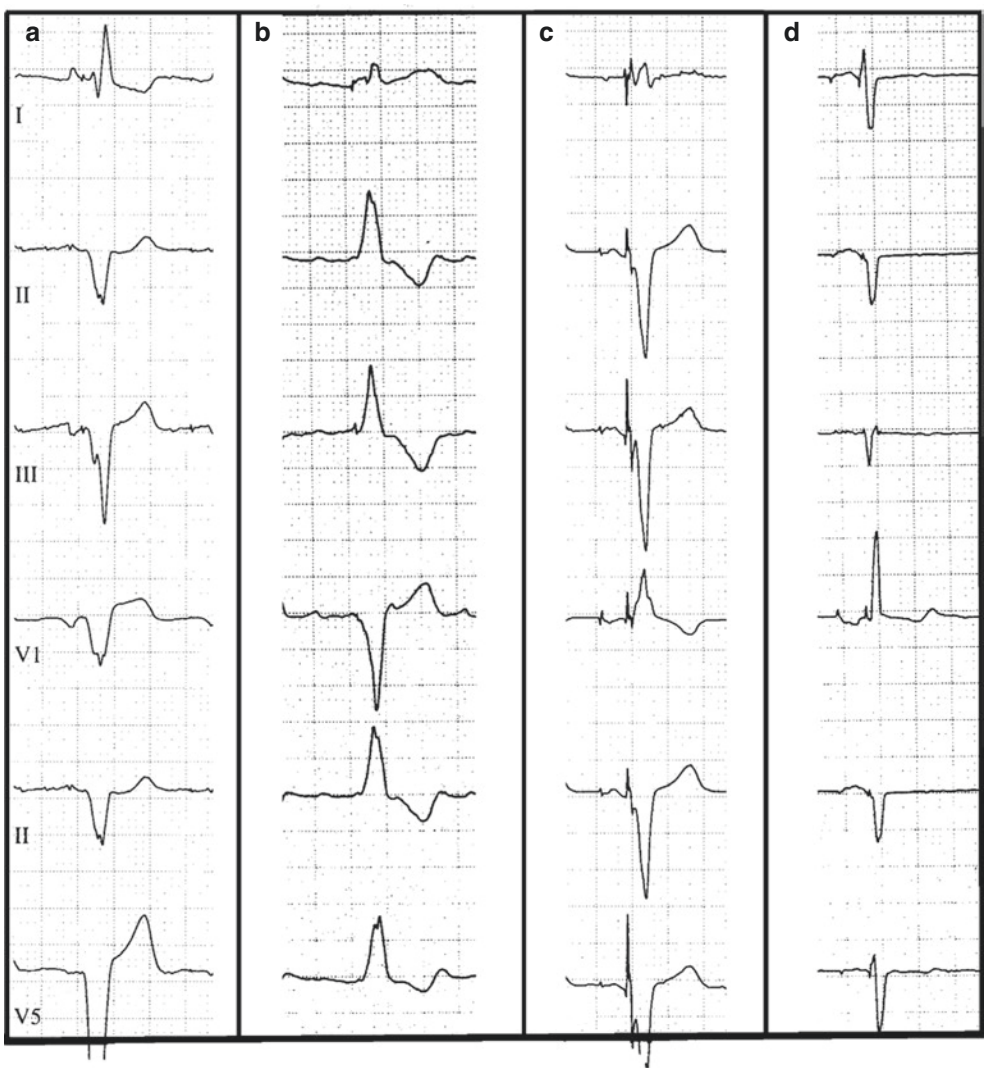

Fig. 23.25 QRS morphology is dependent on ventricular lead placement. (**a**) Pacing in the right ventricular apex gives rise to a left bundle branch block (LBBB) superior axis. (**b**) Right ventricular outflow tract pacing gives rise to a normal axis LBBB pattern. (**c**) Left ventricular apical pacing results in a superior axis, right bundle branch block (RBBB) pattern. (**d**) Simultaneous right and left ventricular activation results in a narrow, RBBB pattern with a superior axis

23.4.1.2 Discussion

The differential diagnosis for this patient is large. He has had a presumed syncopal event while operating a motor vehicle. Altered consciousness secondary to metabolic derangement, rapid atrial or ventricular arrhythmias, or heart block should be entertained due to the patients' history of palpitations and an abnormal ECG. There are symptoms to also suggest significant pulmonary disease, and the history is concerning for sleep apnea.

The patient was hospitalized. Overnight telemetry demonstrated sinus arrhythmia and nocturnal pauses of 4.2 s. Heavy snoring while sleeping was noted by nursing staff.

Bedside oximetry revealed frequent desaturation to 78% during apnea events. An echocardiogram revealed mild left ventricular hypertrophy with normal left ventricular function. Bi-atrial enlargement and right ventricular enlargement with an estimated systolic pulmonary pressure of 47 mmHg was noted. An exercise stress test was abnormal. Subsequent coronary angiography revealed mild, nonocclusive coronary disease.

The tentative diagnosis of sleep apnea was made. However, symptoms of palpitations suggested associated atrial fibrillation, and underlying incomplete bundle branch block made heart block a possibility. Electrophysiology testing for evaluation of heart block revealed normal baseline intracardiac intervals and no evidence to suggest block within or inferior to the bundle of His. The patient was instructed to not drive until outpatient evaluation was complete. Formal sleep apnea testing was performed revealing severe sleep apnea. Continuous positive airway pressure therapy was initiated. In follow-up, additional ambulatory testing was performed revealing paroxysmal atrial fibrillation with rapid ventricular response. The patient was anticoagulated with warfarin given the presence of multiple risk factors for stroke. He was also given verapamil for hypertension and rate control during recurrent atrial fibrillation events. In follow-up, he has lost 55 pounds, has not had a recurrence of syncope, and his quality of life appears to have improved.

23.4.2 Case Study 2

TF is a 46-year-old electrician. He presented to the emergency room following cardiac arrest. His event was witnessed. Cardiopulmonary resuscitation (CPR) was initiated, and he was promptly defibrillated at his workplace by a trained bystander using a new automated external defibrillator (AED). Paramedics transferred the patient to the ER. He was on nasal cannula and complained of chest pain. He reports feeling fine prior to the event and remembers his colleague at his side after defibrillation.

Initial evaluation revealed a normally developed 6′2″ male. Blood pressure was 128/68, respirations 18 and unlabored, and his pulse was 110. Oxygen saturation was 99%. Exam also revealed a prominent, sustained cardiac PMI. A systolic murmur was noted in the aortic outflow position. Arterial pulses in the upper and extremity were normal.

23.4.2.1 Clinical Testing

Initial ECG demonstrated sinus tachycardia. Left ventricular hypertrophy with moderate repolarization changes was seen. No evidence for acute or prior myocardial infarction was noted. Chest X-ray demonstrated cardiac enlargement. Routine serum chemistries and blood cell counts were normal. Cardiac enzymes were normal.

23.4.2.2 Discussion

Ventricular fibrillation may result from metabolic abnormalities, acute or chronic ischemia, genetic arrhythmic disorders, inherited cardiomyopathies, or be associated with mechanical events such as acute pulmonary embolism or severe valvular heart disease. Further clinical history revealed a paternal uncle and grandfather that died suddenly in their early 50s. Autopsies were not performed. No documented family history of premature atherosclerosis was known.

Concentrating on the additional history, cardiac echo revealed severe left ventricular hypertrophy with an interventricular septum measuring 4.2 cm. Near cavitary obliteration with systole is noted. Flow velocities beneath and across the aortic valve are increased but did not demonstrate subvalvular or valvular stenosis. A tentative diagnosis of familial hypertrophic cardiomyopathy was made. Coronary angiography was performed to exclude occult coronary disease. Given high-risk features for sudden cardiac death (interventricular septum greater than 3 cm and prior ventricular arrest), an implantable defibrillator was placed. Beta-blockers at high doses were initiated to limit rapidly conducted atrial arrhythmias and to reduce recurrent ventricular fibrillation.

In follow-up over the next 2 years, the patient developed progressive dyspnea. No recurrent ventricular fibrillation events occurred. Pulmonary pressures assessed by echocardiogram were increased at 52 mmHg and left atrial enlargement noted. Clinical systolic heart failure secondary to left ventricular hypertrophy was made, and after failure of additional oral negative inotrope use to improve symptoms, the patient was referred for surgical myomectomy. Following successful surgery, the patient has returned to work and is with minimal symptoms. Recurrent ventricular events have subsequently been appropriately treated by his implantable defibrillator, and sotalol was initiated to reduce recurrent arrhythmic events.

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Evidence-Based Management of the Patient with Congestive Heart Failure

24

Nicolas W. Shammas

24.1 Epidemiology of Congestive Heart Failure

Congestive heart failure (CHF) is the result of either a weak heart muscle (systolic failure) or a stiff ventricle (diastolic failure). Systolic and diastolic failure may coexist in the same patient [1]. Irrespective of the etiology, it leads to an inadequate amount of oxygenated blood to meet cellular demand.

CHF is a growing problem in the United States and particularly in the elderly [2]. Over half a million cases are diagnosed on an annual basis with subsequent high mortality [3] and a large cost to our economic system [4].

Although less studied, diastolic failure occurs in approximately 30–35% of all patients and 55% of the elderly with CHF [5, 6]. Recently heart failure with normal left ventricular function (HFNEF) is a term that has been more widely used than "diastolic heart failure" and describes a heterogeneous group of patients with a number of pathological mechanisms [7]. It is estimated that 50% of HF patients have HFNEF and display similar physiologic and neurohormonal phenotypes to patients with HF and reduced systolic function. Unless more effective acute and preventative therapies are implemented in treating CHF patients, the social burden in treating these patients will continue to rise [8].

CHF appears to be on the rise in the United States [4, 9] and is partly due to the high prevalence of the metabolic syndrome, diabetes mellitus, hypertension, and obesity [10]. Although improvement in survival has been noted in the younger heart failure patient over the past two decades, this benefit has not been seen in the elderly and females [11]. Survival has improved however in both genders over the past 50 years [12].

N. W. Shammas
Midwest Cardiovascular Research Foundation,
Davenport, IA, USA

24.2 Pathophysiology of Congestive Heart Failure

There are multiple risk factors that lead to injury to the myocardium including coronary artery disease (CAD), hypertension, valvular heart disease, diabetes mellitus, congenital heart defects, anemia, metabolic syndrome, cardiotoxins, and alcoholism [13, 14]. Left ventricular remodeling with reduction of left ventricular function (as measured by the ejection fraction) and dilatation of the left ventricle subsequently occurs. The remodeling process is initially an adaptation mechanism to reduce wall stress and increase cardiac output by hypertrophy of viable myocytes. Hypertrophy, however, eventually leads to an increase in mass-to-volume ratio and premature myocyte cell death [15]. As the syndrome of heart failure occurs, a patient presents with fatigue, increased weight, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and chest pain. A reduced left ventricular function increases the risk of arrhythmias and sudden cardiac death as well as pump failure [16, 17].

Cardiac remodeling is mediated partly by activation of the renin–angiotensin–aldosterone (RAAS) system and the sympathetic nervous system (SNS) (Fig. 24.1). Activation of the RAAS system leads to a rise in angiotensin II (AII); sodium retention and myocardial fibrosis mediated by angiotensin II and aldosterone; peripheral vasoconstriction; and endothelial injury [18], which lead to programmed cell death (apoptosis), hypertrophy, and fibrosis. AII also promotes aldosterone secretion. In addition, vasoconstrictors such as endothelin-1 and reactive oxygen species (ROS) are increased, and nitric oxide (NO) synthesis and release are reduced, all contributing to vasoconstriction [18–20]. Furthermore, endothelial dysfunction is further impaired by the increase in inflammatory markers and cytokines [19, 21, 22].

Elevated sympathetic tone is part of the syndrome of heart failure with elevation of circulating catecholamines and suppression of adrenergic receptors [23]. Adrenaline has direct toxic effect on the myocardium [24]. Also, it induces cellular

P. P. Toth, C. P. Cannon (eds.), *Comprehensive Cardiovascular Medicine in the Primary Care Setting*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-319-97622-8_24

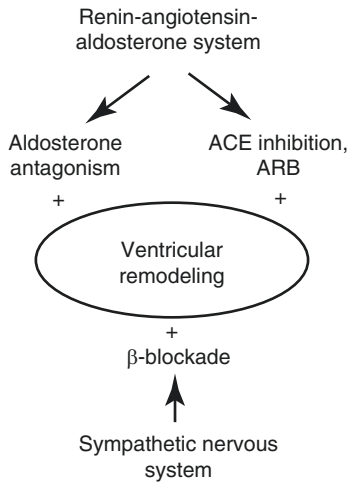

Fig. 24.1 The renin–angiotensin–aldosterone system and the sympathetic nervous system promote ventricular remodeling, a process that can be reversed with aldosterone antagonism, ACEI, or ARB and beta blockade

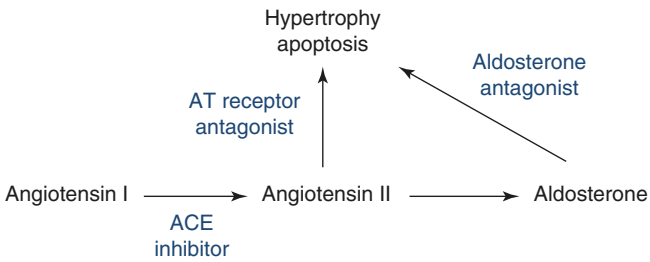

Fig. 24.2 Interventions to block the renin–angiotensin–aldosterone system

calcium overload [25], decreases myocardial mechanical efficiency, precipitates arrhythmias, increases myocardial oxygen consumption and coronary blood flow requirements, and induces left ventricular hypertrophy [26].

The SNS and the RAAS systems are therapeutic targets, and blocking their activation has been shown to reduce mortality and morbidity in patients with CHF. Aldosterone is only partially produced as a result of angiotensin activation, and therefore, AII suppression [27] is not adequate to block its secretion. The addition of aldosterone blockers is, therefore, needed for optimal suppression of aldosterone, and it has been shown to provide additional reductions in mortality and morbidity in patients with CHF [28, 29] (Fig. 24.2). Finally, beta adrenergic blockade also contributes in reducing the activity of the RAAS [30].

The activation of the RAAS and the SNS is generally partially counter-regulated by the production of vasoactive peptides including the natriuretic peptide (NP) system. These vasoactive peptides, particularly, brain natriuretic peptides (BNP) lead to vasodilation and increase sodium/water excretion. Also they inhibit aldosterone release and prevent cardiac and vascular fibrosis. In patients with heart failure, NP renal effects are blunted for unclear reasons, and they are also degraded by the neprilysin system. Recently, the advent of angiotensin receptor neprilysin inhibitor (ARNI) sacubitril/valsartan provided a novel pharmacologic approach that is capable of inhibiting the neutral endopeptidase enzyme neprilysin (with sacubitril) and concomitantly blocks the adverse effects of angiotensin II (with valsartan).

In the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) study [31], a double-blind, randomized, multicenter trial, 8442 patients with Class II–IV heart failure and an ejection fraction of 40% or less were randomized to receive either sacubitril/valsartan (at a dose of 97/103 mg orally twice daily, respectively) or enalapril (at a dose of 10 mg twice daily). The primary outcome of death from cardiovascular causes or heart failure rehospitalization was significantly reduced in the ARNI arm (21.8%) compared to enalapril (26.5%) ($p < 0.001$). Cardiovascular death was reduced by 20% (HR 0.80 (95% CI, 0.71; 0.89)) and risk of first heart failure hospitalization by 21% (HR 0.79 (95% CI, 0.71; 0.89)). Also total mortality was reduced by 16% (absolute risk reduction 2.8%) (HR 0.84 (95% CI, 0.76; 0.93)). The study was prematurely stopped because of the overwhelming benefit of ARNI when compared to ACEI.

Adverse reactions of ARNI were reported in more than 5% of patients in the double-blind study, and these included hypotension, hyperkalemia, cough, dizziness, and renal failure. The incidence of angioedema was also higher in patients treated with ARNI compared to enalapril (0.5% versus 0.2% respectively; 2.4% in the black population). These adverse events are likely to be encountered more frequently in practice as the double-blind period of PARADIGM-HF was preceded by a single-blind run-in period where patients were excluded if they could not tolerate the high dose of ARNI or ACEI.

Several other therapies have been tested in CHF patients and have shown conflicting results. These include endothelin antagonists, immunomodulating agents, and growth hormone [32]. At the present time, interventions that modulate the SNS and RAAS and inhibit the neprilysin enzyme (in conjunction with ARB) remain the only proven treatment to reduce mortality and morbidity in patients with congestive heart failure.

Another pharmacologic advent in treating patients with reduced EF and heart failure is ivabradine, an HCN channel blocker. It is indicated in patients in normal sinus rhythm and who are intolerant to beta blocker or on maximum tolerable dose of a beta blocker. Ivabradine was tested in The Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial (SHIFT) [33] which randomized 6505 patients with chronic heart failure and reduced EF to ivabradine versus placebo on top of optimal medical treatment. Patients had to be in normal sinus rhythm with a heart rate of more or equal 70 bpm, NYHC Class II–IV, EF less or equal 35%, and have

been hospitalized with heart failure in the past 12 months. Ivabradine significantly reduced the relative risk of hospitalization for worsening HF or CV death (RRR 18%, $p < 0.0001$); the significance is driven mostly by a reduction of rehospitalization.

HFNEF describes a heterogeneous pool of patients that make about 50% of HF patients with a unique set of pathophysiologic mechanisms. These patients are typically older with hypertension, obesity, renal failure, anemia, and atrial fibrillation and are more likely to be females. There is also a high incidence of diabetes and coronary artery disease in these patients [7]. In contrast to patients with impaired left ventricular EF, HFNEF patients have non-dilated left ventricular cavity size, concentric instead of eccentric left ventricular hypertrophy, and a normal EF [34].

It is controversial whether LV systolic function is truly normal in patients with HFNEF because EF is an imprecise measure of left ventricular systolic function. However, invasive conductance studies suggested from pressure–volume loops that end-systolic pressure–volume relationship is steeper or normal in HFNEF suggesting a normal systolic function. On the other hand, end-diastolic pressure–volume relationship is shifted leftward and upward indicating diastolic dysfunction [35, 36].

Diastolic dysfunction is not uncommon among elderly patients estimated at about 5.6%, but only 1% has HFNEF [37]. In one study, the product of left ventricular mass index and left atrial volume has the highest predictive accuracy for HFNEF [38]. In addition to ventricular stiffness, arterial stiffness has also been suggested to contribute to HFNEF, and the combined ventricular–arterial stiffness leads to an exaggerated hypertensive response after small increases in LV end-diastolic volume [7].

24.3 ACC/AHA Classification of Congestive Heart Failure

The current ACC/AHA classification for CHF [3] is complementary to the New York Heart Classification (NYHC) [39] and helps define the evolution of symptoms of patients with CHF. In addition, the ACC/AHA classification focuses on the risk factors for CHF by identifying patients who have risk factors for CHF.

This classification includes four stages of CHF:

Stage A: Asymptomatic patients with no left ventricular dysfunction but are at risk of developing CHF including patients with coronary artery disease, hypertension, diabetes mellitus, family history of cardiomyopathy, and the metabolic syndrome.

Stage A is not represented in the NYHC.

Stage B: Asymptomatic patients with left ventricular dysfunction. This is equivalent to Class I of the NYHC.

Stage C: Symptomatic patients with exertion and with left ventricular dysfunction. This is equivalent to the NYHC Class II and Class III and includes about five million people in the United States.

Stage D: Symptomatic patients at rest. This is equivalent to Class IV of the NYHC and includes about 200,000 people in the United States.

24.4 Pharmacologic Therapy of Congestive Heart Failure

24.4.1 Heart Failure with Normal Ejection Fraction (HFNEF) and Diastolic Dysfunction

As noted above, one of the main pathophysiologic mechanisms of HFNEF is diastolic dysfunction, but not all patients with diastolic dysfunction have heart failure, and not all patients with HF and diastolic dysfunction represent "true" HFNEF. "True" HFNEF does not include those with coronary artery disease, valvular heart disease, restrictive or constrictive cardiomyopathy, obesity, pulmonary hypertension and right-sided failure, high-output failure caused by anemia, thyrotoxicosis or arteriovenous fistula, constrictive pericarditis, or intracardiac shunt.

Diastolic dysfunction has been associated with many conditions including coronary artery disease, hypertension, valvular disease, age [40], elevated triglyceride levels possibly secondary to intracellular lipid accumulation [41], sleep apnea [42], and hypertrophic cardiomyopathy. Treatment with an ARB (losartan) has yielded improvement in diastolic function but did not change left ventricular cavity size or mass [43].

Isolated diastolic dysfunction is uncommon and has been identified in 11.5% of patients with no CAD or valvular disease with the use of echocardiography [44]. Increase in left atrial size and N-terminal pro B-type natriuretic peptide (NT-proBNP) appears to be predictors of LV diastolic dysfunction [45]. Also, varying degrees of diastolic dysfunction are seen with different left ventricular geometric patterns [46].

Recently an algorithm to diagnose HFNEF has been proposed by the working group of the European Society of Cardiology [47]. In general, patients with signs and symptoms of HF, normal EF > 50%, and LVEDVI < 97 mL/m^2 and with evidence of abnormal LV relaxation, filling, diastolic distensibility, and diastolic stiffness will meet the diagnosis of HFNEF if one of the following three criteria is met: mean PCWP > 12 mmHg or LVEDP > 16 mmHg by invasive testing, E/E′ > 15 by tissue Doppler, or 8 < E/E′ < 15 by tissue Doppler with a BNP > 200 pg/mL and/or NT-proBNP > 220 pg/mL or BNP > 200 pg/mL and/or NT-proBNP > 220 pg/mL and LVH or atrial fibrillation or left atrial dilation or abnormal pulmonary venous return.

Patients with left ventricular diastolic dysfunction need to be treated with aggressive blood pressure control with the use of diuretics, beta blockers, or non-dihydropyridine calcium channel blockers (diltiazem or verapamil) [48]. The *ACC/AHA 2005 Guidelines* recommend blood pressure control as a Class I level A in patients with HFNEF [49].

ACE inhibitors or angiotensin receptor blockers (ARBs) can have long-term value in reducing left ventricular hypertrophy and theoretically may improve left ventricular compliance [50] and improve diastolic function in contrast to hydralazine and hydrochlorothiazide [51]. In the Hong Kong Diastolic Heart Failure Study [52], diuretics in combination with an ACEI (ramipril) or ARB (irbesartan) marginally improved LV systolic and diastolic function and lowered BNP at 1 year.

Aldosterone antagonist appears to have a beneficial effect on diastolic function particularly in the elderly, possibly by reducing myocardial fibrosis [53]. Losartan and amlodipine were compared in the effect of losartan and amlodipine on left ventricular diastolic function in patients with mild-to-moderate hypertension (J-ELAN) to determine their role in improving diastolic function [54, 55]. Fifty-seven patients were randomized to losartan or amlodipine and were followed up for 18 months. Despite similar blood pressure in both regimens, there was no statistical difference between the two drugs in shortening the transmitral E-wave deceleration time or reducing LV mass index; However, mean carotid intima-media thickness (mean IMT) and plaque score significantly increased in the amlodipine group (pre, 1.05 ± 0.26 mm; follow-up, 1.23 ± 0.33 mm, $p = 0.0015$), but not in the losartan group indicating that losartan may reduce against progression of atherosclerosis in these patients.

Diastolic dysfunction also has been described in diabetic patients with impaired glucose tolerance and insulin resistance [56] and is associated with endothelial dysfunction and abnormalities on stress myocardial single-photon emission computed tomography [57]. Glycemic control shows an improvement in diastolic parameters that was inversely correlated with percent changes in glycated hemoglobin [58].

In the Euro Heart Failure Survey I, preserved systolic function is also seen in elderly patients with HF [59]. These patients typically have a high mortality. Measurements of EF and lifesaving therapies are quite often underutilized in this group of patients with multiple comorbidities. The use of beta blockers and ACEI was associated with a better outcome in these patients.

In conclusion, ACEI and ARB are important therapies in reducing left ventricular hypertrophy and improving left ventricular diastolic function. The role of beta blockers and calcium channel blockers remains unclear but of concern is the likelihood of progression of atherosclerosis in patients on amlodipine when compared to ARB. Diuretics reduce left ventricular filling pressures and improve symptoms. Risk factor modification is also important including treatment of hypertension, diabetes, sleep apnea, elevated triglycerides, coronary artery disease, and valvular disease.

24.4.2 Asymptomatic Left Ventricular Systolic Dysfunction

Asymptomatic left ventricular dysfunction (Stage B, ACC/AHA classification) is prevalent and typically identified by echocardiography [60]. Asymptomatic left ventricular systolic dysfunction (ejection fraction ≤50%) was reported in 6.0% of men and 0.8% of women with a hazard ratio for CHF of 4.7 on 12 years follow-up [61]. Neurohormonal activation is present in patients with asymptomatic left ventricular dysfunction and leads to worsening left ventricular function and progression to symptomatic failure [62].

Risk factors modification is also important in these patients including treatment of hypertension, diabetes, sleep apnea, elevated triglycerides, coronary artery disease [63], valvular disease, smoking cessation, reducing alcohol intake or illicit drug use, and routine exercise. Tachycardia-induced cardiomyopathy needs to be recognized and treated. Anemia has been associated with asymptomatic left ventricular dysfunction and progression to heart failure particularly when the hematocrit is ≤40% [64].

Beta blockers and ACEI are important therapies in Stage B CHF including the post-myocardial infarction patients [64, 65] and have been shown to improve left ventricular EF [66] and reduce progression to heart failure [67]. In the SOLVD trial [68], asymptomatic patients with reduced left ventricular function (EF < 35%) were randomized to enalapril ($n = 2117$) versus placebo ($n = 2111$) and followed for an average of 37.4 months. The reduction in cardiovascular mortality was larger in the enalapril group than placebo (risk reduction of 12%, $p = 0.12$). Also, the combined endpoint of death and heart failure was 36% lower in the enalapril group ($p < 0.001$).

ARBs are a reasonable alternative to ACEI [69]. The role of calcium channel blockers or digoxin in Stage B CHF is unclear. Endothelin A/B receptor antagonists (enrasentan) increases resting cardiac index but was associated with more serious adverse events (16.7% and 2.8%, respectively, $p = 0.02$) than enalapril [70].

As per *ACC/AHA Guideline Update 2005*, patients with asymptomatic left ventricular dysfunction post-myocardial infarction and an EF of ≤30% despite optimal medical therapy for at least 40 days post-MI need to be considered for an implantable defibrillator (ICD) without requiring screening for ventricular arrhythmias, whether occurring spontaneously or induced by electrophysiologic testing [71–73]. ICD therapy in this population yielded a 31%

reduction in mortality during an average follow-up of 20 months [73].

Echocardiography or isotope ventriculography has been used for periodic follow-up of patients with asymptomatic left ventricular dysfunction. Patients with familial cardiomyopathy need to have their immediate family members screened for asymptomatic left ventricular dysfunction [74].

24.4.3 Symptomatic Left Ventricular Systolic Dysfunction

Symptomatic left ventricular systolic dysfunction (Stage C, ACC/AHA classification) requires close follow-up and intense pharmacologic treatment (Table 24.1). In addition to risk factor modifications, patients will need to be treated with pharmacologic and mechanical means to improve their morbidity and mortality. Serial monitoring of ejection fraction is also important. A summary of therapies for Stage C CHF is presented below.

Table 24.1 Commonly used drugs in the treatment of congestive heart failure

Angiotensin-converting enzyme inhibitors
Accupril 5–40 mg PO QD, max 40 mg/day, start 5–10 mg PO QD
Captopril 12.5–50 mg PO TID, max 150 mg/day, start 6.25–12.5 mg PO TID
Enalapril 2.5–20 mg PO BID, max 40 mg/day, start at 2.5 mg QD
Lisinopril 5–20 mg PO QD, max 40 mg/day, start 2.5–5 mg PO QD
Monopril 10–40 mg PO QD/BID, max 80 mg/day, start 10 mg PO QD
Perindopril 4–16 mg PO QD, max 16 mg/day, start 2 mg PO QD
Ramipril 5 mg PO BID, max 10 mg/day, start at 2.5 mg PO BID
Angiotensin receptor blockers
Losartan 25–100 mg PO QD, max 100 mg/day, start 25–50 mg PO QD[a]
Candesartan 8–32 mg PO QD, max 32 mg/day, start 16 mg PO QD[a]
Valsartan 40–160 mg PO BID, max 320 mg/day, start 40 mg PO BID
Irbesartan 75–300 mg PO QD, max 300 mg/day, start 75 mg PO QD[a]
Beta blockers
Carvedilol 3.125–25 mg PO BID, max 50 mg PO QD, start 3.125 mg PO BID
Metoprolol succinate 12.5–200 mg PO QD, max 200 mg/day, start 12.5 mg PO QD
Bisoprolol 5–10 mg PO QD, max 10 mg PO QD, start 2.5 mg PO QD[a]
Aldosterone antagonists
Spironolactone 12.5–25 mg PO BID, max 50 mg/day, start 12.5 mg PO BID
Eplerenone 50 mg PO QD, max 50 mg/day, start 25 mg PO QD[b]
Angiotension receptor neprilysin inhibitor (ARNI)
Sacubitril/valsartan 24 mg sacubitril/26 mg valsartan PO BID to be increased to 49 mg/51 mg PO BID and 97 mg/103 mg PO BID as tolerated every 2 weeks[c]
HCN channel blocker
Ivabradine 5 mg PO BID. Can increase to maximum dose of 7.5 mg PO BD

[a]Off-label use
[b]For CHF patients post-myocardial infarction
[c]Sacubitril/valsartan should not be used with ACEI

24.4.4 Angiotensin-Converting Enzyme Inhibitors (ACEI)

ACEIs reduce mortality by 15–20% and rehospitalizations by 30–35% in patients with left ventricular systolic dysfunction (ejection fraction of <40%). The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) compared the effects of enalapril versus placebo on mortality in patients with severe CHF. Enalapril reduced mortality by 31% at 1 year ($p = 0.001$) as well as congestive heart failure hospitalization [75]. The SOLVD trial also confirmed the same findings. Patients receiving conventional treatment for Class II and III heart failure were randomly assigned to receive either placebo ($n = 1284$) or enalapril ($n = 1285$). Enalapril reduced mortality by 16% ($p = 0.0036$) and congestive heart failure by 26% ($p < 0.0001$) at an average follow-up of 41.4 months [76]. Furthermore, SOLVD showed that enalapril attenuates progressive increases in left ventricular dilatation and hypertrophy in patients with reduced left ventricular function [77]. Finally, Pitt and colleagues also has shown that enalapril reduced development of heart failure by 37% and hospitalization from heart failure by 36% ($p < 0.001$) [78].

ACEI post-MI has also shown a significant mortality benefit. The Acute Infarction Ramipril Efficacy (AIRE) study [79] showed a 27% ($p = 0.002$) reduction in the 30-month cumulative mortality with ramipril over placebo in post-MI CHF patients. Also, in the Survival and Ventricular Enlargement (SAVE) trial [80], captopril was administered 3–16 days after myocardial infarction in patients with asymptomatic left ventricular dysfunction (EF < 40%) and followed for an average of 42 months. Captopril improved survival (risk reduction was 19%, $p = 0.019$) and morbidity. In addition, in the Trandolapril Cardiac Evaluation (TRACE) study, trandolapril reduced mortality by 22% ($p = 0.01$) in patients with reduced left ventricular function after an MI. Trandolapril reduced overall mortality, mortality from cardiovascular causes, sudden death, and the development of severe heart failure [81]. Finally, in the Survival of Myocardial Infarction Long-Term Evaluation (SMILE) study [82], zofenopril reduced the risk of death or severe congestive heart failure by 34% ($p = 0.018$) at 6 weeks when initiated early after MI. At 1 year, the reduction in mortality risk was 29% ($p = 0.011$).

Early initiation of ACEI in hospital leads to a higher use of ACEI on an outpatient basis, and, therefore, initiating ACEI early is important in all patients with CHF.

24.4.5 Angiotensin Receptor Blockers (ARB)

ARB is an effective treatment in patients with CHF. In the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) pilot study [27], 768 patients in NYHC II–IV and EF <40% received candesartan, candesartan plus enalapril, or enalapril alone for 43 weeks. Left ventricular cavity size increased less, and BNP levels decreased more with combination therapy compared to ARB or ACEI alone [69].

In the Evaluation of Losartan in the Elderly (ELITE) trial [83], 722 patients with EF ≤ 40%, ≥65 years of age, and in NYHC Class II–IV were included. The primary endpoint was death and/or hospital admission for heart failure and occurred at a rate of 9.4% in the losartan group compared to 13.2% in the captopril group (risk reduction 32%, $p = 0.075$). This risk reduction was primarily due to a decrease in all-cause mortality (4.8% versus 8.7%; risk reduction 46%, $p = 0.035$) with similar rates of hospital admissions in both groups (5.7%). ELITE II [84] randomized 3152 patients aged 60 years or older with NYHC II–IV and ejection fraction of <40% to losartan ($n = 1578$) titrated to 50 mg once daily or captopril ($n = 1574$) titrated to 50 mg three times daily. ELITE II showed no differences in mortality between losartan and captopril and confirmed that ARB therapy can be a potential substitute to ACEI.

The Valsartan in Heart Failure Trial (Val-HeFT) [85] randomized 5010 patients with heart failure of New York Heart Association (NYHA) Class II, III, or IV to receive 160 mg of valsartan or placebo twice daily. The primary outcomes were mortality and the combined endpoint of mortality and morbidity, defined as the incidence of cardiac arrest with resuscitation, hospitalization for heart failure, or receipt of intravenous inotropic or vasodilator therapy for at least 4 h. Mortality was similar in both groups, but the combined endpoint of morbidity and mortality was reduced by 13.2% with valsartan ($p = 0.009$), predominantly driven by a reduction in heart failure hospitalizations (13.8% versus 18.2%, $p < 0.001$). In patients intolerant to ACEI, valsartan (titrated to 160 mg twice daily) reduced both all-cause mortality and combined mortality and morbidity compared with placebo (17.3% versus 27.1%, $p = 0.017$ and 24.9% versus 42.5%, $p < 0.001$, respectively) [86]. In a substudy of this trial, valsartan taken with either ACEI or beta blockers reversed left ventricular remodeling [87]. Of interest, in the Val-HeFT, valsartan with either a beta blocker or ACEIs showed a positive effect on outcome [88], but an adverse effect in patients receiving both types of drugs [85]. This concern of adding an ARB to patients on both ACEI and beta blockers was not confirmed in the CHARM trial.

The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) [86] was a randomized, double-blind, placebo-controlled, multicenter study in patients with NYHC Class II–IV. This trial had three complementary arms: CHARM-added, candesartan (titrated to 32 mg once daily) is added to an ACEI; CHARM-alternative, candesartan administered to patients who cannot tolerate ACEIs; and CHARM-preserved, candesartan is administered to patients with preserved left ventricular function irrespective of whether they are on ACEI or not. In the CHARM-added and CHARM-alternative arms, patients with EF ≤ 40% were included. In the "overall program" of this study [87], which included both preserved and reduced left ventricular function, total mortality was not reduced compared to placebo. However, in a subgroup analysis of patients with symptomatic heart failure and reduced left ventricular function, candesartan significantly reduced all-cause mortality (28% versus 31%, $p = 0.0018$), cardiovascular death (22.8% versus 26.2%, $p = 0.005$), and CHF hospitalizations (22.5% versus 28.1%, $p < 0.001$) when added to standard therapies including ACEI, beta blockers, and aldosterone antagonists [88]. Candesartan also reduced progression to diabetes [89], sudden cardiac death, and death from worsening heart failure in patients with symptomatic failure [86].

The Valsartan in Acute Myocardial Infarction Trial (VALIANT) [90] randomized patients 0.5–10 days after an acute MI with reduced left ventricular function to valsartan (4909 patients) titrated to 160 mg twice a day, valsartan (80 mg twice a day) plus captopril (50 mg three times a day) (4885 patients), or captopril (4909 patients) alone titrated to 50 mg three times a day in addition to standard therapy. The primary endpoint of the study was all-cause mortality at a median follow-up of 24.7 months. Valsartan was equally effective compared to captopril in reducing all-cause mortality. Also combining valsartan with captopril increased the rate of adverse events without improving survival.

In the Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL), patients after an acute myocardial infarction were randomized to losartan versus captopril. The primary endpoint was reduction in all-cause mortality at a mean follow-up of 2.7 years. A nonsignificant difference was seen in total mortality in favor of captopril (18% versus 16% in the losartan versus captopril, respectively, $p = 0.07$). However, there were significantly more cardiovascular deaths with losartan (15%) than with captopril (13%) ($p = 0.03$) [91]. Losartan was better tolerated than captopril with fewer patients discontinuing their medications (17% versus 23%, $p < 0.0001$) [92]. An echocardiographic substudy of the OPTIMAAL trial has shown that both losartan and captopril improve systolic function after an acute MI, but the benefit is greater for captopril [93].

A growing body of evidence suggests that an ARB can be an alternative to an ACEI in patients with CHF [74].

24.4.6 Aldosterone Blockers

Angiotensin II is a dominant stimulus of aldosterone secretion [94]. Aldosterone secretion, however, continues to escape ACEI or ARB [27, 95, 96]. A reduction, however, in aldosterone plasma level is seen with angiotensin blockers [97]. Recent data confirms that aldosterone blockers are important to improve morbidity and mortality in patients with CHF and reduced left ventricular systolic function. Aldosterone blockade reduces myocardial fibrosis and ventricular remodeling and has important effects on autonomic balance, fibrinolysis, oxidative stress, and activation of the NF-kappaB and AP-1 signaling pathways [98].

The Randomized Aldactone Evaluation Study (RALES) [28] randomized patients ($n = 1663$) with advanced CHF and EF $\leq$ 35% to spironolactone 25 mg daily ($n = 822$) or placebo ($n = 841$) including ACEI, digoxin, and diuretics. After a mean follow-up of 24 months, the trial was stopped early. Spironolactone reduced the primary endpoint of mortality by 30% (46% versus 35%, $p < 0.001$) primarily due to reduction of progression of CHF and sudden cardiac death. In addition, spironolactone significantly improved New York Heart Association functional class ($p < 0.001$) and reduced rehospitalization due to worsening CHF by 35% ($p < 0.001$). Spironolactone also increases the risk of hyperkalemia [99], which accounted for an increase in hospitalization from 2.4 per 1000 patients in 1994 to 11.0 per 1000 patients in 2001 ($p < 0.001$) and a mortality increase from 0.3 per 1000 to 2.0 per 1000 patients ($p < 0.001$). Therefore, close follow-up of patients for serum potassium levels is needed when spironolactone is initiated. Avoiding spironolactone in patients with elevated potassium levels (>5 mEq/L) and high baseline creatinine (>2.0) is advised to avoid serious hyperkalemia problem.

Another recent trial, Eplerenone Post-AMI Heart Failure Efficacy and Survival Study (EPHESUS) [29], randomized patients with CHF and an EF < 40%, 3–14 days post-MI, to eplerenone (25–50 mg daily) or placebo. At a mean follow-up of 27 months, eplerenone reduced total mortality by 15% ($p = 0.008$), cardiovascular mortality or cardiovascular hospitalizations by 13% ($p = 0.002$), and sudden cardiac death by 21% ($p = 0.03$). The EPHESUS established the importance of aldosterone antagonism in post-MI patients with reduced left ventricular function irrespective of the degree of heart failure.

24.4.7 β(Beta) Blockade in Heart Failure

Multiple β(beta) blockers have been shown to reduce mortality and morbidity in patients with heart failure and reduced left ventricular systolic function. Current guidelines support the use of carvedilol, metoprolol, and bisoprolol to treat patients with CHF. Beta blockers reduce mortality by approximately 35% when added to standard therapy in mild-to-moderate [100–102] or advanced CHF [103] and reduced hospitalizations by 33–38% [100, 101, 104]. Beta blockers have a positive impact on positive remodeling by reducing cavity size and improving ejection fraction [105].

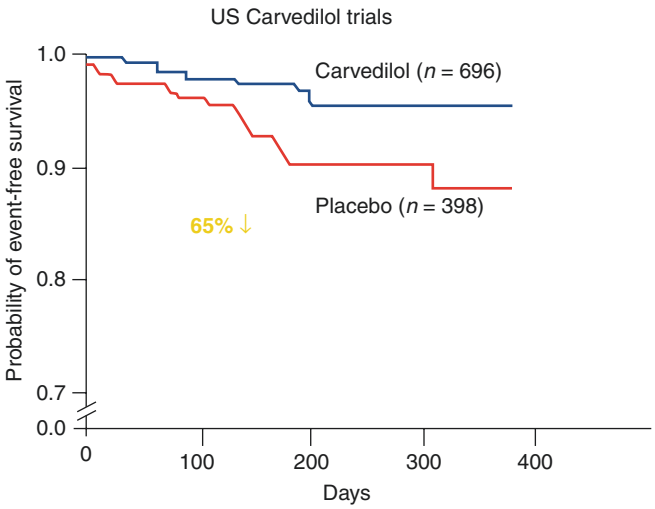

Fig. 24.3 US Carvedilol trials showing a significant reduction in mortality with carvedilol compared to placebo in patients with left ventricular systolic dysfunction

In the US Carvedilol Heart Failure Study [100] (Fig. 24.3), 1094 patients were enrolled in a double-blind, placebo-controlled, stratified program in which they received one of four treatment protocols based on their exercise capacity. Patients with heart failure were randomized to placebo ($n = 398$) or carvedilol ($n = 696$) in addition to conventional therapy. The overall mortality at 6-month follow-up was reduced by 65% ($p < 0.001$) and rehospitalization by 27% with carvedilol ($p = 0.036$). This effect was seen in both black and non-black patients [106]. Carvedilol also reduced length of hospital stay and length of stay in the intensive care unit leading to a 57% reduction in inpatient care costs for cardiovascular admissions ($p = 0.016$) and 81% lower for heart failure admissions ($p = 0.022$) [104]. Finally, severe heart failure (EF < 22%, markedly reduced 6-min corridor walk test, and severe impairment of quality of life) had an improvement in EF with carvedilol ($p = 0.004$) [107]. In the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study group [108], 2289 patients with severe heart failure symptoms were randomly assigned to receive carvedilol ($n = 1156$) or placebo ($n = 1133$). The carvedilol group experienced no increase in cardiovascular risk and had fewer patients who died (19 versus 25; hazard ratio [HR] 0.75; 95% confidence interval [CI] 0.41–1.35) and were hospitalized (134 versus 153; HR 0.85; 95% CI 0.67–1.07). Carvedilol was well tolerated in euvolemic patients with fewer patients withdrawn from treatment than placebo.

In the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) study 991 patients with chronic heart failure in NYHC II–IV and EF ≤ 40% were enrolled in a double-blind, randomized, placebo-controlled study of metoprolol CR/XL versus placebo [101]. All-cause mortality and sudden death were reduced by 34% ($p = 0.00009$) and 41% ($p = 0.0002$) in the metoprolol group. Also, metoprolol CR/XL reduced the number of hospitalizations due to worsening heart failure ($p < 0.001$) and number of days in hospital due to worsening heart failure ($p < 0.001$). In post-MI patients with symptomatic CHF and an EF ≤ 40% and receiving contemporary management, metoprolol CR/XL reduced total mortality by 40% ($p = 0.0004$) and sudden death by 50% ($p = 0.0004$) [109].

The Cardiac Insufficiency Bisoprolol II (CIBS-II) study was a double-blind, placebo-controlled trial in Europe that enrolled 2647 symptomatic patient with Class III or IV heart failure and an EF ≤ 35% randomized to bisoprolol or placebo. At 1.3 years, all-cause mortality and sudden death were reduced by 34% ($p < 0.0001$) and 44% ($p = 0.0011$), respectively, with bisoprolol. Also, bisoprolol resulted in fewer hospital admissions per patient hospitalized, fewer hospital admissions overall, and fewer days spent in hospital or intensive care unit leading to a reduction in the cost of care by 5–10% compared to placebo [110].

The Carvedilol Or Metoprolol European Trial (COMET) [111, 112] is the only randomized trial that compared two beta blockers in a randomized, double-blind study in the management of CHF patients. 3029 patients with Class II–IV heart failure were recruited at 317 centers in 15 European countries. At 58 months, there was a 17% reduction in mortality with carvedilol compared to metoprolol tartrate ($p = 0.0017$). Recently, carvedilol (6.25–25 mg twice daily) was also shown in The Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) study not to alter glycemic control in diabetics when compared to metoprolol tartrate (50–200 mg twice a day). Furthermore, it did improve some components of the metabolic syndrome such as improving insulin sensitivity [113].

Currently recommended beta blockers in the management of CHF are carvedilol, metoprolol succinate, and bisoprolol [74]. Adherence to the use of beta blockade is of paramount importance to reduce the economic burden of CHF. Beta blockers are currently underutilized in patients with CHF [114], and continued educational efforts are needed to promote guidelines in heart failure management.

Aggressive titration of beta blockers is needed in patients with CHF. Higher levels of beta blockade and ACEI are associated with better improvement of ejection fraction and greater reductions in cardiovascular hospitalizations [115–117]. In a substudy of the Assessment of Treatment with Lisinopril and Survival (ATLAS) trial, the composite endpoint of mortality or hospitalization decreased incrementally with the use of high-dose ACE inhibitors ($n = 475$) (adjusted odds ratio (aOR) 0.93; p = NS), high-dose ACE inhibitors plus beta blockers ($n = 72$) (aOR 0.89; p = NS), and high-dose ACE inhibitors plus beta blockers plus digoxin ($n = 77$) (aOR 0.47; $p = 0.006$) compared with low-dose ACE inhibitors ($n = 471$) [117]. A stepwise approach in titration of beta blockade is generally followed with an increase in the dose every 2 weeks as tolerated until achieving the maximum tolerable dose.

24.4.8 Angiotensin Receptor Neprilysin Inhibitor (ARNI) in Heart Failure

The natriuretic peptide (NP) system counter-regulates the activation of the RAAS and the SNS. Recently, the angiotensin receptor neprilysin inhibitor (ARNI) sacubitril/valsartan was introduced to inhibit the neutral endopeptidase enzyme neprilysin (with sacubitril) and concomitantly blocks the adverse effects of angiotensin II (with valsartan). In the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) study [31], ARNI reduced the primary outcome of death from cardiovascular causes or heart failure rehospitalization (21.8%) when compared to ACEI (26.5%) ($p < 0.001$). The individual endpoint of cardiovascular death was reduced by 20% (HR 0.80 (95% CI, 0.71; 0.89)), the risk of first heart failure hospitalization by 21% (HR 0.79 (95% CI, 0.71; 0.89)), and total mortality by 16% (absolute risk reduction 2.8%) (HR 0.84 (95% CI, 0.76; 0.93)). Current ACC/AHA/HFSA guidelines [118] consider ARNI as a Class I indication for treating patients with congestive heart failure and are preferred over an ACEI to further reduce mortality.

24.4.9 HCN Channel Blocker in Heart Failure

Ivabradine, an HCN channel blocker was recently introduced to reduce heart failure hospitalization. It is indicated in patients in normal sinus rhythm and who are intolerant to beta blocker or on maximum tolerable dose of a beta blocker. Ivabradine was tested in The Systolic Heart failure treatment with the If inhibitor ivabradine Trial (SHIFT) [33]. It included patients in normal sinus rhythm with a heart rate of more or equal to 70 bpm, NYHC Class II–IV, EF less or equal to 35%, and have been hospitalized with heart failure in the past 12 months. Ivabradine significantly reduced the relative risk of hospitalization for worsening HF or CV death (RRR 18%, $p < 0.0001$); the significance is driven mostly by a reduction of rehospitalization.

24.4.10 Digoxin Therapy in Congestive Heart Failure

Digoxin was introduced by William Withering and has been used therapeutically for more than 250 years [119]. It has been widely used in the treatment of atrial fibrillation as a rate control agent, but its utility in CHF has been debated.

The Digitalis Investigation Group (DIG) [120] is a randomized, double-blind clinical trial that studied the effects of digoxin on mortality and hospitalization in patients with congestive heart failure. DIG showed no advantage of digoxin on mortality at 37 months follow-up. Digoxin, however, reduced the rate of hospitalization for worsening heart failure. A comprehensive post hoc analysis, however, of the DIG showed that digoxin at a serum concentration of 0.5–0.9 ng/mL did reduce mortality (29% versus 33%, adjusted hazard ratio (AHR) of 0.77) and heart failure hospitalizations (23% versus 33%, AHR of 0.68) in all heart failure patients with no interaction with EF > 45% ($p = 0.834$) or gender ($p = 0.917$) [121]. In another substudy of the DIG trial, perceived health, quality of life measures, and the 6-min walk test were not statistically different between digoxin and placebo in patients in normal sinus rhythm at 12-month follow-up [122]. Furthermore, digoxin efficacy was not altered by renal glomerular filtration, but renal dysfunction was a predictor of mortality in patients with GFR < 50 mL/min [123].

Patients on digoxin and receiving standard treatment for congestive heart failure might experience a slight reduction in EF [124–127], worsening maximal exercise capacity, and increased incidence of treatment failure upon withdrawal of this drug [125, 127].

Currently, digoxin is indicated for the treatment of chronic heart failure in patients with left ventricular dysfunction and NYHC Class II–III despite optimal medical treatment with ACEI, beta blockers, and diuretics (ACC/AHA Class IIa indication). Digoxin is not indicated for the acute treatment of CHF, and serial measurements of digoxin levels are currently considered unnecessary. Digoxin dose needs to be reduced when administered with amiodarone.

24.4.11 Mechanical Treatment of Stage C Heart Failure

24.4.11.1 Cardiac Resynchronization Therapy

Cardiac resynchronization therapy (CRT) is indicated in patients with advanced heart failure symptoms (Class III or IV) despite optimal medical management, an EF ≤ 35%, sinus rhythm, and cardiac dyssynchrony defined as a wide QRS complex >120 ms. The outcomes of CRT system implantation in 2078 patients from a multicenter study program showed that the procedure is safe, well-tolerated, and has a high success rate [128].

In the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial [128], 369 patients with EF ≤ 35%, QRS duration ≥130 ms, and Class III–IV NYHC, despite optimal medical treatment, were randomized to controls ($n = 182$, ICD activated, CRT off) and the CRT group ($n = 187$, ICD activated, CRT on). CRT improved quality of life, functional status, and exercise capacity without adversely influencing ICD function. In addition, in the InSyncIII study [129], a multicenter, prospective, non-randomized, 6-month trial of 422 patients with wide QRS complex and a Class III or IV heart failure, sequential CRT therapy provided a modest increase in stroke volume and improved exercise capacity but had no change in functional status or quality of life compared to a historic control from the MIRACLE trial. Furthermore, improvement in left ventricular function that occurs with CRT is more prominent in patients with nonischemic heart failure and less severe mitral insufficiency [130]. Finally, in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial, the risk of the combined endpoint of death from, or hospitalization for, heart failure was reduced by 34% ($p < 0.002$). In the same trial, death from any cause was reduced by 24% ($p = 0.059$) in the pacemaker group compared to the medical therapy alone [131]. In this trial, the addition of a defibrillator reduced mortality beyond that achieved with CRT therapy alone.

Current guidelines recommend CRT therapy in patients with advanced heart failure symptoms and wide QRS complex who are already optimized on medical treatment with the goal to improve exercise capacity, functional status, and quality of life and to help reverse left ventricular remodeling [74].

24.4.11.2 Implantable Cardioverter Defibrillators

Sudden death is a major cause of mortality in patients with left ventricular dysfunction. Implantable cardioverter defibrillators (ICD) are currently indicated in patients with moderate CHF and reduced EF < 30% on optimal medical therapy who have a reasonable expectation of survival for more than 1 year who are at least 40 days post-myocardial infarction, have nonischemic cardiomyopathy, or have had a serious arrhythmia such as ventricular fibrillation, ventricular tachycardia, or cardiac arrest [73, 132].

In the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), 2521 patients with moderate heart failure and an EF ≤ 35% were randomized to conventional therapy for CHF plus placebo, conventional therapy plus amiodarone, or conventional therapy plus ICD. Amiodarone had no

favorable effect on survival, whereas ICD reduced overall mortality by 23% at 45.5 months mean follow-up [132]. In addition, the COMPANION [131] trial showed that ICD therapy can reduce death by 36% ($p = 0.003$) in patients with advanced heart failure due to ischemic or nonischemic cardiomyopathy and a QRS ≥ 120 ms when compared to optimal medical therapy. The Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) randomized 1232 patients with EF ≤ 30% to ICD or conventional medical therapy. Death was the primary endpoint, and the average follow-up was 20 months. The mortality rates were 19.8% in the conventional therapy group and 14.2% in the defibrillator group (hazard ratio for the risk of death in the ICD group was 0.69, $p = 0.016$) [133]. A long-term follow-up study from MADIT-II showed that the probability of survival after successful therapy with an ICD for ventricular fibrillation or tachycardia was 80% at 1 year [134]. The MADIT-II also indicated that benefit from ICD therapy is similar among all the different heart failure subgroups [71]. Currently the MADIT-CRT is ongoing and is testing whether CRT-D will reduce the risk of mortality in patients with reduced EF (≤30%) and prolonged QRS ≥ 130 ms and NYHC Class I–II [135].

24.4.12 Miscellaneous Therapy

CHF patients need to be instructed on dietary salt restriction (2 g sodium/day), fluid restriction, daily weight monitoring, smoking cessation, regular exercise, avoidance of alcohol intake, and aggressive treatment of high blood pressure and dyslipidemia. Aggressive treatment of sleep apnea is also indicated [136]. In general CHF patients need to avoid nonsteroidal anti-inflammatory drugs (NSAIDS), most calcium channel blockers, and antiarrhythmic agents. Finally, exercise testing and enrolment in an exercise structured program are advised in these patients.

24.4.13 Management of the ACC/AHA Stage D Congestive Heart Failure Patient

Acutely decompensated CHF patients with severe left ventricular dysfunction require intense pharmacologic and mechanical management. Patients with advanced decompensated failure have a poor short-term prognosis. In the Initiation Management Pre-discharge Assessment of Carvedilol Heart Failure (IMPACT-HF) registry [137], mortality and rehospitalization rate was 31% at 60-day follow-up.

Positive inotropic agents such as dopamine and milrinone might be utilized for palliative reasons because they improve symptoms and increase functional capacity, but they could worsen arrhythmias and possibly increase the risk of mortality [138, 139]. In a randomized trial of milrinone versus placebo in 951 patients with decompensated CHF, milrinone caused more sustained hypotension and atrial arrhythmias compared to placebo with no positive impact on mortality [140]. An analysis from the Acute Decompensated Heart Failure National Registry (ADHERE), a large retrospective registry of patients with acute decompensated CHF, patients who received milrinone and dobutamine had a higher in-hospital mortality than those who received nitroglycerin and nesiritide. Both nesiritide and nitroglycerin had similar in-hospital mortality [141].

Current *ACC/AHA Guidelines* consider the use of intermittent positive inotropic agents for the management of decompensated heart failure as a Class III indication, indicating that their use should be discouraged.

Data on IV nesiritide suggest that this drug is effective in lowering wedge pressure and improving patient's symptoms [142]. In the Vasodilatation in the Management of Acute CHF (VMAC) trial, 489 inpatients with decompensated CHF were enrolled in a randomized trial of nesiritide versus nitroglycerin or placebo for 3 h followed by nesiritide or nitroglycerin for 24 h. The primary and secondary outcomes of the study are pulmonary capillary wedge pressure (PCWP) at 3 and 24 h, respectively. IV nesiritide was administered as a bolus of 2 μg/kg followed by continuous infusion of 0.01 μg/kg/min. At 3 h, dyspnea improved with nesiritide compared with placebo ($p = 0.03$), but there was no difference compared to nitroglycerin. At 24 h, the reduction in PCWP was greater in the nesiritide group (−8.2 mmHg) than the nitroglycerin group (−6.3 mmHg) with a modest improvement in clinical status (VMAC investigators). In VMAC, there was no significant difference between nesiritide and nitroglycerin subjects in 6-month mortality. The hemodynamic benefits and safety of nesiritide in patients with acutely decompensated CHF are maintained in patients receiving chronic beta blockers [143].

In the Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natrecor Therapy (PRECEDENT), 255 patients were randomized to dobutamine or nesiritide in

Table 24.2 Percent 30-day mortality in seven nesiritide trials

Trial	Natrecor (%)	Control (%)	Hazard ratio	Confidence interval
Mills et al.	2.70	7.50	0.38	(0.05–2.67)
PRECEDENT	3.70	6.10	0.6	(0.18–1.97)
Efficacy	5.90	5.80	1.25	(0.24–6.45)
Comparative	6.90	4.90	1.43	(0.53–3.97)
VMAC	8.10	5.10	1.56	(0.75–3.24)
PROACTION	4.2	0.90	4.99	(0.58–42.73)
FUSION I	1.40	2.90	0.49	(0.07–3.47)
Pooled (all)	5.30	4.30	1.27	(0.81–2.01)

the management of decompensated congestive heart failure. Dobutamine was associated with arrhythmia and tachycardia, whereas nesiritide reduced ventricular ectopy and did not increase heart rate suggesting a safer profile of nesiritide over dobutamine [144].

The 30-day mortality from pooled data from seven clinical trials (Table 24.2) [142, 144–148] was 5.3% for Natrecor and 4.3% for control (hazard ratio 1.27 [0.81–2.01]). In a recent pooled analysis of three randomized studies [149], 485 patients were randomized to nesiritide and 377 to control therapy. Death at 30 days occurred more frequently in patients treated with nesiritide than placebo at 30 days of follow-up (7.2% versus 4%, $p = 0.059$).

24.4.14 Mechanical Support of the Failing Heart

The Randomized Evaluation of Mechanical Assistance in Treatment of Chronic Heart Failure (REMATCH) trial [150, 151] randomized 129 patients with end-stage heart failure who were ineligible for cardiac transplantation to receive a left ventricular assist device ($n = 68$) or optimal medical management ($n = 61$). Survival (52% versus 25%, $p = 0.002$) and quality of life were significantly improved with the device compared to medical therapy at 1 year. Serious adverse events did occur in the group when compared to medical therapy and included infection, bleeding, and device malfunction. In this trial, patients undergoing inotropic support derived major mortality and quality of life benefits from the assist device compared to patients receiving medical therapy. Also, patients not undergoing inotropic support had an overall better survival rates both with and without the assist device, but differences did not reach significance.

Recent improvements in the HeartMate VE left ventricular assist device (LVAD) to the HeartMate XVE LVAD have recently led to significant improvements in outcomes [152] indicating that as technology and experience with LVAD evolve this therapy might become more accessible to the Class IV heart failure patient who is ineligible for cardiac transplantation.

24.5 Case Studies

24.5.1 Case Study 1

P.S. is a 57-year-old male with history of old myocardial infarction, ischemic cardiomyopathy, and an ejection fraction of 32%. He has been short of breath with minimal home activity, placing him in a Class III New York Heart Classification for failure. Patient has been on carvedilol 25 mg PO BID, lisinopril 20 mg PO daily, furosemide 60 mg PO daily, and spironolactone 25 mg PO BID. Patient is euvolemic on his current medical regimen. His electrocardiogram showed a normal sinus rhythm with a left bundle branch block and a QRS complex duration of 140 ms. Patient was referred for biventricular pacing defibrillator placement. Two weeks post-procedure, the patient's symptoms improved, and he was in Class II NYHC. Lisinopril was then discontinued, and 36 h after, he was started on sacubitril/valsartan 24 mg/26 mg PO BID for 2 weeks. This was well tolerated, and in 2 weeks ARNI dose was increased to 97 mg/103 mg PO BID.

24.5.2 Case Study 2

M.S. is a 35-year-old female with a recent viral infection and subsequent congestive heart failure. Echocardiography showed an ejection fraction of 25% and no evidence of significant valvular disease. Blood testing showed normal thyroid function tests, negative antinuclear antibody, normal iron and iron saturation, normal liver function tests, and electrolytes. Computed tomography of the coronaries showed a calcium score of 0 and normal coronaries in a right dominant system. Patient was started on carvedilol 3.125 mg PO BID and titrated to 25 mg PO BID over a period of 2 months. She was also started on lisinopril 5 mg PO daily and increased to 20 mg PO QD. After 6 months, patient's ejection fraction

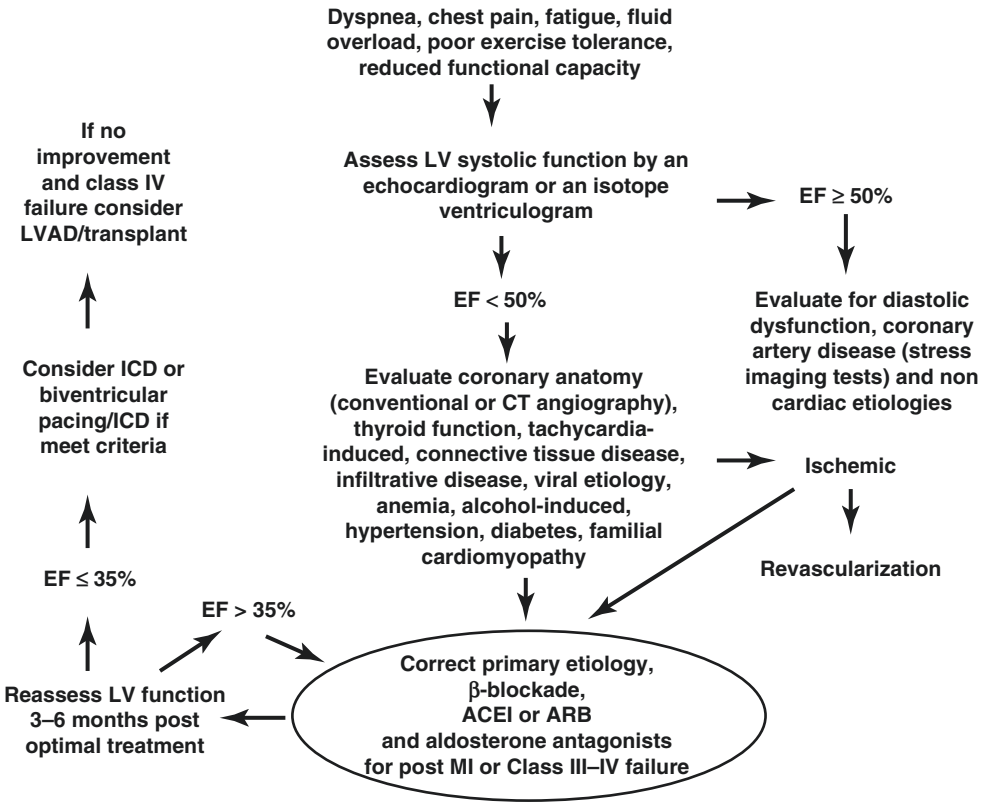

Fig. 24.4 Algorithm

normalized to 56%, and she was completely asymptomatic. She was maintained on her carvedilol and lisinopril, and at 2-year follow-up, she continued to have stable left ventricular function. Patient was presumed to have a viral cardiomyopathy and experienced excellent recovery of cardiac function (Fig. 24.4).

24.6 Conclusion

Treatment of heart failure starts with controlling risk factors, management of asymptomatic systolic dysfunction, and aggressive treatment of symptomatic failure with diuretics, beta blockers, ACEI (or ARB or ARNI), and aldosterone antagonists. The use of IV inotropes should be discouraged except for hemodynamic stability. Eligible patients need to receive biventricular pacing, ICD, or LVAD. Diastolic dysfunction is often a neglected cause of CHF, and diagnosis needs to be considered when CHF is present in the setting of normal left ventricular systolic function. HFNEF diagnosis is a relatively new entity that needs to be considered in the symptomatic heart failure patient.

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Part V

Cardiac Imaging

Coronary Artery Calcium Imaging for Risk Stratification

25

Nikolaos Alexopoulos and Paolo Raggi

25.1 Introduction

Striking advancements in cardiovascular diagnostics and therapeutics during the last several decades produced a marked decrease in mortality due to atherosclerotic diseases in western societies. Nonetheless, coronary artery disease (CAD) remains the main cause of death, being responsible for more deaths than all cancers combined, and it is associated with substantial functional impairment in survivors of acute events, imposing a very large economical burden on society. Numerous risk scores based on identifiable patients' characteristics were developed to improve identification of patients at higher risk of events, to whom intensive preventive therapies should be directed. Nonetheless, most of these tools are incompletely effective and the majority of events develop in subjects not considered to be at high-risk. The attention of several investigators therefore turned to the development of imaging tools to identify atherosclerosis or its *signature* in its preclinical stages. Coronary artery calcium (CAC) imaging (Fig. 25.1) is one of the imaging tests that received the most attention in the past 20 years, and one that has raised a large controversy among field experts. That calcium deposition accompanies the formation of atherosclerotic plaque from its inception has been well-known for two centuries. More recently, it has become apparent that CAC deposition occurs via active processes of calcification resembling bone formation. Finally, the calcified portion represents approximately 15–20% of the total atheroma volume. In this chapter we will review the most relevant literature on the use of CAC as a risk stratification tool of asymptomatic patients as well as the utility of sequential CAC scanning to follow the evolution of atherosclerosis.

N. Alexopoulos
Cardiovascular Imaging Unit, Radiology Department, Euroclinic Athens, SA, Athens, Greece

P. Raggi (✉)
Mazankowski Alberta Heart Institute, Division of Cardiology, University of Alberta, Edmonton, AB, Canada

25.2 CAC Measurement

Originally measured with electron beam computed tomography (EBCT), CAC is nowadays assessed with multidetector CTs (MDCT). CAC can be visualized within a few seconds, with very low radiation exposure (effective dose 0.6–2.0 mSv in most cases), and it is defined as a lesion with an attenuation greater than an arbitrary threshold of 130 Hounsfield units (HU) and an area ≥3 adjacent pixels. Quantitative measurement of CAC can be achieved with three different scores: the Agatston score [1], the volume score [2], and the mass scoring method [3]. While the Agatston method was developed for the EBCT scanners [1], it has been extensively applied to MDCT imaging, and several publications have shown a fair to good numerical correlation between the Agatston score measured by EBCT and MDCT [4, 5]. Despite the fact that the volume and mass scores are more reproducible, especially with MDCT, most publications have reported the Agatston score that has become the universally accepted reporting method.

25.3 Prognostic Value of Coronary Artery Calcium in Asymptomatic Patients

25.3.1 General Population

Several major reports highlighted the independent and incremental prognostic value of CAC over traditional risk factor assessment (Table 25.1). Kondos et al. [6] followed 5635 asymptomatic, middle-aged patients, with predominantly low to moderate Framingham risk score (FRS), for 37 months and found that the presence of any CAC was associated with a 10.5-fold increased relative risk for future cardiac events (soft and hard events combined). Shaw et al. [7] ranked 10,377 asymptomatic patients according to their baseline CAC scores and followed them for a mean of 5 years. They reported that the adjusted relative risk for

P. P. Toth, C. P. Cannon (eds.), *Comprehensive Cardiovascular Medicine in the Primary Care Setting*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-319-97622-8_25

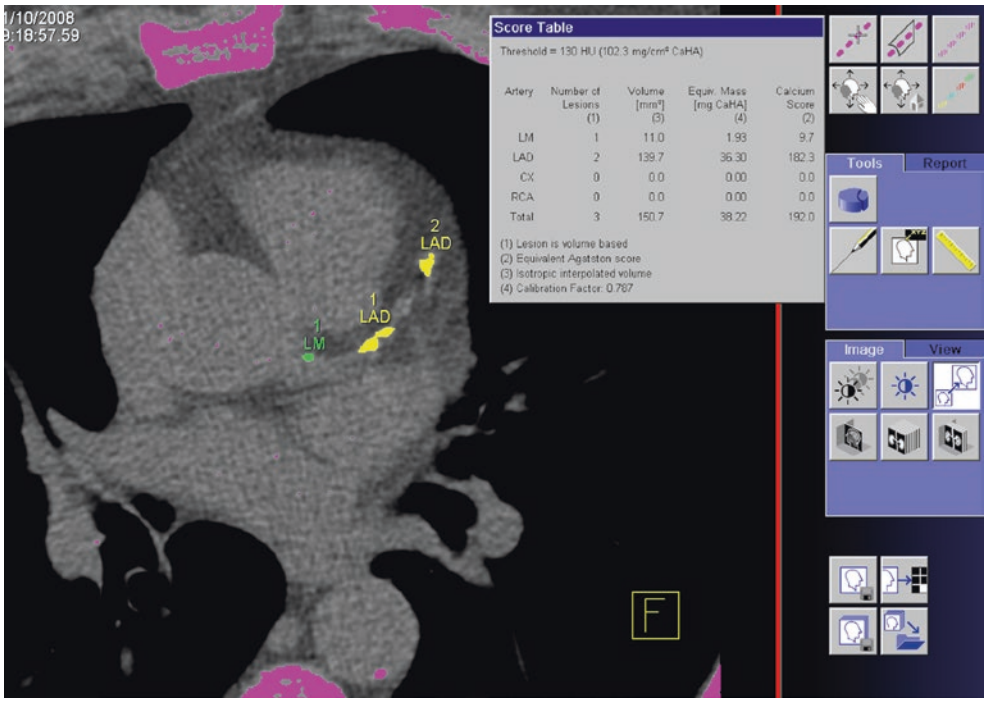

Fig. 25.1 Axial chest CT image showing calcification of the left main trunk (LM) and left anterior descending coronary artery (LAD). The total (Agatston) coronary artery calcium score is 192

Table 25.1 Independent and incremental prognostic value of CAC over traditional risk factor assessment

Primary author	Study type	No. of patients	Mean follow-up (years)	Type of events	No. of events	Incremental prognostic value of coronary artery calcium
Kondos [6]	Observational	5,635	3	Myocardial infarction, death, and revascularizations	224	Not assessed
Shaw [7]	Observational	10,377	5	All-cause death	249	Yes
Budoff [8]	Observational	25,253	6.8	All-cause death	510	Yes
Arad [9]	Prospective	4,613	4.3	Atherosclerotic cardiovascular events	119	Yes
Greenland [10]	Prospective	1,029	7.0 (median)	Myocardial infarction and death	84	Yes
LaMonte [11]	Prospective	10,746	3.5	Myocardial infarction and cardiovascular death	81	Yes
Taylor [12]	Prospective	1,983	3	Acute coronary syndrome and sudden cardiac death	9	Yes
Detrano [13]	Prospective	6,722	3.8	Myocardial infarction and cardiovascular death	89	Yes
Becker [14]	Prospective	1,726	3.4	Myocardial infarction and cardiovascular death	179	Yes
Erbel [15]	Prospective	4,129	5	Myocardial infarction and coronary death	93	Yes

all-cause death was 1.64, 1.74, 2.54, and 4.03 for CAC scores of 11–100, 101–400, 401–1000, and greater than 1000, compared to a CAC score of 1–10. The area under the receiver operating characteristic curve (AUC) to predict death was greater for CAC than for traditional risk factors (0.78 to 0.72, $p < 0.001$). The incremental predictive value of CAC to predict all-cause death, using the same cutoff values, was later confirmed by Budoff et al. [8] in 25,253 asymptomatic subjects followed for 6.8 years. In the St. Francis Heart Study [9], 4613 asymptomatic middle-aged subjects were followed for 4.3 years after CAC screening. The baseline CAC score was higher in the patients who suffered cardiovascular events than in event-free patients during follow-up. The best predictor of cardiac death during follow-up was a CAC score >100. CAC predicted cardiovascular events independently of standard risk factors and CRP

and was superior to the Framingham risk score. Similarly, Greenland et al. [10], LaMonte et al. [11], Taylor et al. [12], Detrano et al. [13], Becker et al. [14], and Erbel et al. [15] added further evidence that CAC works well in intermediate-risk patients to improve risk prediction (Table 25.1). Detrano et al. [13] also showed that CAC maintains its predictive ability in patients of different ethnicities (Caucasian, African-American, Asian, and Hispanic) living in North America.

The net reclassification index (NRI) represents an improvement over the calculation of sensitivity and specificity (i.e., area under the curve) to assess the ability of a new marker to predict an event compared to conventional methods. Three large population-based studies, i.e., the MESA [16], the Heinz Nixdorf Recall [15], and the Rotterdam study [17], consistently showed that CAC allows a higher number of patients to be reclassified to a different risk level (i.e., higher NRI) than the Framingham risk score (FRS), especially in the intermediate-risk group, providing further evidence for the clinical utility of CAC.

In view of the evidence, earlier European and American guidelines supported CAC screening in the intermediate-risk subset of the population [18, 19]. In asymptomatic subjects at intermediate risk, the guidelines denoted that a low CAC score may help reclassify these patients as low-risk, whereas a high CAC score would reclassify them as high-risk. If a patient's risk is raised, stricter preventive treatment goals should be applied. This would include, for example, an LDL goal much lower than the one used in intermediate-risk patients (usually set at 130 mg/dl) and similar to those of patients with established CAD (<100 or <70 mg/dl). The CAC cutoff value used to discriminate high- from intermediate-risk patients is >100, as implied from the St. Francis Heart Study results [9] or a score >75th percentile for age, sex, and race as suggested by the ATP III NCEP guidelines [20]. A CAC score >400 or >90th percentile denotes an even higher annual risk of cardiovascular events (4.8% and 6.5%, respectively) [21, 22] and should prompt far more aggressive therapy goals (e.g., LDL < 70 mg/dl). Importantly, using CAC screening Kalia et al. [23] demonstrated improved patients' adherence to recommended medical treatments and statin therapy. In the EISNER study, designed to test a number of cardiovascular prevention strategies in asymptomatic individuals, patients randomized to CAC screening rather than plain risk factor assessment achieved superior risk factor management during follow-up compared to controls [24]. Additionally, this was achieved without an increase in overall cost of care [24]. In spite of the accumulated evidence, in the 2013 ACC/AHA cholesterol guidelines, the role of CAC was reduced to an alternative option to clarify risk if all other approaches failed to define a patient's risk level [25]. This departure from previous recommendations elicited several concerned comments from various investigators and clinicians [26]. The limitations of the ACC/AHA approach were highlighted in a recent publication by Mortensen et al. [27]. According to the guidelines, all patients with a 10-year risk of cardiovascular events >7.5% are supposed to receive maximal intensity statin treatment. The investigators used CAC scores to select the most appropriate elderly patients to receive treatment: they avoided statins in patients with no CAC and provided statins to all those with a CAC score >100, independent of the baseline calculated risk level. After a mean follow-up of 2.7 years, patients with 0 CAC score had a very low event rate (0.07%/year coronary heart disease and 0.3%/year global cardiovascular events), while the HR for events for patients with CAC > 100 was 4- to 14-fold higher depending on the type of event considered. Confirming prior findings [15–17], CAC afforded a net NRI of 0.20 ($p < 0.0001$), which indicates that 20% of the patients were correctly reclassified to either higher or lower risk levels using CAC categories.

As opposed to intermediate-risk patients, the clinical utility of CAC screening is not well documented in low- and high-risk patients. Most physicians would consider high-risk patients (>20% 10-year risk of hard events) candidates for aggressive risk modification independent of CAC score findings. On the other hand, in most low-risk patients, CAC is either absent or the score is low, and the majority of these patients would not be reclassified to a higher-risk category, rendering CAC screening to be not cost-effective in this subset. However, some patients with a low FRS may benefit from CAC screening, such as younger (35–45 years old) patients with a positive family history of premature CAD, [28] although specific data on these patients are largely missing.

A degree of uncertainty surrounds the need for stress testing in asymptomatic patients, found to harbor large amounts of CAC. Given the low positive predictive value of stress testing in patients with low pretest probability of CAD, most authorities do not recommend the use of stress testing in these patients [19]. However, a CAC score >400 has been associated with a positive result on stress testing with myocardial perfusion imaging (Fig. 25.2) in a proportion varying between 8.9% and 46% of patients [29, 30]. This denotes that in such patients there may be adequate pretest probability to justify stress testing. In no case, however, should a high CAC score justify the performance of an invasive coronary angiogram to exclude the presence of obstructive CAD without having first performed a functional stress test.

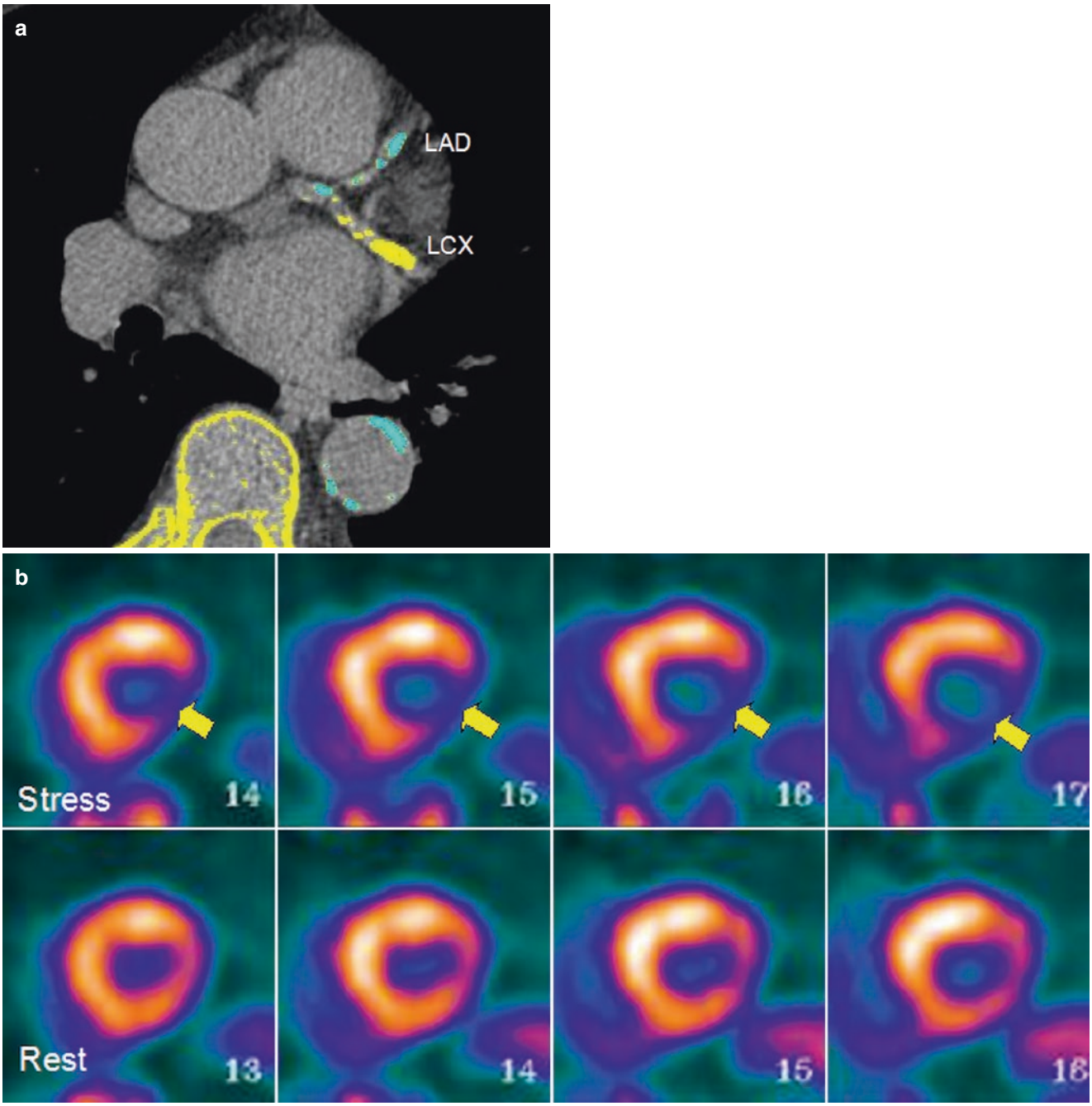

Fig. 25.2 (**a**) Axial chest CT image showing dense calcification of the left anterior descending coronary artery (LAD) and left circumflex coronary artery (LCX). (**b**) Corresponding stress and rest short axis myocardial perfusion images showing an inferolateral perfusion defect during stress (yellow arrow) that resolves with rest. This is suggestive of the presence of obstructive coronary artery disease in the left circumflex coronary artery

25.4 Vascular Age

The seventeenth-century physician Thomas Sydenham once wrote: "a man is as old as his arteries" [31]. In accordance with this notion, the extent of CAC could potentially be used to estimate the vascular age of a given subject. The measurement of CAC score in large populations without apparent cardiovascular disease has led to the development of nomograms of CAC scores according to age and gender [32, 33]. By comparing a subject's CAC score to others of the same race, age, and gender, a CAC percentile rank for the individual under study can be determined. A percentile higher than the median for the individual under exam is an index not only of severity but also of prematurity of atherosclerosis

and hence a measure of increased biological age in the face of a younger chronological age [34]. Using this approach, Shaw et al. [35] were able to assess the number of life-years lost or gained in a large population sample based on the amount of CAC measured on a screening EBCT about 5 years prior. More recently, Valenti et al. [36] showed that in individuals ≥80 years of age, a zero CAC score is suggestive of a vascular age 30 years younger than their chronological age. The concept of coronary age is self-intuitive and may therefore constitute a more effective way to communicate to individual patients their actual risk rather than simply providing an absolute CAC score.

25.5 Special Populations

25.5.1 The Elderly

Several reports supported the independent and incremental prognostic value of CAC in the elderly. In a subgroup of patients older than 70 years of age in the Rotterdam study, subjects with CAC scores of 401–1000 and >1000 had a relative risk of myocardial infarction or cardiovascular death of 5.5 and 8.2, respectively, compared to those with a CAC score of 0–100 [33]. The predictive power of CAC was independent of the FRS category (low, intermediate, or high). Raggi et al. [37] followed 35,388 patients, among whom 3570 subjects were ≥70 year-old at screening for an average of 5.8 ± 3 years. Increasing CAC scores were associated with decreasing survival rates across all age deciles ($p < 0.0001$), suggesting that CAC is predictive of outcome even in older age. Additionally, using CAC score categories, over 40% of elderly patients were reclassified to either lower or higher risk categories compared to their original ranking. This was likely due to a reduction in weight attributed to age, the variable carrying most weight in the Framingham algorithm, in the absence of subclinical atherosclerosis [37]. As discussed above [27] CAC score categories have been successfully used to reclassify risk and to direct preventive treatment in the elderly (>65 years old), attaining an improvement in overall event rates.

25.5.2 Patients with Diabetes Mellitus

Diabetic patients are less likely to experience classic ischemic symptoms despite a high prevalence of CAD. In fact, diabetic patients without known CAD have a similar prevalence of myocardial perfusion defects as nondiabetic patients with known CAD [38–40]. Therefore, the identification of preclinical CAD may be a very desirable goal, and assessment of CAC with functional imaging performed when the CAC score is very high (Agatston score ≥ 400) appears to be a reasonable risk stratification approach [41]. CAC is more prevalent and severe in diabetic patients than the general population [42, 43], and it reflects the larger atherosclerotic burden of these patients. In a study of 9474 nondiabetic and 903 diabetic asymptomatic individuals, diabetic patients had a significantly higher CAC score and a higher death rate than nondiabetic patients [43]. In addition, for any given CAC score, diabetic patients had a greater rate of mortality than nondiabetic patients. Importantly, there was no significant difference in survival between diabetic (98.8% at 5 years) and nondiabetic patients (99% at 5 years) with no CAC, underscoring the powerful negative predictive value of this marker of atherosclerosis. In a more recent study, doubling of the CAC score increased cardiovascular event risk by 32% [44]. Finally, among diabetic patients, CAC has been shown to predict cardiovascular events more accurately then the Framingham or UKPDS risk scores [45]. Investigators have shown that among type 2 diabetic patients, increasing CAC scores are associated with a higher probability of abnormalities on myocardial perfusion imaging (MPI) [46], and for the same level of CAC, the risk of an abnormal MPI is greater than for patients without diabetes mellitus. Wong et al. [47] showed that the presence of diabetes or the metabolic syndrome significantly increased the risk of ischemic defects on MPI among patients with CAC scores ≥100. For a score of 100–399, 13% of diabetic patients had inducible ischemia versus 3.6% among nondiabetic subjects, and for a score ≥400, 23.4% of diabetic patients had inducible ischemia versus 13.6% of nondiabetic subjects. For a score <100, the risk of inducible ischemia by MPI was similarly low for diabetic and nondiabetic patients. This suggests that if CAC screening were to be implemented for asymptomatic type 2 diabetic patients, it would be reasonable to restrict MPI to patients with CAC scores ≥100 in the hope of detecting silent ischemia. This notion is supported by the findings in the study conducted by Anand et al. [46] in which the investigators performed CAC screening in 510 asymptomatic patients with type 2 diabetes mellitus and MPI in those with CAC score >100. During a mean follow-up of 2.2 years, CAC scores and abnormal MPI were equally predictive of cardiovascular morbidity and mortality and demonstrated a statistically significant interaction for the prediction of an adverse cardiovascular outcome. Based on the strength of the evidence, a recent position statement issued by the imaging council of the American College of Cardiology recommended the performance of CAC screening to assess risk of cardiovascular disease in asymptomatic diabetic patients [48]. If the screening CAC score is below 400, the authors recommended medical management alone, although a stress test to rule out obstructive coronary artery disease should be performed if the CAC score is greater than 400.

25.5.3 Screening of Asymptomatic Women

CAD is the leading cause of mortality among both men and women in the United States. Compared to men, women are more likely to have atypical symptoms, and diagnostic testing is often delayed [49]. Almost 40% of initial cardiac events are fatal among women [50], and they also have a worse prognosis after a nonfatal myocardial infarction or revascularization procedures compared to men [51, 52]. Furthermore, current risk prediction algorithms such as the FRS perform poorly in women compared to men [53]. Therefore, CAC screening may be a helpful alternative method for risk stratification. CAC development in women lags 10 years behind men until around the age of 70, when the gender difference in CAC effectively disappears [19]. In a cohort of 10,377 asymptomatic patients (40% women) followed for 5 ± 3.5 years, CAC was an independent predictor of death for both genders and added incremental prognostic value to the FRS in both genders [43]. Of note, for a given absolute CAC score, women demonstrated a higher mortality than men, a result recently confirmed in a cohort of low-intermediate-risk patients [43, 54]. Among 2684 asymptomatic women from the Multi-Ethnic Study of Atherosclerosis (MESA), a CAC score >0 (found in approximately 30% of this population) was predictive of cardiovascular events, while a CAC score ≥300 was associated with an 8.6% absolute risk of events over 3.75 years (23% event rate at 10 years) [55]. A recent meta-analysis of 5 studies among 6739 women with a 10-year atherosclerotic CVD risk lower than 7.5% showed that CAC was present in approximately one third of the subjects and that the presence of CAC doubled their risk of having an event during follow-up (median follow-up 7–11.4 years) [56]. The addition of CAC to traditional risk factors moderately improved the C statistic and provided a net reclassification improvement (NRI) of 0.20 for the prediction of CV event [56]. A meta-analysis of two observational registries and three prospective studies showed that CAC screening is equally accurate for risk stratification in men and women [57]. Importantly, for a CAC score of 0, men and women had an equivalent minimal risk of cardiovascular events [57].

25.5.4 Patients with Chronic Kidney Disease

Cardiac CT has been utilized to investigate the natural history and pathogenesis of CAC, as well as the impact of different therapeutic strategies in chronic kidney disease (CKD). Evidence indicates that the prevalence of CAC increases as the estimated glomerular filtration rate (eGFR) declines [58]. In a prospective study of 313 high-risk hypertensive patients, a reduced eGFR was shown to be the major determinant of the rate of progression of CAC [59]. Additionally, Sigrist et al. [60] reported a prevalence of CAC of 46% in 46 pre-dialysis patients compared to 70% and 73%, respectively, in 60 hemodialysis and 28 peritoneal dialysis patients ($p = 0.02$). Finally, in two randomized studies, CAC was reported in 57% of adult patients who just initiated hemodialysis [61] and in 80–85% of established hemodialysis patients [62]. In two small observational studies, the extent of CAC was significantly predictive of all-cause [63, 64] and cardiovascular mortality [64].

A number of factors have been associated with CAC in dialysis patients. Associations with age and duration of dialysis [62, 65], diabetes mellitus [62], abnormalities of mineral metabolism [66–68], as well as the use and dose of calcium-based phosphate binders [69, 70] have been reported.

Hyperphosphatemia and the therapeutic approach to lowering this biomarker appear particularly important as far as progression of CAC in CKD. To investigate the impact of therapy for hyperphosphatemia on the progression of CAC, two early randomized clinical trials compared the effect of sevelamer- (a nonabsorbable polymer with gut phosphate binding ability) and calcium-based phosphate binders in prevalent [69] and incident [71] hemodialysis patients. Throughout both studies, the drugs provided a comparable phosphate control, although a significantly higher serum calcium concentration was noted in the calcium-treated arm. At study completion, sevelamer-treated subjects experienced a significantly smaller CAC progression in both studies [69, 71]. Importantly, in the trial that enrolled incident dialysis patients [61], the all-cause mortality rate was significantly lower in the sevelamer arm after 4.5 years of follow-up ($p = 0.02$) [61]. Two recent randomized trials extended and confirmed these observations to CKD stage 3–4 [72] and incident dialysis patients [73]. In the former [72], the investigators showed slowing of CAC progression and reduced event rates (all-cause death and dialysis inception) with sevelamer compared to calcium-based binders. In the second study, cardiovascular mortality was significantly reduced with sevelamer treatment compared to calcium-based binders [73].

In summary, CAC is predictive of unfavorable outcomes even in high-risk subjects such as CKD patients. The limited number of studies published so far show evidence of reduced untoward events when unnecessary calcium load is avoided and hyperphosphatemia is treated with neutral binding agents [74].

25.6 Prognostic Value of No Coronary Artery Calcium (Calcium Score 0)

Except for patients with advanced renal failure, in whom calcification of the muscular media can occur, the presence of calcium in the coronary arteries is evidence of atherosclerosis

accumulation in the subintimal space [19, 75]. Furthermore, as already discussed, the extent of CAC correlates closely with total atherosclerotic plaque burden [76–78]. It may therefore be logical to conclude that a CAC score of zero would suggest minimal risk of coronary atherosclerosis and thus minimal risk of cardiovascular events. Indeed, a CAC score of 0 has consistently been shown to have a high negative predictive value among asymptomatic patients. In a cohort of 25,253 asymptomatic subjects the 10-year survival for patients with a CAC score of 0 (44% of the sample) was 99.4% [8]. Similarly, in a cohort of 10,377 asymptomatic patients, the 5-year survival was 99% for those with a CAC score ≤10 [7]. In a meta-analysis including 35,765 asymptomatic patients with a mean follow-up of 4.7 years, those with a CAC score of 0 had an estimated 10-year risk of events of 0.3% [79]; similar results were found in more recent analyses [80]. Finally, long-term data have shown that the warranty period of a CAC score of 0 (i.e., time to development of de novo CAC) may extend to almost 15 years for individuals at low and intermediate risk [36].

In addition to suggesting an excellent clinical prognosis, a CAC score of 0 in a low- to intermediate-risk asymptomatic population suggests a very low risk of obstructive noncalcified plaque (0.5%) on invasive angiography [81]. However, the risk of obstructive disease rises significantly in symptomatic subjects even when the CAC score is low [30]. As mentioned in the previous sections, the low-risk 0 CAC extends even to high-risk patients such as those with advanced renal failure or diabetes mellitus [43, 61, 79], although, for the latter, this is not applicable to the long term [82].

25.7 Coronary Artery Calcium Progression

Since CAC is a sensitive marker of subclinical atherosclerosis, about two decades ago researchers started performing serial CAC studies to monitor progression of atherosclerosis and its response to medical therapy. The underlying assumption was that an increase in CAC, beyond a certain degree that can be expected in the general population, represents progressive disease, while minimal or no change in CAC identifies stable disease. A reliable interpretation of change in CAC score requires that the variability of serial CAC score measurements be very low. Although initially very poor, the interscan variability has now improved to very low levels on sequential scans performed within minutes of each other (~10% with 64 slice MDCT scanners or greater) [83–85]. An important consideration as one sets up a sequential CT scanning program, is the radiation dose provided with each cardiac CT, that mandates that the benefit/risk ratio of repeat scanning be carefully weighed. Progression of CAC is generally calculated as a percent or absolute change from the baseline score or as the square root of the difference between scores [86]. The absolute score change is usually greater in patients with a higher baseline CAC score, although the absolute differences may be small compared to the baseline score (hence a small relative score change). On the contrary, larger percent score changes are expected in patients with a low initial CAC score (e.g., a CAC score change from 10 to 20 = 10 points absolute increase but relative progression of 100%), and do not necessarily reflect a clinically relevant change. The square root method demonstrates less variability and is a more qualitative measurement; a yearly increase >2.5 mm^3 indicates true progression. In subjects at average Framingham risk, the annual CAC progression typically does not exceed 15–20% [79, 87–95]. Factors that may significantly modify rate of change include the patient's baseline CAC score, gender, age, family history of premature CAD, ethnicity, glycemic control, body mass index, hypertension, and renal insufficiency [96–102]. Most patients will exhibit some increase in CAC scores over time [79, 88, 89, 92, 93, 95] although a baseline score of 0 is usually associated with a very slow and delayed appearance of CAC, occurring at low frequency before 4 years [79, 103]. Therefore, in patients with a CAC score of 0, CT scanning should not be repeated prior to 5 years from the initial scan [79].

A number of observational studies and randomized clinical trials have evaluated change in CAC following treatment with statin therapy. In four observational reports, untreated patients had an average CAC score progression of 36%, while statin therapy attenuated CAC progression to about 13% [89, 100, 104, 105]. Unfortunately, these promising initial results were not confirmed by large randomized clinical trials that showed a similar change in CAC scores following placebo and moderate or intensive statin therapy [106, 107]. Indeed, except for a small, crossover prospective trial [108], all other randomized trials failed to confirm the observational data. Furthermore, a recent meta-analysis suggested that long-term and aggressive lipid-lowering therapy with statins may promote calcification of the plaque rather than inhibit it [109], and this may be due to slow replacement of lipid cores with calcium deposits. Other treatments have also been tested to slow CAC progression. In the Women's Health Initiative (WHI), menopausal women between the ages of 50–59 years were randomized to treatment with conjugated estrogens or placebo [110]. In a sub-study of the WHI, 1064 women were submitted to CAC screening after 8.7 years from trial initiation. Women receiving estrogens showed a lower CAC score compared to those receiving placebo (83.1 vs 123.1, $p = 0.02$).

Several reports have noted that a rapid change in CAC score is associated with worse clinical outcomes including incident MI [92, 111, 112]. Patients exhibiting significant CAC progression from their index scan (either a square root increase >2.5 mm^3 or a score increase ≥15%/year) and those

with baseline CAC scores ≥400 have a shorter lag time to the development of acute MI compared to those with a progression <15%/year and CAC scores ≤100. Thus, the baseline CAC score provides an insight into not only the expected rate of progression but also the timeline of conversion to symptomatic CAD. Recently, the association of CAC score progression with the risk of incident cardiovascular events was examined in a prospective observational study [113]. CAC progression was significantly associated with total CVD events, even if baseline CAC was taken into account in the statistical model. However, the contribution of CAC progression was small relative to baseline CAC. Furthermore, if the follow-up absolute CAC score was taken into account, CAC progression was no longer associated with total CVD events. A model that included the follow-up absolute CAC score alone performed as well as the model that included baseline CAC and CAC progression [113]. These findings simplified, in a sense, the debate as to what method is most appropriate to follow progression of CAC. The authors stress that since the most recent score is the best predictor of outcomes, there is no need to focus on the absolute, percent, or square root change of the score. The observed increased risk of events in the context of CAC progression likely applies only to untreated patients and not patients treated with lipid-lowering medications. Indeed, these drugs may promote rather than inhibit calcification of the plaque [109] and are associated with a decreased risk of events.

25.8 Conclusions

The field of preventive cardiology has advanced rapidly over the past few decades as the public's and physicians' awareness of the importance of avoidance of risk behaviors have increased, and new and more potent medications aimed at slowing the atherosclerotic process have become available. The success of preventive efforts is reflected by the reduction in fatal events recently reported by the American Heart Association [114], although nonfatal events with substantial consequences for families and society continue to occur at a high rate. The field of atherosclerosis imaging developed in the hope of affecting atherosclerosis outcome through early detection of subclinical disease and aggressive modification of risk (i.e., a more accurate risk stratification). The field has witnessed enormous advancements in just a few years, but it remains to be clearly demonstrated that patients benefit from this "graded therapeutic approach." With one exception of a short-term study limited to elderly patients [27], there have been no prospective, long-term trials to show that treating patients with CAC and avoiding treatment in those without CAC result in a better outcome than treating patients based on risk factor assessment alone. In a reanalysis of the MESA data, Blaha et al. [115] suggested that this could indeed be the case. In a subset of MESA patients selected to match patients enrolled in the JUPITER trial, the authors showed that serum levels of hsCRP were not predictive of cardiovascular outcome, while increasing CAC scores provided a graded increase in risk. Furthermore, the "number need to treat" to avoid one event was estimated at 19 in the presence of CAC > 100 and 124 in the absence of CAC independent of any other risk factor including hsCRP level. Hence, it would seem very plausible that a therapeutic approach tailored to the burden of atherosclerosis rather than other indirect markers of risk may improve the outcome of patients and funnel resources more appropriately.

While the field of atherosclerosis imaging deserves support, it is important to educate public and physicians as to the advantages and disadvantages of imaging tools to put them to their most appropriate use. Screening of asymptomatic, intermediate-risk patients with CAC is currently the most accurate imaging method to improve risk stratification. However, careful selection of patients is mandatory to avoid unnecessary radiation exposure and low yield [116].

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Cardiac Computed Tomography

26

Borek Foldyna, Michael Lu, and Udo Hoffmann

26.1 Introduction

Computed tomography (CT) is one of the most significant innovations of the twentieth century and has revolutionized the clinical practice. Sir Godfrey Hounsfield, an English engineer, working for EMI, and Allan Cormack of Tufts University, Massachusetts, a South African-born physicist, developed the concept and the first axial CT scanner in 1972. For the first time, a large volume of data could be collected in an orthogonal plane by using a thin X-ray beam to rotate around a region of interest. The earliest scanners took hours to acquire data and several days to reconstruct the final image for analysis. Subsequent advances such as "slip-ring" technology removed the need for a rigid mechanical linkage between the power cables and the X-ray tube enabling the X-ray tube to rotate indefinitely resulting in "spiral" or "helical" CT as we know it today. CT imaging is now a cornerstone of clinical practice, and it is thought that over 62 million CT scans are performed each year in the USA [1].

Evaluation of the heart and coronary arteries, which are constantly in motion, is one of the most technically challenging applications of the CT but thanks to improvements in CT technology is increasingly becoming a routine. One percent of all CT examinations performed per annum in the USA are thought to have a cardiac indication. While this represents a small proportion to the total number of CT examinations, interest in cardiac CT has been unprecedented, and this has directly contributed to rapid CT platform development. Before cardiac CT could be applied to the clinical arena, challenges such as respiratory motion, cardiac motion, heart rate variability, and the relative motion of submillimeter coronary arteries had to be overcome. Since 1998, "multidetector" CT technology became commercially available allowing rapid image acquisition of wide parts of human anatomy. The acquisition of the X-ray data was synchronized with the electrocardiogram (ECG), and the respiratory motion was negated by a short breath-holds (< 10 s). These innovative concepts produced the earliest mechanical cardiac CT images [2], and the quick biannual advances in the CT technology have revolutionized how the heart is assessed.

26.2 Technical Background

26.2.1 Basic Principles of Cardiac Computed Tomography

Cardiac CT has been made possible by improvements in CT platform design, ECG-gated image acquisition, faster post-processing, and improved image archiving capabilities. All mechanical CT scanners have two core components: a gantry and a movable table. The main components of the gantry are an X-ray source and a detector array (Fig. 26.1).

Inside the gantry, the X-ray tube and the detector array rotate around the patient as the table, on which the patient is placed, moves through the gantry. This relative movement combination effectively produces a spiral path (Fig. 26.2).

X-rays are generated within the X-ray tube by high-energy electrons, which bombard a metal target. On striking the metal target, most of this energy is lost as heat, but a small proportion generates X-rays. As this X-ray photon beam passes through the patient, some of the constituent photons are absorbed or scattered. This reduction in X-ray photons is called attenuation, and it is dependent on the initial photon energy and the tissue density.

The emergent X-ray beam strikes the detector array where the photon energy is converted into electronic impulses, similar to the light striking sensor of a digital camera. The electronic impulses are converted into digital information from which the attenuation value can be calculated. The attenuation value is described in Hounsfield units (HU) and is relative to the attenuation value of water, which is calibrated to 0 (range 1024–3071 HU). The final image is composed of a

B. Foldyna · M. Lu · U. Hoffmann (✉)
Department of Radiology, Massachusetts General Hospital - Harvard Medical School, Boston, MA, USA
e-mail: uhoffmann@mgh.harvard.edu

P. P. Toth, C. P. Cannon (eds.), *Comprehensive Cardiovascular Medicine in the Primary Care Setting*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-319-97622-8_26

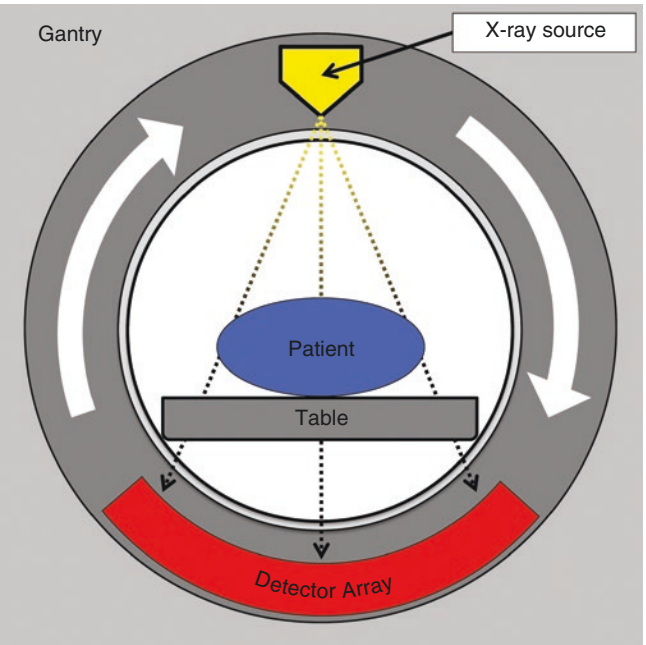

Fig. 26.1 Anatomy of a CT scanner

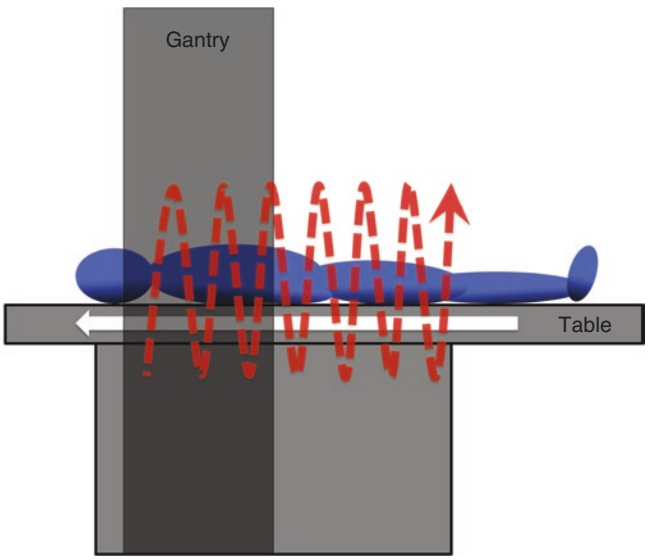

Fig. 26.2 Helical CT. The patient table moves through the center of the CT scanner gantry (gray rectangle). In the scanner, the X-ray source rotates around the patient in a circular path. The relative motion of the patient table to the X-ray source creates a helical path (red arrow)

matrix of tiny squares (pixels), with each pixel designated an attenuation value that corresponds to the tissue from which it originated. The greater the tissue density through which the X-ray beam passes, the higher is the attenuation value and brighter is the final image. Two-dimensional (2D) cardiac CT images are displayed on an image matrix of 512 × 512 pixels. Three-dimensional (3D) pixels carry additional information about the slice thickness and are called voxels (Fig. 26.3).

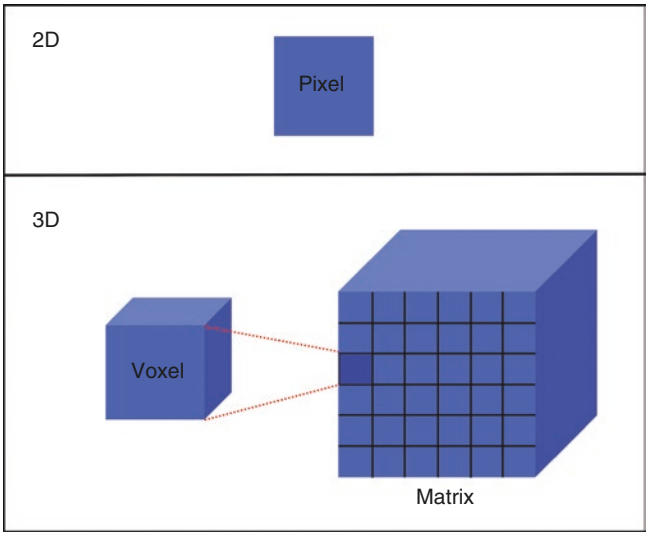

Fig. 26.3 Image reconstruction: pixel–voxel–matrix

Similar to sensors in a digital camera, detector array characteristics are crucial for the spatial resolution of the final image. As in digital photography, the spatial resolution of CT is a measure of how close together two lines can be and still be resolved independently. These line pairs, and not the total number of pixels within an image, define the spatial resolution. The smaller the detector size, the greater the potential for a higher spatial resolution due to the creation of an image matrix composed of smaller voxels (i.e., the smallest 3D element in the CT dataset). In the current context, high-end cardiac CT scanners can reach a maximal spatial resolution down to 0.26 mm. The most widely used CT scanners have a maximal spatial resolution of 0.4–0.6 mm. The recently published guidelines recommend a spatial resolution of 0.6 mm and reconstruction field of view of maximally 250 mm [3]. This resolution is sufficient to visualize the major epicardial coronary arteries down to a vessel caliber of 2 mm.

Besides spatial resolution, temporal resolution is one of the main issues in the cardiac CT, and the fast movement of the heart can lead to movement artifacts and nondiagnostic image quality. The temporal resolution can be thought of as the frequency by which the data that generates an image is acquired. The time it takes for the X-ray source to complete one full 360° rotation around the patient is called the gantry rotation time. Therefore, if it takes one full gantry rotation time of 500 ms to acquire all of the information, the temporal resolution would be 500 ms. In practice, data can be acquired using a 180° rotation or even less than 90° if using systems with two sources and two detectors at the same time (i.e., dual-source). Current dual-source systems have two X-ray tubes, and two detectors placed at 90° to each other and reach effective gantry rotation times of less than 250 ms and a minimum temporal resolution of 66 ms.

The introduction of full-volume coverage scanners represents another exciting innovation improving the temporal resolution. Detectors with 320 rows capture approximately 16 cm of the body in a single rotation. Cardiac CT of the coronary arteries with 64-detector technology typically takes 8–10 s. Dual-source scanners or scanner with large detectors (e.g., 320-row-detector) can acquire images in < 1 s and thus within a single heartbeat, The ever-improving temporal resolution makes cardiac CT suitable for most clinical scenarios, and in the future, ECG synchronization may even be rendered obsolete, and breath-hold, heart rate, and arrhythmia artifacts may no longer represent a limitation.

26.2.2 Electrocardiographic Synchronization

In most clinical scenarios, the current generation of CT scanners requires a robust acquisition of the X-ray generated data to be synchronized with the cardiac cycle. This ECG synchronization allows the reconstruction of data sets that have been acquired over one or a series of heartbeats to create still images, which then display the heart at a specific time point within the cardiac cycle.

In general, the cardiac cycle can be divided into two phases—systole and diastole. Systole consumes two-thirds of the duration of the cardiac cycle and varies little with heart rate. This period represents significant cardiac and coronary artery motion and pushes current CT platforms to their limits of temporal resolution. There are three recognized systolic phases—isovolumetric contraction, rapid ejection, and reduced ejection. Isovolumetric contraction corresponds with the ECG QRS complex. In this phase, there is virtually no cardiac motion, but the duration of isovolumetric contraction is too narrow for cardiac CT data acquisition in most cases. Late systole, a period of slower ventricular ejection, is a potential target for data acquisition using scanners with high temporal resolution, particularly in patients with high heart rates > 65 bpm [4].

Diastole represents only one-third of the cardiac cycle, but it is the favored phase for imaging. Ideally, in cardiac CT images should be reconstructed in mid- to late-diastole [5]. Unfortunately, with increased heart rates, the diastolic time window contracts, and the optimal temporal window for acquisition advances from 75% of the R–R interval for subjects with heart rates < 70 bpm to 85% of the R–R interval in subjects with heart rates > 80 bpm (Table 26.1) [5, 6].

There are two basic ECG synchronization techniques—prospective and retrospective. Both methods involve the analysis of a single heartbeat or cardiac cycle as defined by the R–R interval of the ECG signal. Each algorithm intends to acquire isocardiophasic reconstruction of the heart. Consequently, for instance, each coronary artery is sampled

Table 26.1 Heart rate and temporal resolution requirements

Heart rate (bpm)	Temporal resolution (ms)	Imaging phase
40	500	Diastole
50	400	Diastole
60	300	Diastole
70	200	Diastole or systole
80	150	Systole
90	120	Systole
100	100	Systole
120	50–100	Systole

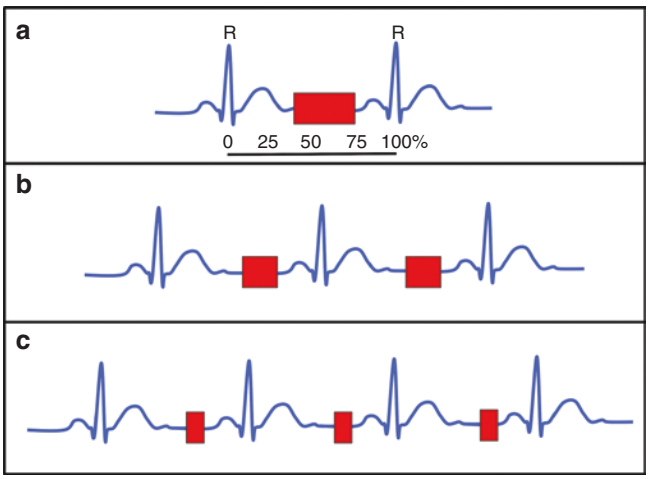

Fig. 26.4 Single versus multi-sector reconstruction. (**a**) Single-sector reconstruction. The image is reconstructedfrom data that is generated-during a single cardiac cycle and utilizes a full 180° rotation. Additional visualization of the R–R interval with corresponding percentages of the cardiac cycle is displayed below. (**b**) Dual-sector reconstruction. Images are acquired at pre-specified time points in the cardiac cycle and acquired over duration of multiple heartbeats (usually 2-3 heart beats). This requires two 90° rotations. (**c**) Multi-sector reconstruction. Images are acquired rapidly over many heartbeats

at the same time point in the same anatomical position within individual heartbeats. A scan can be prospectively triggered or retrospectively gated by three basic methods. The absolute delay method involves data collection at a fixed time interval after the preceding R wave. An absolute reverse delay involves data collection at a fixed time interval from the succeeding R wave. A relative delay involves data collection as a percentage of the R–R interval; therefore, it is relative to the heart rate. The ability of current algorithms to utilize both fixed and relative delay protocols facilitates robust clinical imaging over a greater range of heart rates (Fig. 26.4).

Prospective triggering ensures a rapid scan time and reduces the radiation exposure to the patient. The algorithm recognizes the R wave in the ECG, and after a pre-specified time interval and for a specific duration, data is acquired. In case the heart is not captured entirely within one heartbeat, depending on the width of the detector, the process can be

repeated in several steps until the heart is completely imaged. This so-called "step and shoot" or "axial–sequential" technique generates a series of axial scans. A second prospectively triggered technique is the high-pitch data acquisition, which is available for some of the dual-source scanners. In this case, the rapid movement of the patient (up to 0.75 m/s) through the gantry leads to a high pitch, which stretches the spiral path. On a single-source scanner, the stretching of this spiral path would lead to gaps in the image. Dual-source scanners use both tubes and detectors to create gap-free images. The major limitation of these two techniques is the lack of flexibility during post-processing. If an inappropriate time interval has been selected, image quality may be suboptimal. The timing of the ideal motion-free portion of the cardiac cycle can be difficult to predict, especially at high heart rates. In recognition of this, many prospectively acquired protocols incorporate "padding," a safety mechanism which aims to widen the acquisition window, or includes additional cardiac phases to increase the chances of reaching diagnostic image quality. Greater degrees of padding are employed with higher heart rates and systolic scanning [7]. Some scanners even apply arrhythmia rejection algorithms during prospective triggering and can achieve better image quality compared to the traditional retrospectively gated techniques in patients with arrhythmias [4].

In contrast, retrospectively ECG-gated CT images are acquired in a continuous helical fashion over the entire cardiac cycle. Retrospective gating allows the clinician to review data acquired over the entire cardiac cycle and to choose only the highest-quality data sets for the analysis [8]. The time interval selected can be defined as a percentage (0–100%) of the R–R interval or as a specific time interval after or before the R wave (Fig. 26.5).

This technique acquires data in a continuous spiral. Comprehensive data sets are available for review but at the cost of significantly higher radiation exposure to the patient, prolonged post-processing, and image archiving (Fig. 26.6).

26.3 Cardiac Anatomy

Knowledge of normal cardiac morphology including coronary artery anatomy is essential for the planning and the interpretation of cardiac CT examinations (Fig. 26.7). In general, a normal heart consists of two ventricles and two atria; the right atrium connects to the right ventricle, which in turn is connected to the right ventricular outflow tract and the common pulmonary artery. The left atrium connects to the left ventricle, which in turn is connected to the ascending aorta. Variations in this basic anatomical design exist but are beyond the scope of this chapter.

Normal coronary artery anatomy (Fig. 26.8) is defined as a left main, which originates superior to the right coronary artery from the left coronary sinus. The left main usually bifurcates but may trifurcate beneath the left atrial appendage to form the left anterior descending (LAD), the circumflex (CX), and the ramus intermedius. The LAD follows the anterior interventricular groove until it reaches the left ventricular apex. The LAD supplies two important side branch groups. The septal perforators originate from the right ventricular side of the LAD. They supply the anterior two-thirds of the septum. The diagonal branches arise from the left ventricular side of the LAD and supply the lateral wall of the left ventricle. Typically, there are two or three diagonal branches. The CX is often a short and recessive vessel. It follows a course laterally in the left atrioventricular groove and sup-

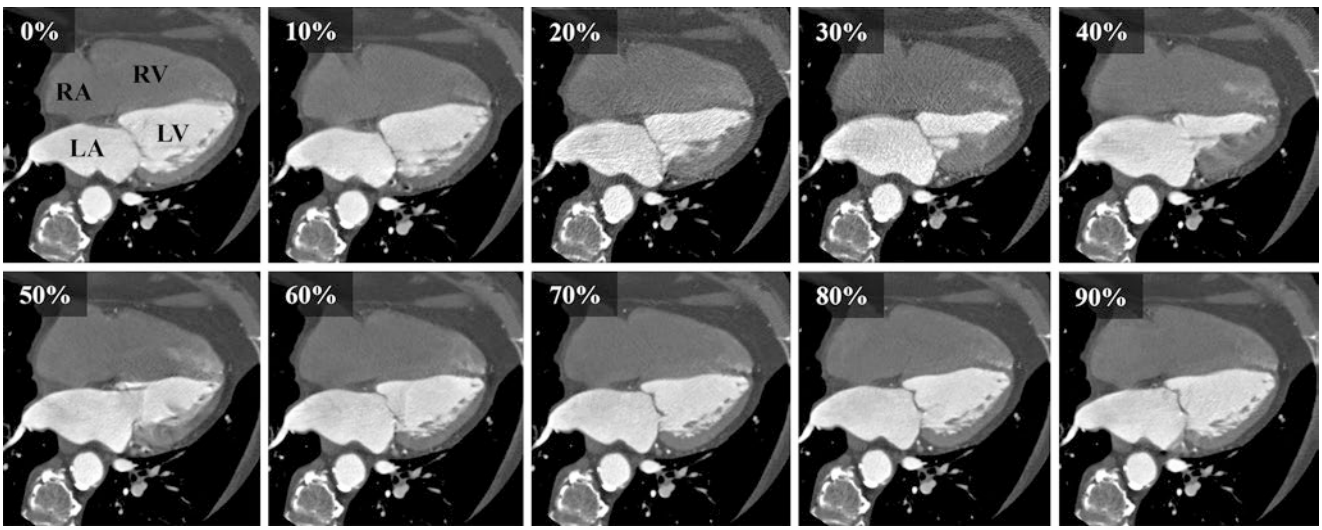

Fig. 26.5 Example of ECG synchronization-based, retrospective reconstruction of the heart, shown as four-chamber view in 10% intervals within the entire cardiac cycle. *LA* left atrium, *LV* left ventricle, *RA* right atrium, *RV* right ventricle

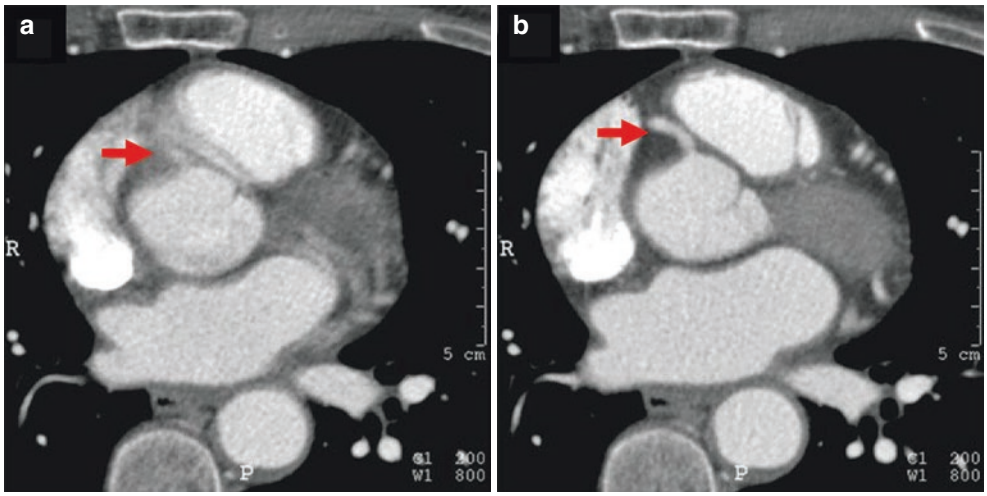

Fig. 26.6 The optimal temporal phase for reconstruction. (**a**) An axial image that demonstrates RCA motion artifact (red arrow) when imaged at 40% of the R–R interval. (**b**) Axial image of the same RCA but imaged at 70% of the R–R interval. The proximal coronary artery is easily identified

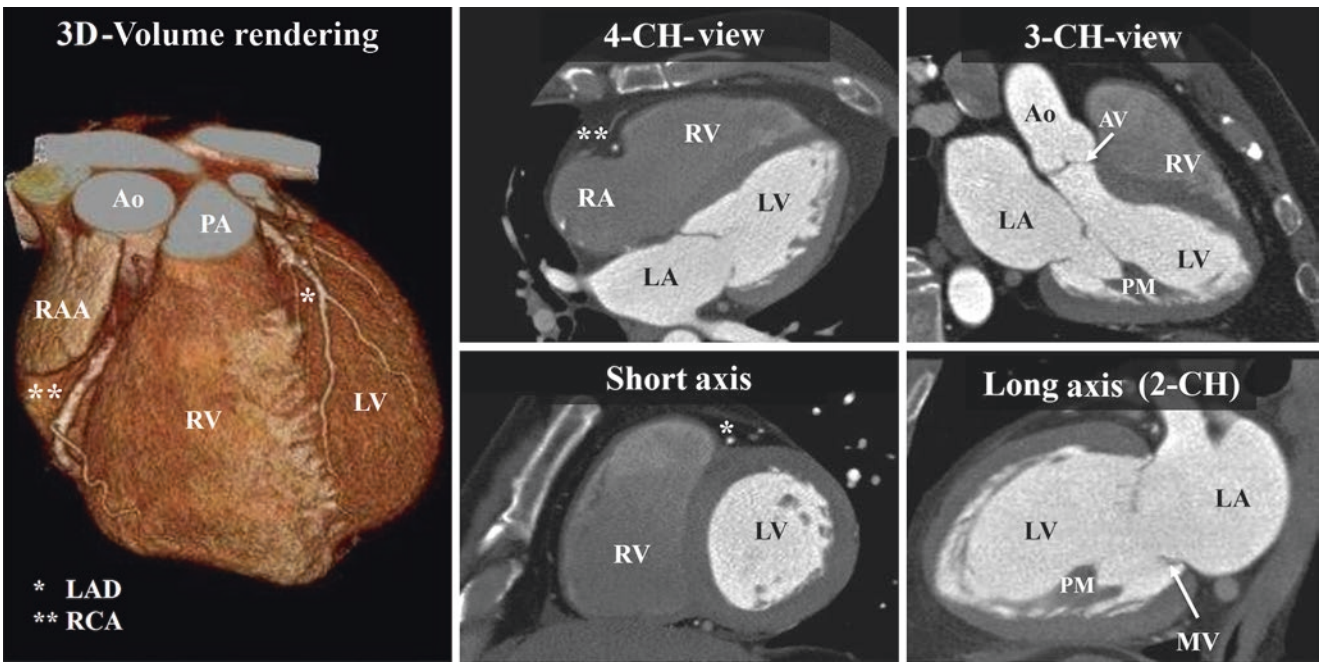

Fig. 26.7 Regular cardiac anatomy displayed as 3D volume-rendered CT image and four most common multiplanar reconstructions in four-chamber, three-chamber, short-axis, and long-axis/two-chamber view. *Ao* aorta, *AV* aortic valve, *LA* left atrium, *LAD* left anterior descending, *LV* left ventricle, *MV* mitral valve, *PM* papillary muscle, *RA* right atrium, *RAA* right atrial appendage, *RCA* right coronary artery, *RV* right ventricle

plies the lateral and posterior walls of the left ventricle with a variable number of obtuse marginal branches. The ramus intermedius may be present in 30% of people and originates between the LAD and the CX coronary arteries to supply the anterolateral wall of the left ventricle. When present the diagonal and marginal systems are less developed or partially missing. The RCA arises from the right coronary cusp, descends in the right atrioventricular groove, continues to the inferior surface of the heart, and bifurcates at the posterior interventricular groove. There are two major branches, the posterior descending artery (PDA) and the posterior-lateral branch (PLB). The PDA arises from the RCA in 80% of the cases. This is described as a right-dominant system. In 15% of subjects, the PDA originates from the CX and is described as a left-dominant system. In the remaining 5% of cases, the posterior interventricular septum is supplied by both the RCA and the CX. This anatomical variation is classified as codominant. The second branch that arises at the crux is the PLB and supplies the posterior and inferior wall of the left ventricle.

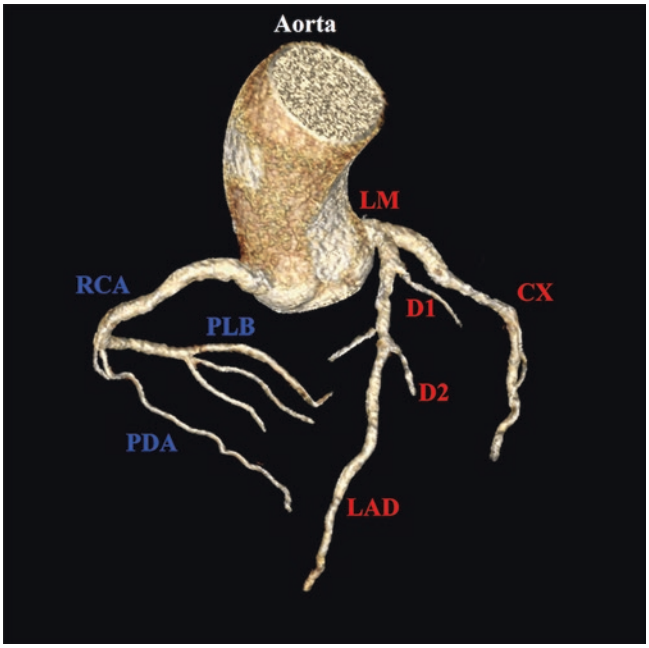

Fig. 26.8 Normal coronary artery anatomy displayed as both left (blue) and right (red) coronary arteries with their main branches (right-dominant system). *CX* circumflex artery, *D1/2* first/second diagonal branch, *LAD* left anterior descending, *LM* left main, *PDA* posterior descending artery, *PLB* posterior–lateral branch, *RCA* right coronary artery

Additional anatomic structures to be described in the cardiac CT are the four cardiac valves including usually the tricuspid aortic and pulmonary valves as well as both atrioventricular valves: the mitral and tricuspid valve. Furthermore, a radiological report should include a description of the pericardium and the major afferent and efferent vessels. The pericardium is commonly only observable as a thin line surrounding the heart confined by the neighboring epi- and pericardial fat tissue. The major efferent vessels are the ascending aorta and the pulmonary trunk dividing into the right and left main pulmonary arteries. Afferent vessels are the superior and inferior vena cava merging into the right atrium as well as in most cases four pulmonary veins merging into the left atrium.

26.4 How to Perform a Coronary CTA Examination

In recent years, cardiac CT has made the transition from an operator-dependent procedure to a semiautomated technique with variables in patient size, heart rate, and rhythm automatically adjusted for by advanced software algorithms. Despite these developments, some essential steps should be strictly followed to achieve consistently images of diagnostic quality. The following steps correspond to the 2016 Society of Cardiac Computed Tomography (SCCT) guidelines [3].

26.4.1 Step 1: Patient Selection

Patient selection is the key and the most crucial step for successful imaging. The referring clinician must have a clear understanding of the strengths and limitations of the technique. The indication for the examination should be placed strictly following guidelines that have recently been issued by professional bodies and are described in detail below in indication part of this chapter.

26.4.2 Step 2: Patient-Related Requirements

If a patient is considered suitable for cardiac CT, physicians should undertake screening for contraindications. In general, severe contrast allergy, high-grade renal impairment, pregnancy, orthopnea, claustrophobia, and arrhythmias with a poorly controlled ventricular response should be considered absolute contraindications to the procedure.

Conventional 64-detector platforms require an 8–10 s breath-hold for coronary artery imaging. Most subjects easily achieve this requirement; however, it is recommended to instruct and train on breath-hold technique, with specific focus to avoid the "Valsalva maneuver." As the breath-hold duration increases, some patients find it difficult to maintain and begin to exhale against a closed glottis forcibly. This contributes to diaphragmatic drift and stimulation of the sympathetic nervous system and leads to an increased heart rate. These alterations in the cardiac anatomical position and shifts in the R–R interval cause image artifacts. This can be avoided by observing breath-hold practices to ensure patient eligibility and to clarify patients' expectations.

The relative risk of contrast nephropathy needs to be considered before a contrast-enhanced cardiac CT. Application of contrast media should be avoided in patients with a serum creatinine levels > 1.8 mL/dL and glomerular filtration rate (GFR) < 60 mL/min/m^2. Patients with mild to moderate renal impairment should be encouraged to hydrate before the procedure to reduce the small risk of contrast-induced nephropathy. Results of a large (n = 21,346), retrospective, single-center trial have shown that patients undergoing contrast-enhanced CT were not at increased risk of acute kidney injury, dialysis, or death compared to patients undergoing non-contrast-enhanced CT [9].

Subjects with a history of mild contrast material allergy may be administered steroids and antihistamines before the examination. Severe reactions with cardiopulmonary dysregulation should be considered an absolute contraindica-

tion. Medication should be documented and all nephrotoxic medications omitted on the day of the CT examination.

26.4.3 Step 3: Appropriate Scanner Technology

Cardiac CT should be performed on a CT platform that is capable of the simultaneous acquisition of at least 64 slices. Scans are more consistently reproducible on CT platforms capable of 64 slices or more. The width of detector elements should be ≤0.65 mm and the gantry rotation time should not exceed 350 ms to allow high spatial and temporal resolution. Scanners with the option for prospective triggering, tube current modulation during retrospective data acquisition, and iterative reconstruction algorithms should be preferred to limit the radiation exposure.

26.4.4 Step 4: Intravenous Access and ECG

Venous access is achieved with a minimum 20 gauge catheter, but preferably 18 gauge, to allow infusion rates of 5–7 mL/s. An access via the right median antecubital vein is preferred, but the left antecubital can also be used. The arms should be placed above the head and out of the scan range to reduce image noise. ECG electrodes should be placed on the torso, and the ECG signal should be checked before initiating the scan. Beware that metal electrodes may cause significant streak artifacts. Two electrodes are placed beneath the right and left clavicle, and the third is placed on the abdomen. All electrodes are positioned to ensure a high-quality ECG with a sizable R wave for ECG synchronization.

26.4.5 Step 5: Pre-scan Medication

26.4.5.1 Heart Rate Control

Low heart rate and regular cardiac rhythm are crucial for excellent image quality and radiation dose salvage [10]. While in general heart rates < 60 bpm and sinus rhythm are desirable for optimal CT image quality, the latest generation of scanners with high temporal resolution acquires diagnostic images for heart rates even over 100 bpm. In general, heart rates < 80 bpm for dual-source CT or scanners with large detectors and < 70 bpm for common 64-row multidetector platforms are recommended. Optimal heart rates can be achieved by the administration of heart-rate-lowering medication. As described by the recent SCCT guidelines, oral, i.v., or combined administration of beta-blockers are the first line to lower the heart rate for the duration of the cardiac CT.

If an adequate heart rate has not been achieved with oral beta-blockers, some sites administer additional intravenous beta-blockers, such as metoprolol, which have demonstrated safety and low costs. After placement of cardiac monitoring, an initial dose of 5 mg metoprolol can be applied, and after 5 min, another 5 mg can be given repeatedly until a maximal dose of 20–25 mg is reached if necessary. Atenolol might be considered as an appropriate alternative in patients with hepatic dysfunction. Ivabradine, a direct I(f) current inhibitor, might be an alternative in patients with congestive heart failure since it reduces heart rate without lowering the myocardial contraction or blood pressure. Dosing and contraindications are detailed in the SCCT guideline documents [3].

26.4.5.2 Vasodilatation

Nitrates lead to a smooth muscle relaxation and should be administered before the cornary computed tomography angiography (CTA) to vasodilate the coronary vascular bed [3]. Nitrates have shown to improve the accuracy for coronary evaluation. After exclusion of contraindications, 400–800 μg of sublingual nitrates (spray or a capsule) should be administered approximately 5 min prior to the examination. Notably, nitrate-naïve subjects may experience reflex tachycardia, presyncopal symptoms, and headache.

26.4.6 Step 6: Scan Protocols

The rapid evolution of cardiac CT has contributed to the development of numerous protocols: the non-contrast-enhanced calcium score, the contrast-enhanced coronary CTA, comprehensive cardiothoracic assessments (e.g., triple rule out), and protocols for evaluation of the cardiac morphology and function. Protocol selection and scan parameters are determined by the clinical question, patient characteristics, and technical scanner-related limitations. A careful consideration of the effective radiation dose should lead to protocol refinements that spare radiation exposure such as prospective triggering and modulation of the tube current.

26.4.7 Step 7: Protocol Initiation

In general, a scout scan is performed to determine the field of view and scan range. This may be followed by a non-contrast-enhanced, prospectively triggered coronary artery calcium scan 120 kV, 80 mAs, and image reconstruction with 3 mm slice thickness.

An optimal scan window of the coronary CTA can be adjusted using the non-contrast calcium scan to avoid scanning areas outside the region of interest which enables further radiation salvage. The coronary CTA is usually performed with 50–100 mL of nonionic contrast media. The

volume of contrast should be minimized and injected at a rate of 4–6 mL/s. A bolus of saline is administered to wash contrast out of the right ventricle, which can otherwise cause hardening artifacts. If an evaluation of the right ventricle should be performed as well, alternatively, three phasic protocols can be chosen with additional injection of 20–30 mL diluted contrast media (1:1) after contrast and before the saline application. This technique allows evaluation of the right ventricle without creating beam-hardening artifacts. The coronary CTA may be initiated by a test bolus or automated bolus-tracking technique.

As another option, a test bolus involves the administration of 20 mL of contrast before the main scan. The transit time is assessed by a series of dynamic low-dose (100 kV, 20 mAs) monitoring scans at the level of the aortic root. The delay between each monitoring scan acquisition is approximately 1 s. Acquisition of the dynamic monitoring scans started 10 s after the beginning of the injection of intravenous contrast material. The region of interest in the aortic root is monitored to generate an enhancement curve. The time needed to reach the peak of maximum enhancement equates to the delay applied before starting the CTA.

An automated bolus-tracking technique monitors in real time a region of interest in the ascending aorta or left atrium. Hereby, a predefined threshold of 120–150 HU defines the threshold for automatic scan initiation. A scan delay of 5–6 s requires breath-hold instruction and inspiration ensuring that the peak contrast attenuation is achieved before the ECG data acquisition. Vascular enhancement should be uniform, and contrast attenuation within the lumen should be over 200 HU.

26.4.8 Step 8: Data Reconstruction and Post-processing

A single cardiac CT study can generate thousands of images and may require more than 750 MB of storage. The final data set can be post-processed using a number of different algorithms. Typically, a slice thickness of 0.5–0.75 mm is utilized while fifty percent overlap of adjacent slices can help reduce MPR image artifacts. The smaller image slice improves the spatial resolution, but this is at the expense of noisier images. Also, the XY plane field of view (image width) should be less than 250 mm, preferably 200 mm; as typical DICOM is only 512 × 512 pixels, the field of view plays a significant role in the resolution of each pixel. In large subjects, thicker slices may improve image quality but at the expense of the spatial resolution. Iterative reconstruction algorithms should be used to reduce image noise if available.

Reconstruction kernels are used to convert the raw data from the spiral scan into interpretable images. Kernels are filters that balance the sharpness of the image with the image noise. High-resolution (sharp) kernels increase the resolution of the image but at higher image noise. Low-resolution (i.e., smooth) kernels reduce the noise but at the cost of resolution. The choice of the smooth or sharp kernel will depend on the clinical requirement. For example, calcium and stents would require a sharp reconstruction kernel; smooth kernels are used frequently to evaluate vascular structures.

26.4.9 Step 9: Reporting

A cardiac CT report should contain appropriate identifying information on both patient and referrer. The date and time of the examination should be recorded. The date, time, indication, and author of the report should be clearly visible. The technical limitations and image quality should be defined. If the coronary arteries are the structure of primary interest, then the reporting should follow the most recent (2014) guidelines for interpretation and reporting of coronary CT angiography [11]. The CT reader should comment on the coronary artery anatomy and the presence, location, and type of coronary lesions. Where possible, the functional significance of the stenosis should be defined. Additionally, to support further diagnostic approach and to recommend potential therapy, it is endorsed to rate every patient using the recently introduced CAD-RAD™ classification [12] as described in detail below in the post-processing part of this chapter. Cardiac structure and function, including regional wall motion abnormalities and perfusion defects, should be assessed if retrospectively gated data with all cardiac phases are available. Additional information on non-coronary structures such as pulmonary venous anatomy, cardiac veins, and valves can be commented on where appropriate. Extracardiac findings should be reported.

26.5 Radiation Dose

The average annual background radiation exposure in the USA is 3.6 mSv [13]. A single cardiac CT can expose the patient in average to 3.5–12.3 mSv depending on examination protocol, used equipment, and patient characteristics such as size and heart rate (Table 26.2) [14].

The radiation exposure of cardiac CT is considered as one of the major limitations of this technique. The American Heart Association scientific statement on cardiac CT suggests that a 10 mSv cardiac CT examination may be associated with an increased lifetime risk of a fatal malignancy. The possibility of fatal malignancy has been quoted as 1 in 2,000 cases [15]. Therefore, a crucial aspect is keeping the radiation dose “as low as reasonably achievable” (ALARA principle) [1]. This goal must be weighed against

Table 26.2 Effective radiation exposure in cardiac examinations

Radiation source	Effective radiation dose (mSv)
Annual background radiation	3.6
Chest X-ray	0.03
Invasive coronary angiography (no ventriculogram)	2–6
SPECT	6–15
Coronary calcium scoring	1–3
Coronary CTA (retrospective)	13–20
Coronary CTA (retrospective + ETCM)	6
Coronary CTA (prospective)	0.1–3.5

CTA computed tomography angiogaphy *ETCM* ECG tube current modulation, *SPECT* single-photon emission computed tomography

the requirement to achieve a diagnostic scan. Radiation dose reduction at the expense of diagnostic image quality should be avoided. A cardiac CT should be viewed as a definitive diagnostic technique for the majority of patients assessed. It should provide accurate diagnostic information and inform treatment strategies. Further diagnostic imaging investigations should rarely be required. The radiation dose should be adjusted for each patient individually depending primarily on the body habitus.

Repeated and unnecessary CT examinations should be avoided. Notably, the effective radiation dose of a cardiac CT examination is higher in women than in men due to the exposure of radiation-sensitive breast tissue that lies within the scan range. The lifetime cancer risk should be considered in the patient context. Older patients have a lower associated risk, and for those patients with specific cardiomyopathies, discussion of cancer risk may be a moot point given that the 5-year survival rate is often less than 50%. In younger individuals, the associated lifetime attributable cancer risk may be estimated based on age, gender, and the scan protocol utilized [16].

According to the recent guidelines, acceptable radiation exposure for a cardiac CT examination is 1–10 mSv [3]. However, due to rapid technological improvement and introduction of wide detectors and high-pitch helical dual-source CT, cardiac CT can be performed with radiation exposure of less than 1 mSv as described in the PROTECTION study series published during the last decade [17]. One mSv is substantially lower than a conventional invasive angiography without left ventriculography, which is thought to be approximately 2–6 mSv. This is not representative of current interventional practice where an increasing number of cardiac catheterizations are performed through a radial artery vascular access site. This change in practice has been driven by the relatively high femoral access site complication rate but at the cost of increased radiation exposure to both patient and staff [18].

At present, myocardial perfusion imaging is considered the noninvasive imaging test of choice for patients with suspected coronary artery disease. However, approximately 50% of the studies performed in the USA use thallium or a dual-isotope imaging protocols. This practice can expose patients to between 17 and 24 mSv of radiation. When technetium radioisotope is used, the radiation exposure may be lower (7–12 mSv) [19] but still exceeds the mean radiation dose of modern CT scanners.

In the CT, the radiation exposure is dependent on the scan parameters utilized. The tube current, scan time, and peak tube voltage (kVp) are major contributors to the effective radiation dose. If cardiac CT can consistently generate diagnostic images with low radiation exposures, it will be considered the imaging method of choice for a broad spectrum of clinical questions (e.g., suspected coronary artery disease).

Reduction of the radiation exposure can be achieved by several methods. The exact determination of the scan length and narrowing of the field of view can reduce the radiation dose directly. Alteration of scan parameters such as the kVp and mAs can lead to a furher dose reduction. For example, if using the retrospectively gated technique, a reduction of the tube current from 120 to 100 kV can result in a substantial reduction of the radiation dose of 8.8–16.9 mSv for 120 kV and 4.9–11.9 mSv for 100 kV [20]. A reduction in mAs from 300 to 150 could reduce the dose by 50%. Especially in the last decade, the radiation dose associated with cardiac CT has dropped significantly with the introduction of novel dose-saving technologies and strategies such as the prospectively triggered high-pitch image acquisition, the tube current modulation in retrospective protocols, and the BMI-tailored tube voltage (often $\leq$100 kVp). Furthermore, post-processing techniques, such as the iterative reconstruction, can improve the image quality in low-dose scans and make these diagnostic even at initially high image noise.

The ECG-controlled tube current modulation reduces the tube current between 4% and 25% of the nominal value but restores the maximal current at a time point pre-specified as optimal for coronary artery imaging. High-quality images can be acquired at a single time point at the cost of noisier images at other phases. Similarly, sequential prospectively triggered protocols can reduce the radiation exposure by reducing the overlap associated with retrospectively gated spiral scanning. These studies provide ultralow radiation doses but at the potential expense suboptimal image quality for interpretation [21].

A multicenter observational study [22] (PROTECTION 1) demonstrated a wide variation in the effective radiation exposure in patients who underwent cardiac CT. Significant factors that influenced the dose included patient weight, scan length, lower tube voltage 100 kV versus 120 kV, tube current modulation, and sequential versus spiral protocols. Tube current modulation or sequential prospectively triggered scan protocols should be considered for all cardiac CT examinations. The radiation dose for CTA that utilizes automated

dose reduction protocols may be as low as 1–10 mSv. In the Protection 1 study, 70% of examinations were performed using these dose-sparing algorithms. However, the median radiation dose for a cardiac CT was found to be 12 mSv. Due to the recent introduction of radiation-sparing algorithms, clinical practice has already changed. Future dose reductions may be achieved by improved detector efficiency, advanced organ shields, advanced filters, and post-processing algorithms using perhaps artificial inteligence to reduce image noise.

26.6 Post-processing

There is a variety of post-processing techniques to edit and to evaluate the cardiac CT data. The right choice of a method is crucial for the success of the imaging and depends strongly on the clinical question. In general, axial images are considered the source data, and axial scrolling is considered the cornerstone for the evaluation of every cardiac CT study. It is recommended to create multiplanar reconstructions (MPR) from a stack of axial images. These MPR images can be easily generated and can be displayed in axial, sagittal, and coronal views. Additional MPRs, specific for cardiac imaging, can be useful as displayed in Fig. 26.7 including reconstructions in two-, three-, and four-chamber views as well as a view of the short axis. These views are useful mainly for the evaluation of cardiac function as commonly used in echocardiography and magnetic resonance imaging (MRI). Curved multiplanar reconstructions (cMPR) are a feasible method to display vessels and allow the tortuous longitudinal course of a coronary artery to be displayed in a single image. Importantly, the curved MPR utilizes an algorithm that distorts the natural anatomical geometry. Coronary artery stenosis quantification using this technique may lead to misinterpretation of the anatomy. Assessment should always be performed or at least validated in at least two orthogonal planes. In maximum intensity projections (MIP), voxels with the highest attenuation values are utilized to create the final 2D images, which can often display long parts of the coronary artery segments (Fig. 26.9). This technique is particularly useful when non-coronary structures obscure coronary artery visualization. The high-density contrast within the lumen can be extracted and the rest of the non-contrast-enhanced data discarded. MIPs should not be used when coronary artery calcifications are present. The calcium frequently is of a comparable or higher density than the coronary artery lumen. The calcium will be most prominent, and the lower-density lumen or non-calcified atherosclerotic plaques will be obscured. Therefore, MIP can lead to an overestimation of calcified lesions and underestimation of non-calcified lesions.

Three-dimensional volume-rendered images of the heart are visually impressive. They provide a quick overview of the cardiac anatomy and are useful for displaying of complex anatomic structures or variants. As shown in the example Fig. 26.10, image voxels can be linked to specific attenuation values based on major tissue densities. The operator has full control over the voxel number, color, and opacity. Therefore, the final image can be adjusted to make certain types of tissue more prominent (e.g, color) or transparent as required.

For stenosis quantification, two 3–6-mm-long orthogonal MPRs should be reconstructed. A comparison of the

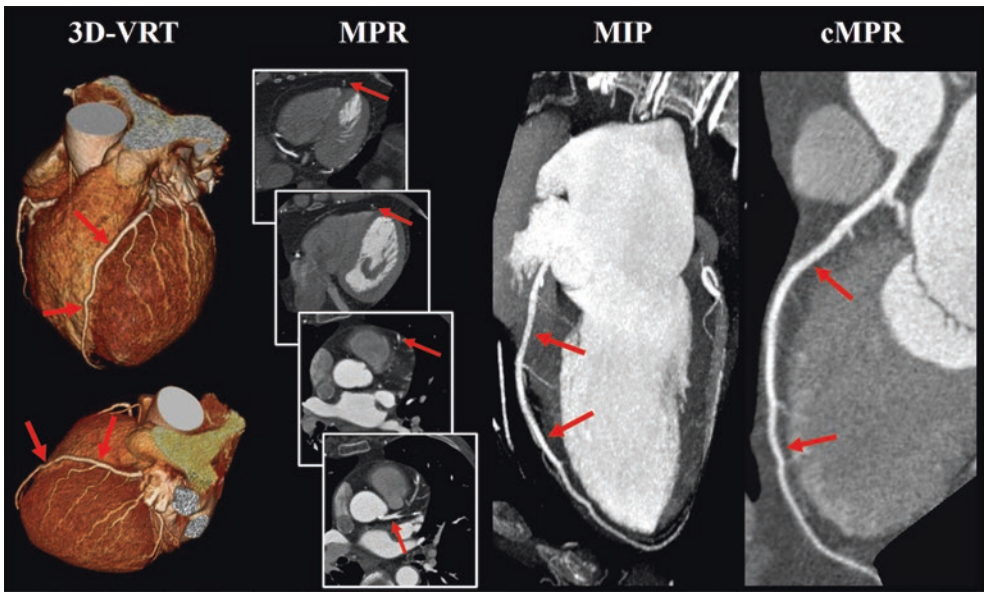

Fig. 26.9 Most common post-processing techniques for visualization of the coronary arteries, here LAD (red arrows). *3D-VRT* 3D volume-rendering technique, *cMPR* curved multi-planar reconstruction, *MIP* maximum intensity projection, *MPR* multi-planar reconstruction (here with an example of axial scrolling)

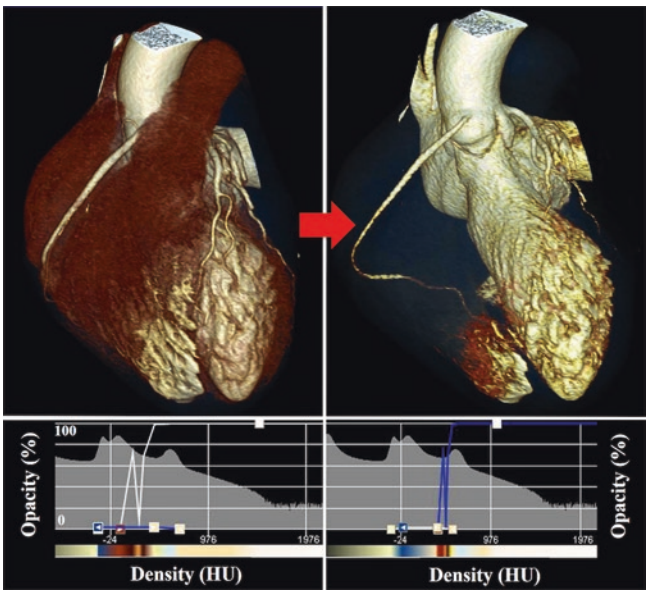

Fig. 26.10 Volume-rendering technique. Example of controlling voxel opacity resulting in hiding/visualization of the right ventricle

Table 26.3 The severity of stenosis in the CTA according to the stenosis grade (SCCT) [12]

Degree of luminal diameter stenosis (%)	Terminology
0	No visible stenosis
1–24	Minimal stenosis
25–49	Mild stenosis
50–69	Moderate stenosis
70–99	Severe stenosis
100	Occlusion

lumen size proximal and distal to the stenosis should be made and defined as a percentage diameter stenosis. Every stenosis should be proofread in at least two other MPR planes. Regarding the stenosis severity, SCCT guidelines from 2016 recommend using a scale as described in Table 26.3.

Using this scale enables recommendations for further diagnostic and therapeutic approaches as described in the CAD-RADS™ classification [12]. This clinically orientated classification includes recommendations for acute as well as stable chest pain patients and gives the physician an idea about further clinical approach based on individual coronary CTA findings. CAD-RADS™ contains Grades 1–5 ranging from recommendation to discharge the patient and search for extra-cardiac sources of the chest pain (Grade 1) up to immediate invasive approach and revascularization (Grade 5). Furthermore, the CAD-RADS™ classification provides information about image quality, stents, bypass grafts, and the presence of high-risk plaque features, which are described in detail in Sect. 26.8.4.

26.7 Cardiac CT Artifacts

Image artifacts are multifactorial (Fig. 26.11). Technical limitations of the current generation of CT scanners, limitations in scan protocol preparation, and patient-related factors can all conspire to reduce the image quality and consequently influence the diagnostic accuracy.

Coronary arteries are submillimeter structures that require the highest possible spatial resolution for accurate analysis. The current technology reaches a spatial resolution of 0.26–0.6 mm. An optimal quantitative stenosis assessment would require a spatial resolution under 0.2 mm.

In order to freeze cardiac motion, the temporal resolution must be higher than the speed of the natural cardiac motion. The cardiac CT exploits the physiology of the cardiac cycle. Images are optimal if acquired at low heart rates (< 65 bpm) and captured or reconstructed at the end-systole or mid-diastole. These time points represent the period of least cardiac motion. For robust cardiac CT imaging, the next generation of scanners will require a temporal resolution of < 50 ms. At this time, commercially available systems reach temporal resolution up to 66 ms.

Furthermore, respiratory and involuntary patient movements contribute to motion artifacts. The cardiac motion includes excessive heart rate variability and arrhythmias. Adequate heart rate control pre-procedure can be achieved with the administration of negatively chronotropic medication (see 26.4.5). Heart rates < 65 bpm provide an optimal diastolic window for data acquisition. ECG editing can facilitate the removal of short-lived extrasystoles or arrhythmias from the final data set that is utilized for image reconstruction. Scanners with a high temporal resolution and systems with large detectors with full-volume coverage achieve diagnostic image quality without motion artifact even at higher heart rates. Respiratory motion can be avoided by careful patient instruction and breath-hold practice. There must be an adequate delay between breath-hold instruction and scan initiation. Barriers to comprehension such as language difficulties and auditory impairment can be overcome with appropriate planning. A shallow breath is all that is required, and it is necessary that the Valsalva maneuver is prevented. Patients that are dyspneic when supine can be oxygenated.

Involuntary patient motion can be avoided by education, optimization of patient position, and increased awareness of the usual sensation of contrast administration, and stressed patients can be given water to avoid throat dryness and cough reflex.

Poor contrast enhancement of the coronary arteries can occur as a consequence of inappropriate and small-caliber cannula placement allowing only small injection rates, contrast extravasation, low-contrast injection rate, insufficient contrast concentration and volume, and inaccurate scan triggering. All of these factors can be avoided with appropriate attention to protocol planning.

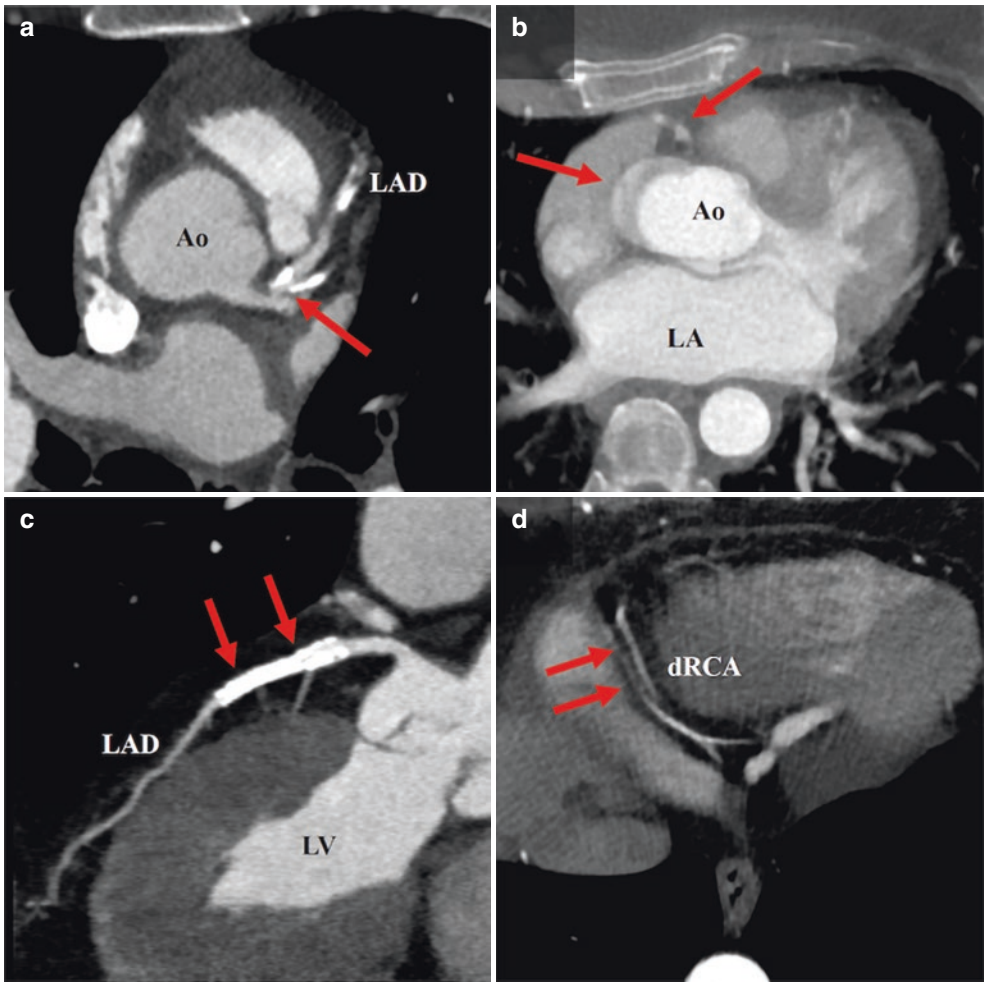

Fig. 26.11 Cardiac CT artifacts. (**a**) Calcification. Sheet calcification limits visualization of the vessel lumen (red arrow). (**b**) Extrasystole during the scan creates a step artifact in the reconstruction of the aortic root and the proximal RCA (red arrows). (**c**) Foreign body-related artifacts. For instance, a stent-related beam hardening in the LAD (red arrows) might hinder the evaluation of the vessel lumen, especially in smooth kernel images. (**d**) Too high heart rate leads to motion artifacts (red arrow) predominantly in the RCA. *Ao* aorta, *dRCA* distal right coronary artery, *LA* left atrium, *LAD* left anterior descending, *LV* left ventricle

Even though the radiation dose reduction is vital, a low dose that contributes to a poor contrast-to-noise ratio and leads to uninterpretable images is unacceptable and might expose patients to further testing that may not otherwise be required.

Finally, high-density structures such as calcium, pacemaker wires, intracardiac occluder devices or stents, and surgical clips may cause beam-hardening artifacts. Increased tube current and the utilization of an appropriate reconstruction filters can limit the impact of this artifact on the final data set.

26.8 Indications for Cardiac CT

Comprehensive guidelines for the clinical utilization of the cardiac CT were issued in 2006 and updated in 2010 [23]. They are summarized in the following top cardiac CT indications.

26.8.1 Emergency Assessment of Acute Coronary Syndromes and Non-specific Chest Pain

Chest pain is one of the most frequent causes of presentation to the emergency department accounting for 9% of all entries in 2007–2008 revealing ACS only in 13% of these patients [24]. Thus, five million emergency department visits result in two million hospitalizations at the cost of $8 billion. While over 60% of admissions are not cardiac, 2% of emergency department discharges are cardiac. Therefore, a rapid and effective method to identify or rule out obstructive CAD and acute coronary syndrome (ACS) is highly desirable [25].

The high negative predictive value of cardiac CT for the early detection of CAD makes it an attractive tool to rule out myocardial infarction. Cardiac CT received the rating of "appropriate" in the recent guidelines (2015) for patients with low- to intermediate pretest probability [26]. Patients with a high pretest probability should undergo invasive diag-

nostic testing to enable a quick intervention if necessary. Ten years ago, the utility of cardiac CT was reported in three single-center studies showing a high accuracy of cardiac CT for ruling out myocardial infarction in patients with low- and intermediate probability entering emergency department [27–29]. More recent scientific evidence is presented by three large multicenter, randomized trials; Rule Out Myocardial Infarction using Computer Assisted Tomography II (ROMICAT II) [30]; Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment (CT-STAT) [31]; and the Randomized Controlled Study of a Rapid "Rule Out" Strategy Using CT Coronary Angiography vs. Traditional Care for Low-Risk Emergency Department Patients with Potential Acute Coronary Syndromes (American College of Radiology Imaging Network, ACRIN-PA) [32]. All three trials together have included > 3,000 patients, provided the highest level of evidence, and consistently demonstrated the safety of CAD exclusion by CT (i.e., completely negative or mild CAD; stenosis < 50%) in an emergency room setting. Patients screened by the CT could be discharged faster at significantly lower costs compared to the standard of care. Moreover, the MACE rates in the follow-up were low and did not differ between the CT and the standard of care strategy.

The Acute coronary syndrome is only one of the numerous causes of non-specific chest pain. An alternative strategy for patients with non-specific acute chest pain is the comprehensive thoracic CT evaluation also known as "triple rule-out" CT. This protocol facilitates the rapid rule-out of the major cardiothoracic causes of chest pain including simultaneous evaluation of ACS, pulmonary embolism, and acute aortic syndrome, all (Fig. 26.12). The particular advantage of CT is the possibility of a rapid evaluation of all three aspects with a high accuracy in excluding these potentially life-threatening conditions [33–35]. Disadvantages of the triple rule out approach are the relatively high radiation dose and high contrast volumes due to the inclusion of the entire thorax in the scan. However, in several large studies, the mean radiation dose did not exceed 10 mSv [36]. Furthermore, higher amount of nondiagnostic images of the coronary arteries (9.6% vs. 6.5%; $p < 0.001$) was observed compared with the regular CTA [36]. Despite these disadvantages, triple rule-out CT reaches similar accuracy in the diagnosis of CAD compared to the CTA with a sensitivity of 94.3%, specificity of 97.4%, and negative predictive value of 99% [37]. Moreover, the triple rule-out has a higher diagnostic yield in identification of pulmonary embolism and aortic pathologies through the larger *z*-axis coverage of the thorax [34]. These studies emphasize the usefulness of using triple rule-out strategy in the emergency setting to evaluate patients with unspecific chest pain. Nevertheless, studies showing a clear advantage in outcome justifying the higher radiation exposure and longer post-processing times are still missing.

Further prospective trials are required; however, a synergistic cardiac CT and biomarker strategy for the rapid assessment of emergency department chest pain appears to hold significant promise. The increasingly used high-sensitivity troponin (hsTn) is a reliable tool in early detection of ACS in the emergency department and might shift the role of the CT to secondary, comprehensive rule-out test in case of inconclusive biomarker status [38]. However, high-level evidence of diagnostic accuracy of the hsTn is still missing.

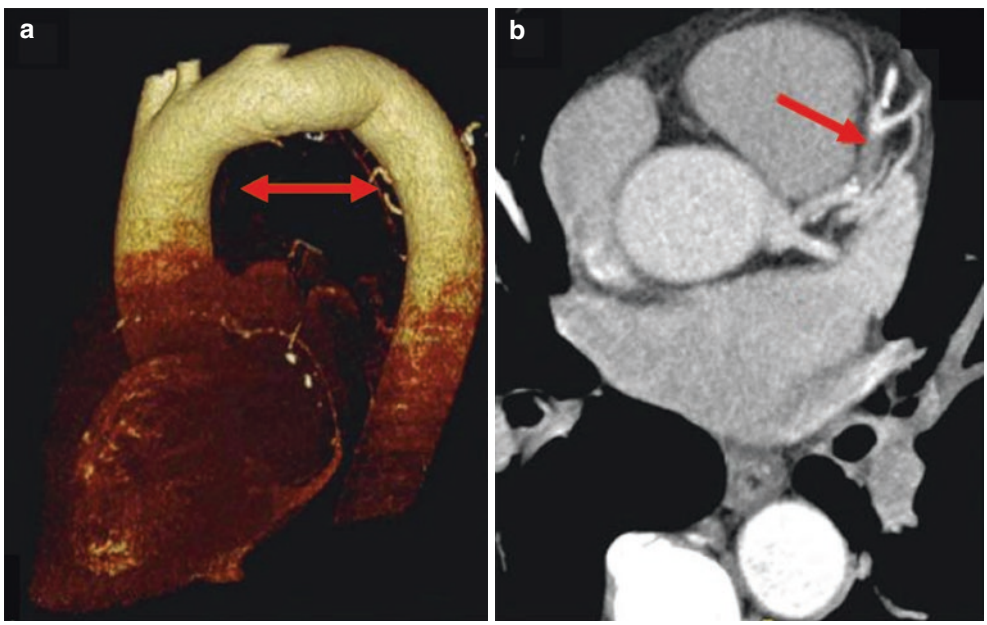

Fig. 26.12 CT for the triage of acute chest pain. A 46-year-old male, no conventional risk factors for CAD. Acute presentation to emergancy department 40 min after the onset of chest and back pain. No ECG changes, CXR suggested a widened mediastinum. Comprehensive cardiac CT demonstrated an unfolded aortic arch (double arrow in the panel **a**) and an acute occlusion of the proximal LAD (single arrow in the panel **b**)

26.8.2 Elective Assessment of Native Coronary Artery Disease

Coronary artery disease presents as chest pain or exertional angina in 50% of patients. The prevalence of non-specific chest pain is much greater than the incidence of typical angina. The need for further assessment of chest pain to rule out an obstructive CAD is determined by the physician, based on the characteristics of symptoms and the patient's pretest probability of underlying CAD (Table 26.4). The majority of patients that present clinically are considered to be at intermediate risk of CAD and further merit investigation. Notably, the routinely used pretest probability tables are based on data from populations referred to invasive testing; in general a group of patients with increased risk for having an obstructive CAD. Thus, these pretest probability tables may overestimate the actual prevalence of obstructive CAD in patients referred to non-invasive tests.

The niche for cardiac CT in this patient population is continuing to evolve. Established noninvasive tests such as dobutamine stress echocardiography and myocardial stress perfusion imaging using single-photon emission CT are well validated, clinically reliable and inform clinical decisions. However, they are not without limitations; they provide functional rather than anatomical information, and high interobserver variability rates have been reported.

The invasive coronary angiography (ICA) remains the gold standard for the assessment of patients with suspected obstructive CAD, but 60–80% of all angiograms demonstrate no evidence of obstructive CAD and remain diagnostic. Cardiac CT has evolved rapidly in the last 20 years, and fast advances in technology have required repetitive validation studies with each technical breakthrough. The advent of 64-detector CT technology has ushered in an era of technical stability, and numerous studies have reported on the clinical efficacy of this technique. The development of the 64-detector CT has significantly increased the accuracy of the test. After the introduction of the 64-slice CT between 2002 and 2006, the negative predictive value of coronary CTA has increased rapidly, and the number of unnecessary invasive angiographies was reduced by approximately 30% [40]. Spatial and temporal resolutions have improved even more by introducing scanners with full coverage of the heart and scanners allowing ultrafast image acquisition. Numerous large multicenter randomized clinical trials have tested the outcomes of symptomatic patients with intermediate pretest probability tested for the presence of CAD. The latest trial (PROspective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE)) has shown no inferiority of cardiac CT in comparison with functional testing as a standard reference in a 2-year follow-up [41].

Cardiac CT can accurately identify coronary artery anatomy and determine the extent of coronary artery stenosis severity. The consistently high negative predictive value allows significant coronary artery pathology to be reliably excluded.

Symptomatic patients who are considered to have an intermediate probability of CAD or even patients with low probability who are not able to exercise, have uninterpretable ECG or positive biomarkers in combination with normal ECG should be considered suitable for coronary CTA [23].

Accurate coronary artery stenosis quantification by cardiac CT is a greater challenge (Fig. 26.13). Several studies have demonstrated the feasibility of this technique in both calcified and non-calcified atheromas. The degree of stenosis as assessed by the coronary CTA correlates moderately with the intravascular ultrasound (IVUS) and ICA [42, 43] and can be improved by dedicated tools evaluating the plaque composition [44]. CT can accurately quantify the stenosis grade in coronary arteries with a caliber exceeding 3 mm. For vessels < 3 mm, correlation with conventional angiography is weak due to the limited spatial resolution. The plaque composition also appears to influence stenosis assessment. There is also a weak correlation if the plaque is predominantly calcified, a moderate correlation for non-calcified plaque, and a good correlation for partially calcified plaque [45].

If the coronary CTA images are evaluated qualitatively, and only stenosis grade is measured, in many cases, clinicians remain unclear about the functional relevance of the lesion. Myocardial perfusion imaging (MPI) is considered the noninvasive investigation for the determination of hemodynamically significant coronary artery stenosis. Patients with stable angina and normal MPI findings have a low risk for future cardiac events [46]. This is valuable information that guides the clinical management. Regarding CT lesion severity compared with MPI, in general, if cardiac CT demonstrates a lesion < 50%, then functional ischemia is rare. If the CTA detected a lesion > 75%, then functional ischemia at MPI is frequently observed. For intermediate lesions by CT, 50–75% hemodynamic significance by MPI can be observed

Table 26.4 Pretest probability for having an obstructive CAD [39]

	Typical angina		Atypical angina		Non-anginal pain		Asymptomatic	
Age	Men	Women	Men	Women	Men	Women	Men	Women
30–39	Intermediate	Intermediate	Intermediate	Very low	Low	Very low	Very low	Very low
40–49	High	Intermediate	Intermediate	Low	Intermediate	Low	Low	Very low
50–59	High	Intermediate	Intermediate	Intermediate	Intermediate	Low	Low	Very low
>60	High	High	Intermediate	Intermediate	Intermediate	Intermediate	Low	Low

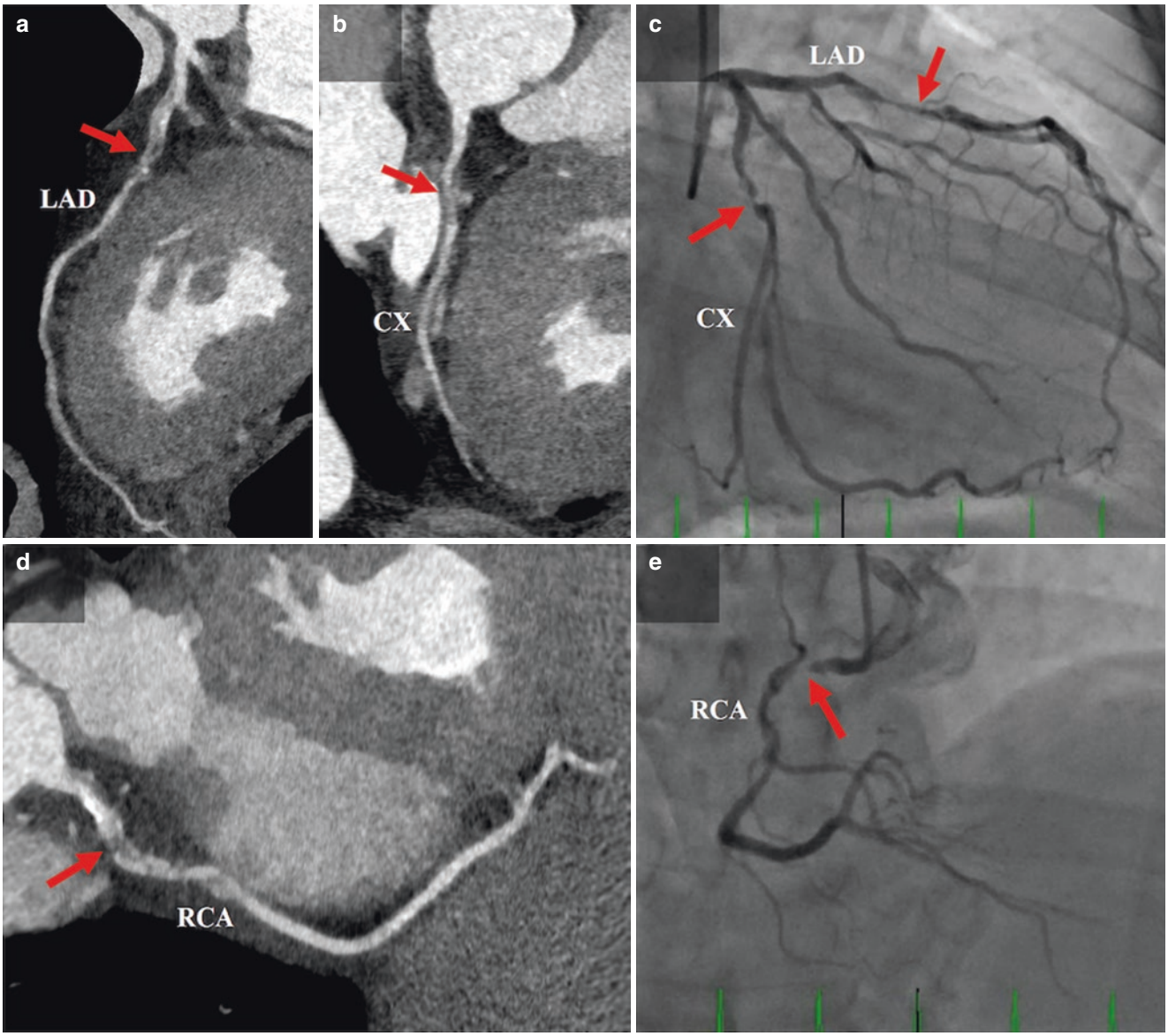

Fig. 26.13 Coronary stenoses detected by the CTA (**a**, **b**, and **d**) and the corresponding findings in the CTA (**c** and **e**). A 46-year-old male with atypical angina and corresponding intermediate pretest probability for having obstructive CAD. Three-vessel disease with a partially calcified plaque and a relevant stenosis in the mid-left anterior descending (**a** and **c**) as well as a subtotal stenosis of the proximal circumflex artery (**b** and **c**) and proximal right coronary artery (**d** and **e**). *CX* circumflex artery, *LAD* left anterior descending, *RCA* right coronary artery

in < 50%. Sato et al. found that the accuracy of CTA to define hemodynamically significant stenosis, applying a stenosis threshold of >70%, results in a 79% sensitivity, 92% specificity, 66% positive predictive value, and 96% negative predictive value [47].

Conventional wisdom suggests that a qualitative assessment of stenosis severity by the ICA may overestimate lesion severity by 20%. A study compared qualitative coronary CTA, quantitative coronary CTA, qualitative ICA, and quantitative ICA to the measurement of the fractional flow reserve (FFR). The diagnostic accuracies of the qulitative and quantitative CTA, as well as qualitative and quantitative ICA in detecting a hemodynamically significant coronary stenosis were 49%, 71%, 61%, and 67%, respectively. The correlation between CTA and ICA with FFR was weak [48]. With improving post-processing technology, especially after the introduction of the fractional flow reserve CT (FFR-CT), cardiac CT has increased its discriminatory capacity for identification of clinically relevant coronary plaques [49], and FFR-CT more than doubles the sensitivity regarding intermediate coronary lesions (37% vs. 82%) [50]. Therefore, an additional FFR-CT can reduce the number of unnecessary ICA by up to 61% resulting in only 12% of the ICA exams being diagnostic.

Improvements in the detector design, spatial resolution, and the development of CT-based stress protocols for the detection of regional wall motion and viability abnormalities are in the scope of the research and will keep revolutionizing the assessment of coronary lesions in the future.

26.8.3 Assessment of Coronary Artery Calcium

The amount of cCoronary artery calcifications is a surrogate marker of atherosclerotic plaque burden. High coronary calcium scores correlate with greater plaque burdens and are associated with higher cardiovascular event rates in asymptomatic population independent of traditional cardiovascular risk factors [51–53]. The assessment of coronary calcium burden is useful in asymptomatic patients thought to be at intermediate risk of a cardiovascular event. This is defined as a 10–20% 10-year risk of a cardiovascular event based on traditional risk factor assessment (i.e., Framingham Risk Score). There is no role for coronary calcium assessment in low- (<10%) and high-risk patients (>20%). Even if calcium scoring has been done before, a new calcium scan might be useful in symptomatic patients with low and intermediate likelihood and previous calcium score under 400. A calcium score of 0 indicates an extremely low probability of 3–5-year cardiovascular events, but the coronary artery calcium score of 0 in intermediate-risk patients should not reduce the therapeutic measures taken to reduce traditional risk factors (e.g., hypertension, hypercholesterolemia). In patients with atypical symptoms, the coronary calcium assessment may be helpful to rule out cardiac etiology. Patients with a dilated cardiomyopathy may have a calcium score to rule out an ischemic etiology. Finally, coronary calcium may be useful in the assessment of patients with acute chest pain and non-specific ECGs. A large meta-analysis reported an annualized event rate of 0.6% for calcium score of 0 [54]. Thus, a calcium score of 0 may find its way to risk stratification guidelines as a negative marker in the future [55]. However, the calcium score of 0 does not exclude CAD and should be followed by coronary CTA to exclude the presence of non-calcified plaques. Only in combination, CT reaches the high negative predictive value for excluding CAD.

Coronary calcification can be measured in non-contrast scans usually with 2–3-mm-thick slices as shown in Fig. 26.14.

26.8.4 Atherosclerotic Plaque Assessment and High-Risk Plaque Features

Coronary artery disease is the major cause of death in the western world. Rupture or erosion of vulnerable atherosclerotic plaques can result in MACE or sudden cardiac death. Identification and treatment of these plaques are crucial to prevent future events. Compared with stable lesions, vulnerable plaques present distinct morphology. Recently, with the help of cardiac CTA, several high-risk plaque features have been identified. Atherosclerotic lesions with the following structural characteristics are defined as high-risk coronary plaques (Fig. 26.15):

1. *Positive remodeling* (Fig. 26.15a) represents a thickening of the coronary artery wall, which occurs at the site of the atherosclerotic plaque during its eccentric growth, without a relevant or only with a slight narrowing of the arterial lumen. To identify and quantify positive remodeling, a threshold factor of 1.1 should be used, defined as the maximal diameter of the vessel at the level of the atherosclerotic lesion (II) divided by the average diameter of the vessel proximal and distal to the lesion (i.e., reference diamter).
2. *Low Hounsfield unit (HU) plaque* (Fig. 26.15b) is described as a non-calcified atherosclerotic lesion with low-attenuation areas within the plaque. Histological studies have shown that in most cases, these areas represent the lipid-rich necrotic core within a plaque. Low attenuation is defined as an average density of < 30 HU measured at three regions of interest (ROI) (approximately 0.5–1.0 mm^2) in the non-calcified low-density portion of the lesion.
3. *Spotty calcifications* (Fig. 26.15c) are small (< 3 mm), dense (> 130 HU) tissue areas within atherosclerotic plaques. In histological exvivo studies of coronary plaques, micro-calcifications were found in two thirds of the patients who have experienced sudden cardiac death. In general, to detect all micro-calcifications, which are often smaller than 1 mm, is not feasible yet in the CTA due to the limited spatial resulution.
4. *Napkin-ring sign* (Fig. 26.15d) is a qualitative feature and stands for a specific attenuation pattern in the cross-section of the coronary plaque. The napkin-ring sign is defined as a ring-like peripheral higher attenuation which surrounds a central hypodense core of a non-calcified plaque.

The combination of morphologic and functional features of coronary lesions might revolutionize the noninvasive identification of coronary plaques prone to rupture.

26.8.5 Elective Assessment of Coronary Artery Bypass Grafts

Coronary artery bypass grafts (CABG) are considered the best revascularization strategy for patients with multivessel or left main stem obstructive CAD. The ever-increasing prevalence of CAD leads to an increase of CABG procedures

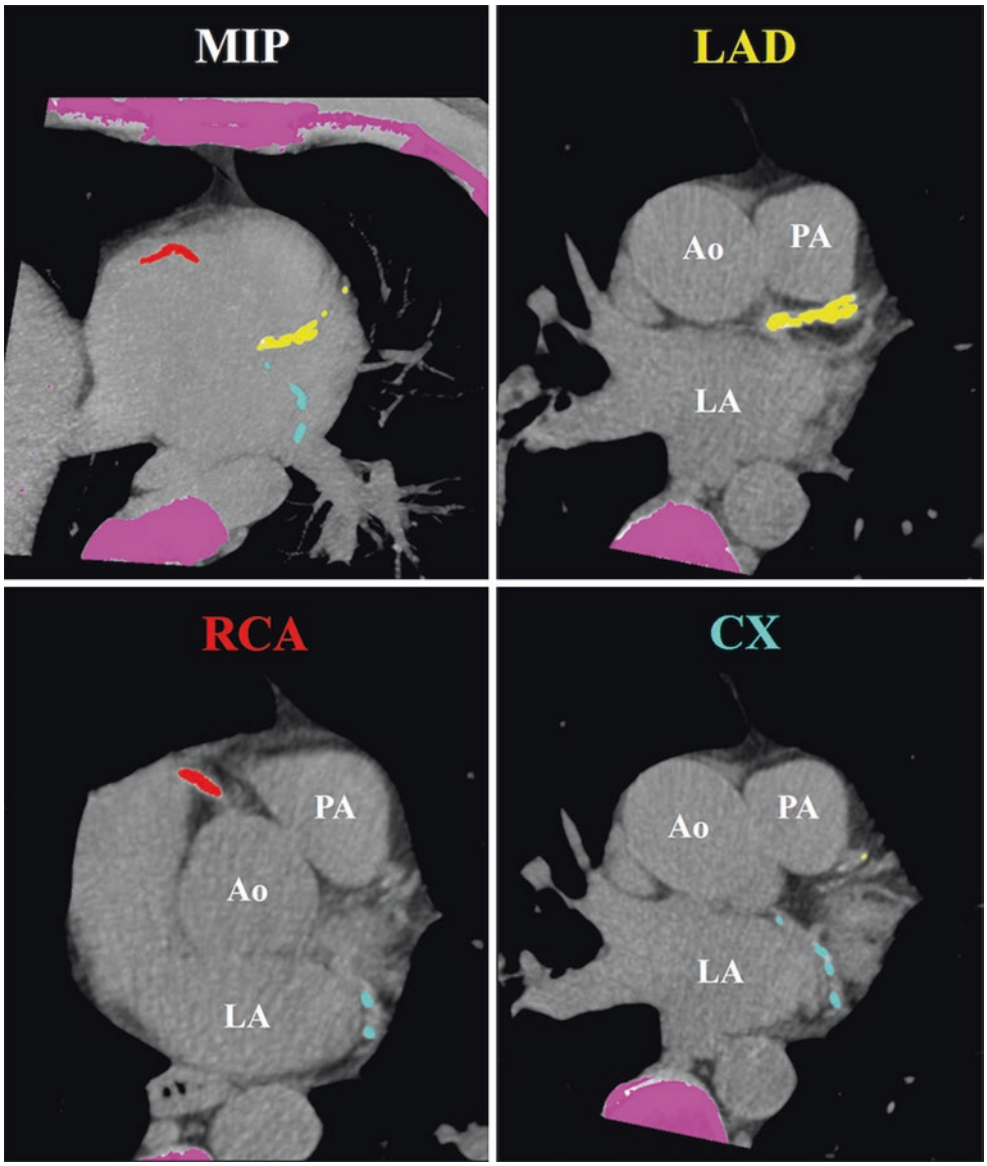

Fig. 26.14 Coronary artery calcium score. Non-contrast CT scan demonstrates calcium in the proximal left anterior descending (yellow), proximal right coronary artery (red), and circumflex artery (blue). *Ao* aorta, *CX* circumflex artery, *LA* left atrium, *LAD* left anterior descending, *PA* pulmonary artery, *RCA* right coronary artery

[56]. Graft occlusion rates can exceed 20% in the first year after surgery and are thought to occlude at a rate of 4% per year after four years. Graft occlusion is a major cause for readmission after surgery, and late survival after CABG strongly depends on graft patency and, therefore, indirectly on appropriate follow-up [57]. Invasive catheter angiography in these patients can be difficult. Vascular access limitations, poor catheter engagement of the grafts, prolonged screening times, and significant morbidity and mortality risk have made cardiac CT an attractive alternative. Cardiac CT has become a reliable alternative for ruling out stable CAD in patients with low to intermediate pretest probability and is a level IIa recommendation in recent international guidelines [58]. Parallel cardiac CT has been established well to access CABG patency [23] (Fig. 26.16).

Conventional CT platforms have demonstrated the feasibility of CT for imaging coronary artery bypass grafts [59–65]. Initial results demonstrated that the proximal anastomosis site could be assessed, but no information could be reliably obtained on graft stenosis or the distal anastomosis site (one of the most frequent areas for disease recurrence). Improvements in CT technology have created increasing interest in CT evaluation of grafts. Saphenous vein grafts are less challenging for CT than the native coronary arteries due to their large caliber, thin wall, the absence of calcified atheroma, and relative immobility. Arterial grafts, however, continue to be challenging due to their size, tortuosity, mobility, and metallic clips. In patients where graft disease is considered, cardiac CT can rapidly identify the bypass graft anatomy and determine the suitability for percutaneous revascularization of the graft.

A meta-analysis of 12 studies, which were performed between 2006 and 2012, used 64-slice scanners and included 959 patients, demonstrated very high accuracy of the CT for

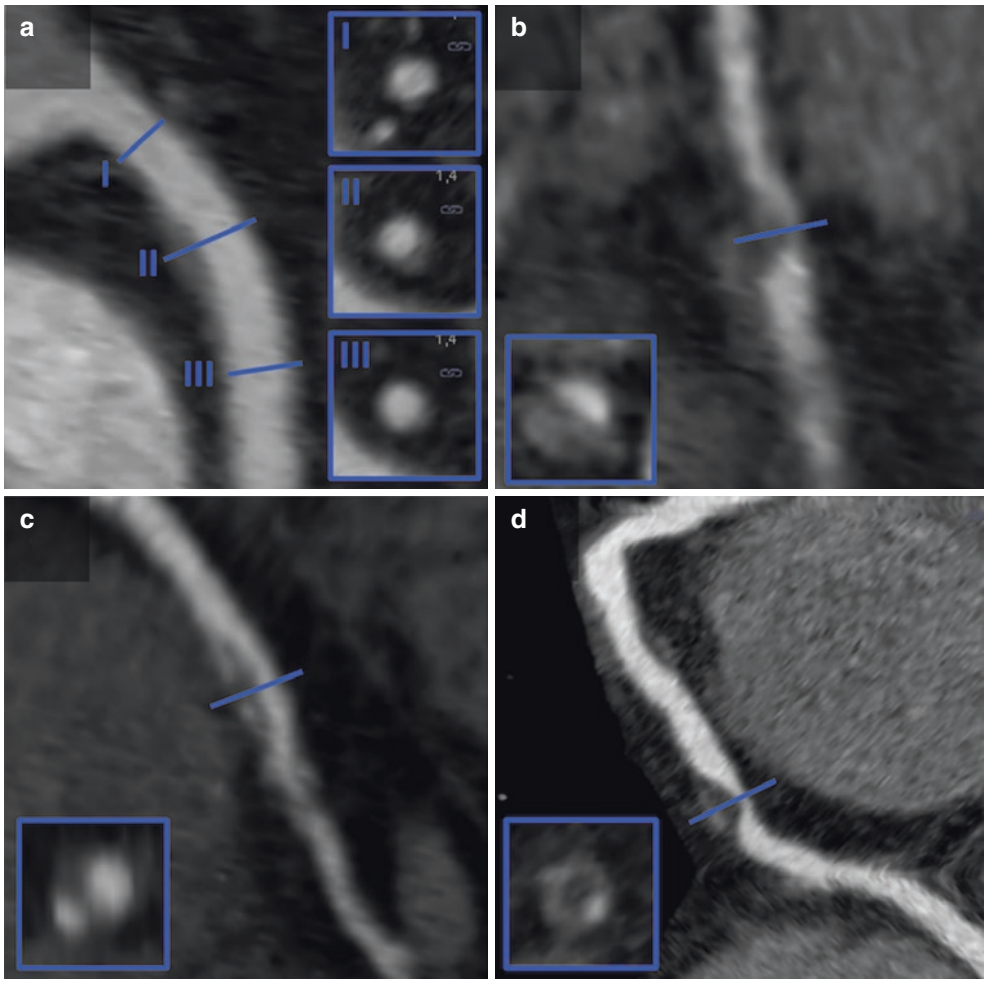

Fig. 26.15 Examples of high-risk coronary plaque features as assessed by CTA with corresponding cross-sections at the level of the plaque (blue lines). (**a**) Positive remodeling (I and III, reference cross-sections; II, cross-section at the level of maximal stenosis), (**b**) low attenuation plaque, (**c**) napkin-ring sign, (**d**) spotty calcifications

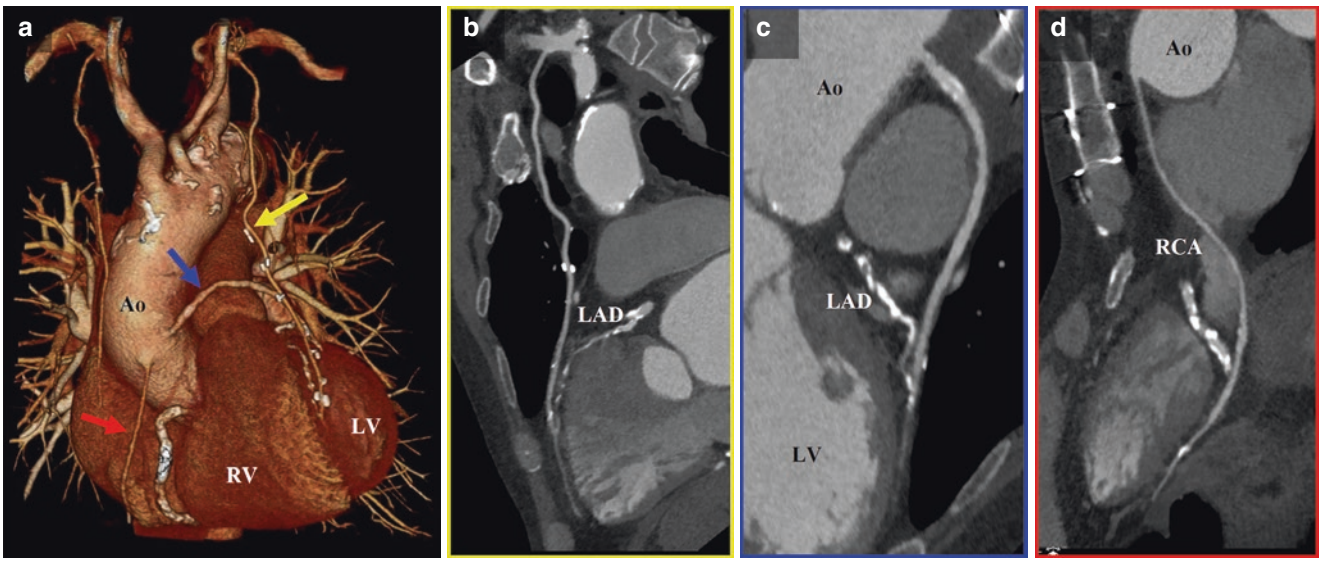

Fig. 26.16 Coronary artery bypass grafts. (**a**) 3D volume-rendered reconstruction and corresponding curved multiplanar reconstructions (**b**–**d**). There are three patent coronary artery bypass grafts; a saphenous vein graft to the RCA (red arrow, **d**), a saphenous vein graft to the LCX territory (blue arrow, **c**), and a left internal mammary artery graft to the distal LAD (yellow arrow, **b**)

the detection of graft obstruction (occlusion and > 50% stenosis). The sensitivity and specificity were both 99% for the detection of occlusion and 98% for detection of stenosis > 50% [66]. Accordingly, cardiac CT with at least 64 slices is a reliable noninvasive method to evaluate graft patency in patients with CABG.

26.8.6 Assessment of Suspected Coronary Artery Anomaly

Coronary artery anomalies are a rare form of congenital heart disease and are reported to affect < 0.1% of the general population. Although the majority of coronary artery anomalies are of no hemodynamic significance, a small proportion is responsible for 20% of all sudden cardiac deaths reported in individuals younger than 35 years of age [67–72].

An anomalous origin of a coronary artery from an opposite coronary sinus associated with an inter-arterial path (i.e., between the aortic root and pulmonary trunk), a single coronary artery, and a coronary artery fistula has all been associated with adverse cardiovascular outcomes. Basso et al. [68] demonstrated that, in as many as 30% of young athletes, symptoms could occur. They concluded that investigation should be mandatory, particularly in symptomatic athletes who are at highest risk of sudden cardiac death.

In the current context, there is no real consensus for the classification, investigation, management, and follow-up of these patients [73]. Most are detected at autopsy or coincidently at cardiac catheterization. Cardiac catheterization is invasive, and due to nonstandard anatomy, it is challenging even with appropriate catheter selection. The determination of the course of an anomalous artery will require multiple projections and experienced interpretation. In contrast, cardiac CT is noninvasive and can facilitate a rapid determination of the course of an anomalous coronary artery and thereby determine the significance if any (Fig. 26.17).

26.8.7 Transcatheter Aortic Valve Replacement (TAVR)

Cardiac CT has been increasingly utilized in the preoperative evaluation of patients who are to undergo cardiac surgery [74]. Within the last decade, especially, TAVR has become a frequent treatment in elderly and high- and intermediate-risk patients with severe aortic valve stenosis. Multiple prospective randomized trials have validated TAVR and have shown that this method is beneficial compared to medical therapy and reveals similar short-term and long-term outcomes in comparison to conventional surgical approach [75–77]. While open-heart surgery allows direct inspection and sizing of the aortic root, TAVR requires that anatomical structures are known prior to the procedure to allow adequate preprocedural planning. In contrast to the conventional aortic valve replacement, which is associated with prolonged operation time, frequent postoperative bleeding, and sternotomy-related complications, TAVR presents own spectrum of complications such as vascular injuries and a higher rate of strokes [77]. The outcome of TAVR patients relies heavily on the pre-

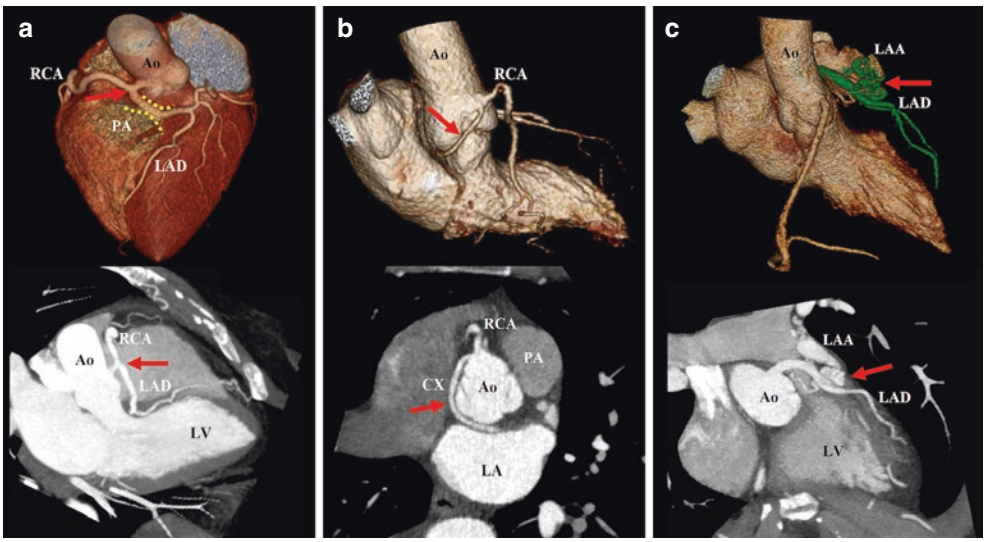

Fig. 26.17 Coronary artery variation and anomalies. (**a**) Left circumflex coronary artery which arises from the right coronary sinus together with the right coronary artery (red arrow). Potentially malignant, angina-causing variant with the left coronary artery, which crosses between the aorta and pulmonary artery (the area between scattered yellow lines). (**b**) The retro-aortic crossing of the circumflex artery, which arises from the left coronary sinus. (**c**) Fistula between left anterior descending (green) and left atrial appendage. *Ao* aorta, *CX* circumflex artery, *LA* left atrium, *LAA* left atrial appendage, *LAD* left anterior descending, *LV* left ventricle, *PA* pulmonary artery, *RCA* right coronary artery

procedural imaging [78]. Computed tomography is a powerful method in preoperative assessment of patients scheduled for TAVR. CT allows not only a precise sizing of the aortic annulus, which is crucial for the prosthesis selection but also allows evaluation of vascular access routes including detection of relevant calcifications and possible stenoses. According to a current expert consensus paper [79], the crucial measurement steps are shown in Fig. 26.18. Furthermore, cardiac CT enables the identification of significant CAD which is common (prevalence, 57%) in this specific patient group as described previously by Opolski et al. [80].

Both retrospectively gated and prospectively triggered protocols can be chosen for evaluation of patients undergoing TAVR. Prospective protocols achieve lower radiation doses but enable only imaging in a predefined cardiac phase. Lehmkuhl et al. have shown that the shape of the aortic annulus changes during the cardiac cycle and the effective diameter is at largest in the end-systole [81]. Therefore, this phase should be considered to determine the maximal effective diameter of the aortic annulus. Retrospective protocols allow reconstruction of the aortic root in all cardiac phases and enable even a functional analysis of the aortic valve, unfortu-

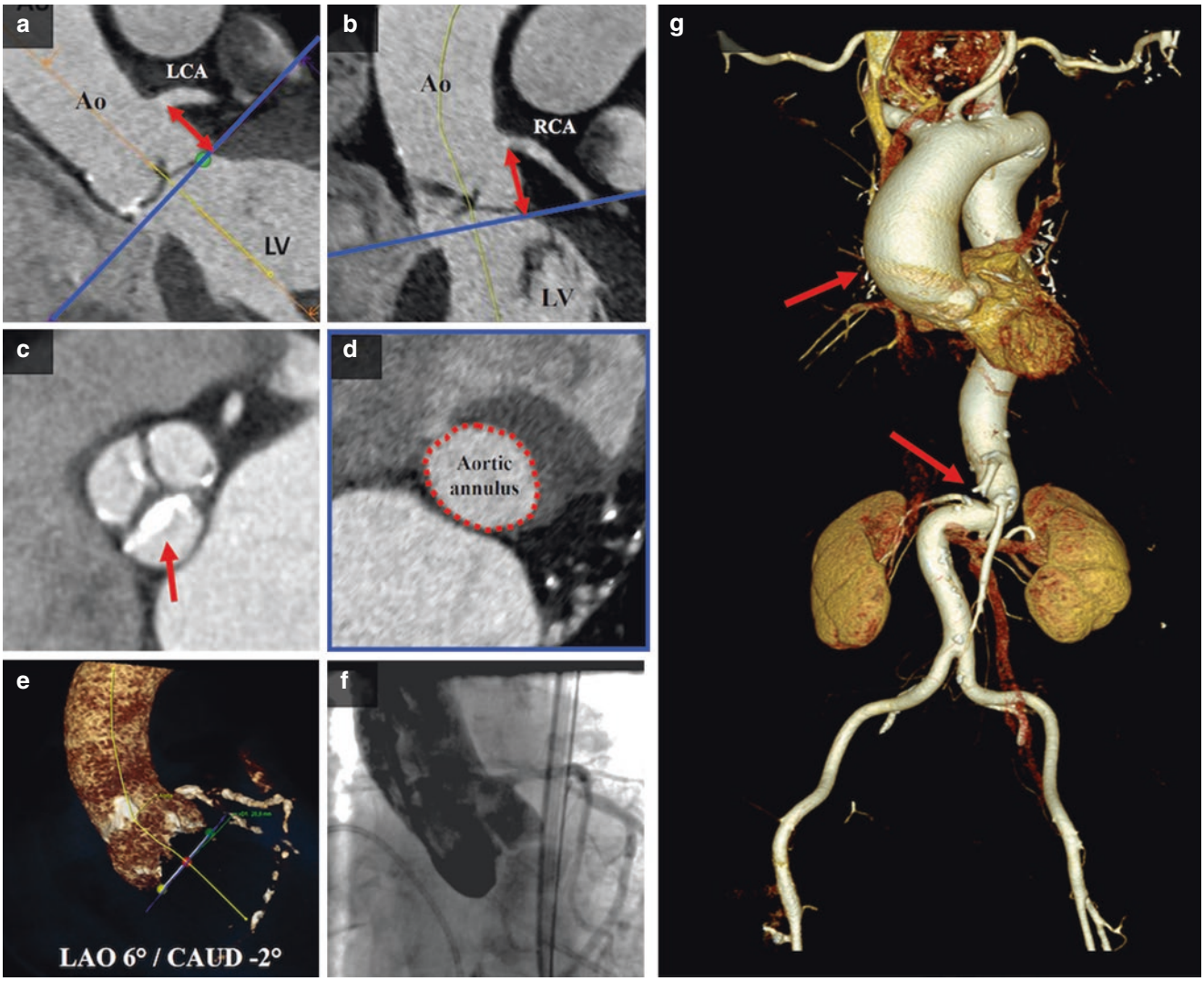

Fig. 26.18 Aortic root assessment before TAVR. MPR of the aortic root is displayed at the level of LCA (**a**) and RCA (**b**) with corresponding distances to the aortic annulus plane (red arrows). Panel (**c**) shows tricuspid aortic valve with extensive calcifications of the non-coronary leaflet (red arrow). The aortic annulus at the level of most basal hinge points of the aortic valve leaflets is shown in (**d**) with the corresponding measurement of its circumference/surface area (red dotted line) used for calculation of the effective diameter. The spatial orientation of the aortic annulus is displayed in the CT 3D-rendered image (**e**) and corresponding invasive aortogram (**f**). 3D-VRT of the entire aorta and iliac runoffs (**g**) is useful to visualize anatomic structures to detect possible TAVR contraindications, as in this example aneurysm of the ascending aorta and severe kinking of the juxtarenal aorta (red arrows)

nately, at the expense of higher radiation dose [82]. Radiation exposure is essential to consider with any CT examination but might be of less importance in the elderly patients undergoing TAVR.

This dedicated patient group often has reduced renal function, which makes application of contrast media critical. With ever-improving scanner technology including fast image acquisition and excellent post-processing techniques, the volume of contrast medium can be as low as 38 mL (350 mg Iodine/mL) [83]. CT-based acquirement of the spatial position of the aortic annulus speeds up the orientation at the beginning of the implantation procedure and reduces the number of required aortograms resulting in lower contrast usage and lower radiation exposure [84, 85].

26.8.8 Pulmonary Vein Isolation

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and a major risk factor for cerebrovascular ischemia. It is present in 10% of the population more than 80 years old and has a mortality rate twice that of control subjects. AF often presents with short self-terminating episodes of arrhythmia. Forty percent of patients develop persistent atrial fibrillation, which requires chemical or electrical cardioversion to restore the sinus rhythm. Half of these patients have a recurrent episodes within the first year and often develop a permanent AF. Atrial fibrillation is most commonly seen in structurally abnormal hearts especially those with enlarged left atrium; however, it may occur in normal hearts in times of stress, infection, or after stimulants such as caffeine, alcohol, cocaine, or amphetamines. Medical treatments with antiarrhythmic drugs, which can reduce the heart rate, suppress the arrhythmia recurrence. Refractory symptomatic atrial fibrillation can be treated by percutaneous or surgical ablation. Catheter-based pulmonary vein isolation (PVI) has become an established percutaneous procedure using the radiofrequency technique for isolating pulmonary veins at the level of the ostia [86]. Over 90% of AF arises from sleeves of ectopic atrial tissue found around the pulmonary veins (PV). Fifty percent of these ectopic foci originate from the left superior PV. The left atrium, including the PVs, is a complex anatomic structure (Fig. 26.19). Great inter-patient variability in the number, size, and branching of PV is known. Most common variants are the additional right PV in 18–29% of patients and common left pulmonary trunk in > 30% of patients [87]. Traditional imaging techniques such as echocardiography and pulmonary venography can be challenging to perform, and often only limited views of the PV can be obtained.

Cardiac CT can map the anatomical distribution of the PVs and left atrium both before and after the procedure; it can also assess the PV size, which can influence the size of the ablation catheter [88, 89]. Knowledge of the distance from the ostium of the PV to the first side branch is also helpful to the electrophysiologist as ablation within 5 mm of the ostium or the first bifurcation increases the risk for PV stenosis. Furthermore, CT enables evaluation of PV-neighboring structures such as the esophagus or periesophageal vagal nerves, which represent known sources of post-procedural complications such as mediastinitis if injured. These complications are somewhat rare in comparison to the more common PV stenosis, cardiac tamponade, strokes, and vascular complications. At least one of these major complications occurs in 3.9–6% of treated patients [90, 91].

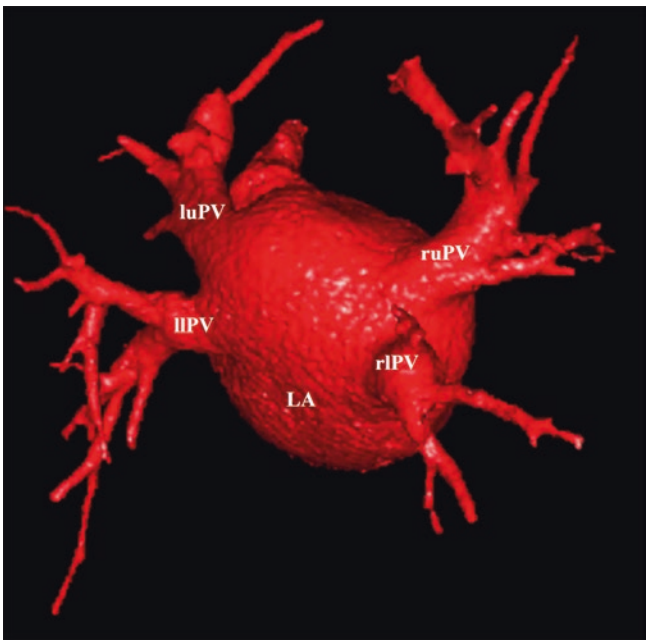

Fig. 26.19 3D volume-rendered reconstruction of cardiac venous anatomy showing all four pulmonary veins merging into the left atrium. *LA* left atrium, *llPV* left lower pulmonary vein, *luPV* left upper pulmonary vein, *rlPV* right lower pulmonary vein, *ruPV* right upper pulmonary vein

An additional benefit of the cardiac CT is the possibility to export preprocedural cardiac CT images directly into the ablation and electro-anatomic mapping systems helping to facilitate the ablation by providing patient-tailored information about the left atrial and PV anatomy. Specialized electrophysiology laboratories can fuse the anatomical CT information with the electrophysiological maps. This image fusion may improve the orienatition during the procedure and the success rate.

Due to limited movement of the left atrium and pulmonary veins during the cardiac cycle, ECG gating is not necessary. Nevertheless, prospectively triggered techniques enable rapid image acquisition and might reduce the required contrast volume. Atrial fibrillation can occur in younger and older patients; therefore, radiation exposure remains the limiting factor, and radiation dose-saving protocols should be used.

26.8.9 Left Ventricular Function

While radiation exposure and the high amount of contrast media remain an issue, cardiac CT is unlikely to replace echocardiography or MRI in the functional analysis of the heart. However, the CT may be a suitable option to determine cardiac morphology and function in subjects with poor acoustic images, limited echocardiographic windows, or contraindications for cardiac MRI. Usually, multiple image series within multiple temporal phases of the cardiac cycle are reconstructed. Ideally, these should be at 5–10% intervalls (i.e., time points) throughout the R–R interval. The end-systolic and end-diastolic time points are identified from the ECG and visually from images that identify the largest and smallest left ventricular cavity area and corresponding open or closed status of cardiac valves (Fig. 26.20).

CT utilizes two established methods to assess ventricular function. The area length method applied to long-axis images and the Simpson's method applied to short-axis views. The area length method utilizes the area (A) defined within the endocardial contour trace in long-axis two-chamber view and the length (L) from the left ventricular apex to the level of the mitral valve ring. The left ventricular volume (LV) is calculated by the following formula:

$$\mathrm{LV}_{\text{long axis}} = \frac{8}{3} \times \frac{A^2}{3.125 \times L} 3$$

Simpson's method utilizes the endocardial contours if the entire short-axis images of the left ventricular cavity. The cross-sectional area of each left ventricular image is calculated. Left ventricular volume is calculated by adding all the cross-sectional areas and multiplied by the distance between each slice thickness.

Left ventricular ejection fraction is calculated from the end-diastolic and end-systolic volumes and is given by:

$$\text{Ejection fraction}(\%) = \frac{\left(\mathrm{LV}_{\text{enddiastole}} - \mathrm{LV}_{\text{endsystole}}\right)}{\mathrm{LV}_{\text{enddiastole}}} \times 100$$

The correlation between cardiac CT, cardiac MRI, and gated myocardial perfusion imaging is good [92, 93].

26.8.10 Pericardial Assessment

The pericardium is a thin, two-layered structure that envelops the heart. The parietal and visceral pericardia are separated by < 50 mL of serous fluid. The pericardium reduces friction and limits infection between the heart and the adjacent mediastinal structures. In subjects with limited echocardiography windows, cardiac CT may be an attractive diagnostic alternative (Fig. 26.21). Pericardial effusions commonly develop with infection, myocardial infarction, cardiac dysfunction, and malignancy. Loculated pericardial effusions, particularly if located anteriorly, are difficult to identify by echocardiography. Attenuation values may help to differentiate the cause of the effusion. Increased values indicate fluid other than serous (e.g., blood). Cardiac CT may also be useful in assessing patients with suspected constrictive pericarditis. The presence of pericardial calcification, a pericardial thickness > 4 mm, reduced right ventricular

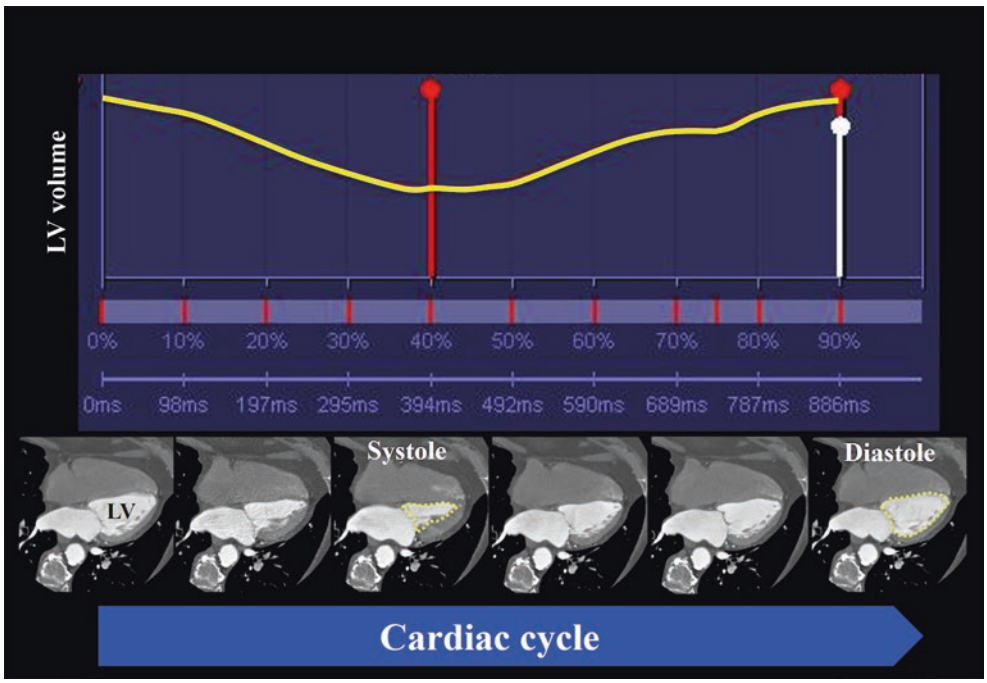

Fig. 26.20 Cardiac function can be assessed by the determination of the time points in the cardiac cycle that correspond to end-systole and diastole. Correct alignment along the cardiac axis and knowledge of the slice thickness allow for the determination of the stroke volume, ejection fraction, and cardiac output. Tracings of the endocardial (yellow dotted line) and epicardial contours facilitate the assessment of wall thickness and left ventricular wall mass. Cine imaging can determine regional wall motion abnormalities. *LV* left ventricle

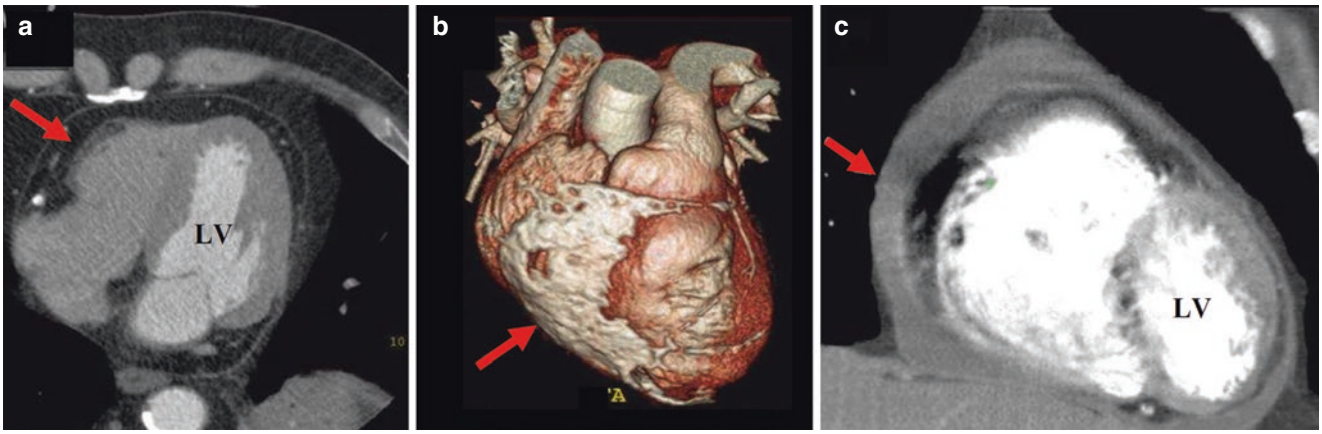

Fig. 26.21 Potential findings during the pericardial assessment. (**a**) Pericardial/epicardial fat, (red arrow), (**b**) extensive pericardial calcification (pericarditis constrictiva) (red arrow), (**c**) large circumferential pericardial effusion (red arrow). *LV* left ventricle

volume, a paradoxical septal bounce, and systemic venous dilatation may all correlate with a pericardial constriction in symptomatic patients. CT may be useful in the identification and characterization of pericardial cysts and neoplasm.

26.9 Emerging Indications

26.9.1 Virtual Histology of Coronary Plaques

The spatial resolution of current CT scanners is approximately 0.4–0.6 mm, and the most advanced scanners can reach spatial resolution up to 0.28 mm. The prerequisite increase in resolution to determine plaque composition comparable to conventional histopathological studies is becoming feasible. Cardiac CT can detect atherosclerotic plaque and qualitative markers of plaque vulnerability as described above. In a series of large multicenter prospective studies, cardiac CT was compared to IVUS for plaque detection. Cardiac CT could reliably detect atherosclerotic plaque with sensitivities of 83–96% [94, 95]. Calcified plaque can consistently be detected with sensitivities > 95%. Further plaque characterization is more difficult but possible and depends strongly on the image resolution and quality. Past studies have demonstrated that the differentiation of non-calcified plaque into lipid and fibrous by attenuation value is an oversimplification of the complexity of atherosclerotic plaque components [96]. There is significant overlap between fibrous and lipid plaque when compared to plaque identified on the IVUS. This in part is attributable to the arbitrary definition of atherosclerotic plaque to facilitate comparison between the CT and IVUS, and it is influenced by the contrast enhancement of the coronary artery lumen [97, 98]. Non-calcified plaque detection is limited by the reader experience, motion artifacts, image noise, amount of surrounding calcifications, and lack of exvivo validation. The plaque area, volume, and remodeling index defined by the CT have demonstrated a moderate correlation with IVUS.

Novel post-processing solutions have been introduced recently allowing a more detailed evaluation of coronary plaques [99, 100] (Fig. 26.22). Besides classical stenosis detection and visualization, these tools allow a quantitative assessment of plaque tissue characteristics. This new approach uses adaptive thresholds, which consider the attenuation of the coronary vessel lumen and make more accurate tissue differentiation possible. This kind of analysis reaches a good correlation compared to IVUS [44, 101, 102].

Numerous studies in the past have demonstrated that coronary CTA with high diagnostic image quality can detect and quantify surrogate qualitative markers of plaque vulnerability [103–105]. The use of virtual histology tools, especially in combination with images of a high spatial resolution, might bring plaque classification to an entirely new level by combining the traditional qualitative and the more reproducible quantitative assessment. Furthermore, the knowledge of the coronary plaque compounds and their specific volumes could improve drug monitoring, change treatment strategies, and might even make the development of targeted drugs possible.

26.9.2 Fractional Flow Reserve CT (FFR-CT)

Histopathological studies have shown that ruptured coronary plaques were commonly lesions with significant lumen narrowing at the time of the event [106]. Therefore, assessment of stenosis grade and its functional relevance might be an additional indicator for plaque vulnerability. As described above, with cardiac CT coronary stenosis can be measured directly using one or two reference vessel points proximal and distal to the lesion. Coronary lesions with a stenosis of > 75% are more likely to cause angina and get treated more

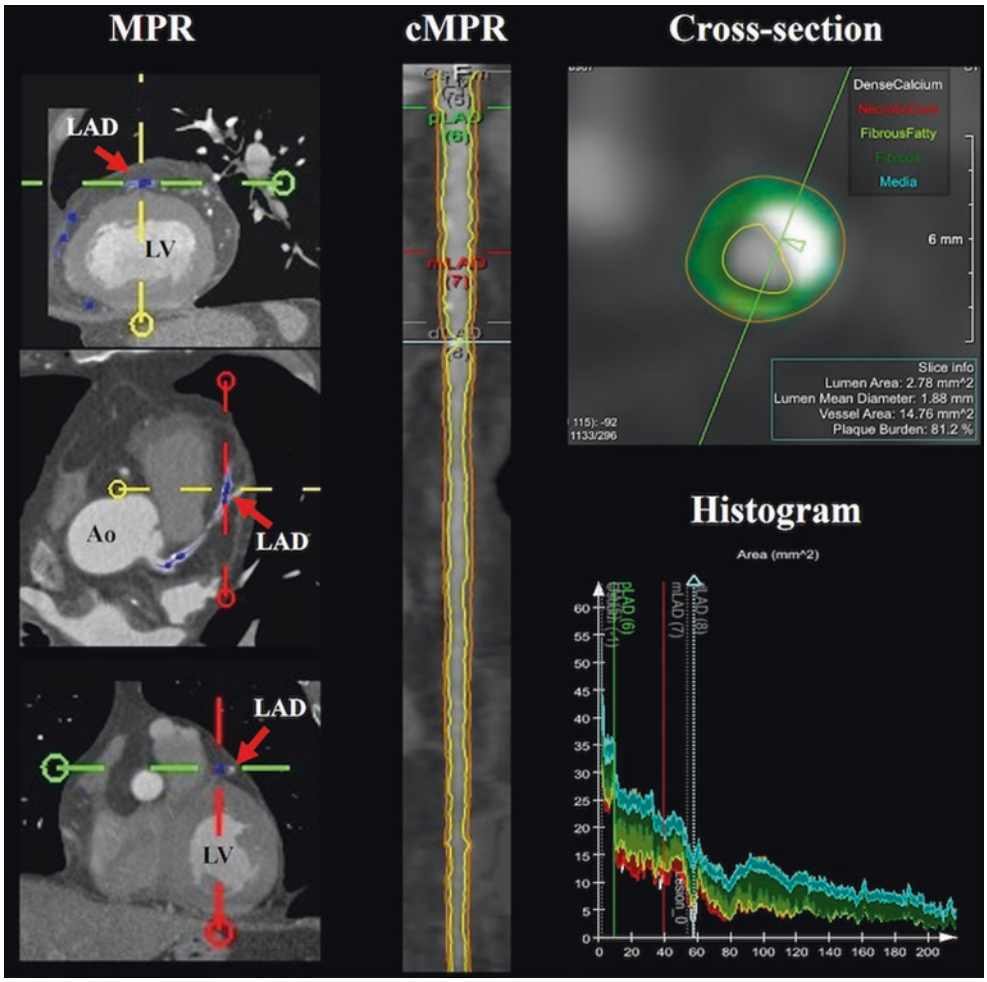

Fig. 26.22 Virtual histology plaque analysis consists of three major steps: 1) vessel identification and segmentation in MPR; 2) vessel visualization in the cMPR with corresponding tracing of the endo- and exoluminal contours (yellow and orange lines); and 3) final tissue characterization and volume analysis displayed as a histogram

frequently. Lumen narrowing < 50% is considered mild and is not likely to cause angina. The remaining intermediate (50–75%) lesions are often large but not necessarily associated with symptoms of angina and represent an appropriate target for noninvasive imaging for further investigation.

Invasive fractional flow reserve (FFR) measurements have shown that approximately half of intermediate coronary lesions lead to angina [107], and in a 5-year follow-up, < 1% of the patients with intermediate stenosis but without ischemia (FFR ≥ 0.8) develop myocardial infarction [108]. Furthermore, coronary lesions with pathological FFR often present with a disrupted blood flow and altered local shear stress on the initma of the coronary walls which might be responsible for the development of vulnerable coronary lesions [109].

Fractional flow reserve-CT, a new and promising method derived from coronary CTA without the need for additional imaging, has the potential to deliver similar results compared with the reference standard invasive FFR [49, 50]. Especially in combination with coronary CTA, FFR-CT improves the diagnostic accuracy in identification of clinically relevant coronary plaques [49], and FFR-CT more than doubles the sensitivity regarding intermediate coronary lesions (37% vs. 82%) [50]. Thus, FFR-CT improves the patient selection and can reduce the number of unnecessary ICA procedures by 61% [110]. An example of FFR-CT is shown in Fig. 26.23.

26.9.3 Perfusion Imaging

The computed tomography has shown to be a reliable and safe method to rule out CAD [26]. However, CT has only a limited specificity and positive predictive value, and the assessment of the functional relevance of stenosis, particularly of moderate lesions, remains difficult. Hybrid CT–PET and CT–SPECT scanners allow the combination of anatomical information acquired with CT and the functional information obtained from SPECT or PET. While these protocols facilitate high costs and require high radiation exposure and a considerable amount of expertise in both cardiac CT and nuclear imaging, the utilization of cardiac CT as a standalone test for myocardial perfusion has become a focus of research during the past decade.

Preliminary ex- and invivo studies have proved that the CT perfusion (CTP) is feasible to assess myocardial viability [111–117]. Ongoing improvements of the cardiac CT have led to accurate visualization of myocardial tissue and

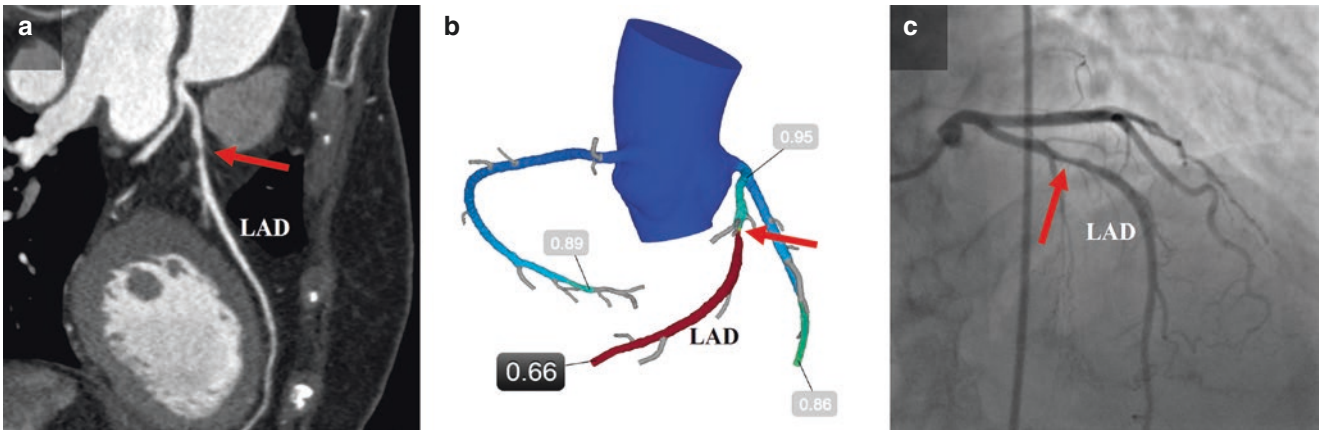

Fig. 26.23 Example of high-grade stenosis (red arrow) in left anterior descending. (**a**) Curved multiplanar reconstruction of the LAD. (**b**) CT-based virtual quantification of fractional flow reserve (CT-FFR). CT-FFR < 0.8 indicates hemodynamically relevant stenosis. Here 0.66 and displayed as the red part of the LAD. Panel (**c**) shows a corresponding finding in the ICA. *LAD* left anterior descending

corresponding iodine distribution. Cardiac CT allows to access myocardial perfusion defects in both acute and chronic myocardial infarction and can display late enhancement images comparable to MRI [118]. CTP provides comparable information to MRI and PET regarding myocardial viability [119, 120]. Especially, the combination of viability assessment, coronary CTA, and functional analysis might improve the identification of ischemia cause. MRI and nuclear perfusion imaging represent powerful and established tools to assess myocardial viability, but both mehtods provide only limited anatomical information.

However, the CTP evidence is still limited, and the recently published meta-analysis, which has revealed a high accuracy of the CTP to detect myocardial ischemia, had to rely on small-sized single-center studies and one multicenter study which was performed on various CT scanners and using different reference methods [121]. On the one hand, these studies demonstrate a promise, and on the other hand, technical limitations, namely, insufficient temporal resolution, beam-hardening artifacts, and relatively high radiation dose, need to be overcome before robust clinical CTP becomes reality. Low dose protocols using prospective triggering may substantially reduce the radiation exposure but at the cost of reduced contrast–noise ratio [122]. Nevertheless, a single imaging modality that could quickly determine both anatomical and functional status of the coronary arteries and myocardium could revolutionize the noninvasive cardiac imaging.

26.10 Cardiac CT Present and Future

Cardiac CT has evolved beyond the evaluation of coronary artery stenosis. CT has been increasingly used for investigation of suspected coronary anomalies, assessment of pulmonary veins, or evaluation of cardiac anatomy before operative procedures. In the recent years, new indications have found their way into the daily clinical routine including CT scans for evaluation of patients prior to minimally invasive aortic valve repair or assessment of coronary arteries in stable chest pain patients with suspected CAD and low or intermediate pretest probabilities. Especially regarding the coronaries, feasibility studies followed by large randomized controlled multicenter trials have consistently demonstrated that cardiac CT is robust, operator-independent, safe, and not inferior to other functional or invasive clinical tests in detection of obstructive CAD in patients with stable chest pain. Prognostic information comparable to that existing for alternative imaging modalities is highly desirable. Within the past years, promising reports have suggested that a normal coronary CTA is associated with a very low cardiovascular event rates. There appears to be a < 1% chance of a cardiovascular event in the subjects in a long-term follow-up. Additional prognostic information may be acquired by defining the location, extent, and character of coronary atherosclerotic plaques [123]. The consistently high negative predictive value of coronary CTA in excluding CAD (95–99%) supersedes existing noninvasive imaging. This, in addition to the left ventricular systolic function and regional wall motion abnormalities, may facilitate the development of a cardiac CT risk scores, which could influence but more importantly individualize patient management.

Scientific guidelines provide unequivocal recommendations for the standards on clinical competency and reporting, technical specifications, protocol selection for cardiac CT examinations, and appropriateness criteria/indications for cardiac CT examinations [3, 26, 58]. These are likely to be revised in the face of ongoing technological advances and the publication of prospective, multicenter clinical trials.

Manufacturers have addressed the concerns of high radiation doses with the introduction of advanced scanner technologies and scan algorithms that allow cardiac CT to be performed with exposures way less than 1 mSv. Further tech-

nical innovations in CT platform and detector design, in addition to advanced post-processing algorithms, may improve the spatial resolution under the currently available 0.28 mm. With the improvement of novel technologies such as photon counting the spatial resolution may keep improving and allow better tissue characterization or even molecular imaging in the near future. Even 4D flow measurements, based on CT data, are in the scope of the research and may allow better physiology assessment as well as preprocedural virtual simulations of cardiac changes after specific surgical procedures (e.g., valve replacement). Lastly, the recently introduced image postprecessing methods using artificial inteligence for improvement of image quality and risk stratification may revolutionize the way we use cardiac CT at the moment.

If this is achieved, cardiac CT will have "crossed the Rubicon," and a new era in noninvasive cardiac imaging and patient-centric treatment will be defined.

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Cardiac Magnetic Resonance Imaging

27

Róisín Morgan and Raymond Y. Kwong

27.1 Introduction

Heart disease is the leading cause of deaths in the United States [1]. Every year approximately 735,000 Americans suffer a myocardial infarction (MI). Of these, 525,000 are a first MI and 210,000 occur in people who have known CAD and a history of prior MI [2]. Approximately 5.7 million adults in the United States have a diagnosis of heart failure [2]. It is estimated that in 2010, over 2 million infants, children, adolescents, and adults were living with congenital heart disease (CHD) in the United States [3], and the number is ever-increasing as surgical approaches for underlying CHD and medical treatments improve. An estimated 2.7–6.1 million people in the United States have atrial fibrillation [2]. With the aging of the US population, this number is expected to increase. Each of these cardiac conditions can be evaluated with cardiac MRI, either as a baseline diagnostic tool or as a therapeutic roadmap as in the case of atrial and ventricular arrhythmias. With its increasing clinical availability, improved duration scan times (under 1 h), and lack of ionizing radiation, CMR is an excellent tool for the evaluation of cardiac structure and function in most cardiac patients.

Several CMR techniques are currently in clinical use. In this chapter, we illustrate some of these techniques as well as the expanding roles of CMR in the noninvasive diagnosis of various cardiac disorders by case scenarios followed by a brief discussion.

Electronic Supplementary Material The online version of this chapter (https://doi.org/10.1007/978-3-319-97622-8_27) contains supplementary material, which is available to authorized users.

R. Morgan
Brigham and Women's Hospital, Boston, MA, USA

R. Y. Kwong (✉)
Cardiovascular Division, Department of Medicine,
Brigham and Women's Hospital, Boston, MA, USA
e-mail: rykwong@partners.org

27.2 General Indications

The current recognized indications for cardiac magnetic resonance imaging were summarized by Pennell et al. [4] in 2004 (Table 27.1), and more recently, appropriateness criteria have been put forward by the joint collaboration of the American College of Cardiology Foundation [6–8] . In 2010 the ACCF/ACR/AHA/NASCI/SCMR Expert Consensus Document on Cardiovascular Magnetic Resonance outlined, among other details, the clinical use of CMR in the evaluation of patients with such conditions as heart failure, CAD, valvular disease, cardiac masses, pericardial disease, congenital disease, AF, peripheral arterial disease, and renal and thoracic aortic disease [9]. The Society of Cardiovascular Magnetic Resonance (SCMR) has developed standardized protocols and guidelines for postprocessing, which are readily available for clinicians on their website.

Of particular importance in recent guidelines is that CMR is now acknowledged as providing clinically relevant information when used as a first-line imaging technique for the assessment of global ventricular (left and right) function and mass [8] and for the detection and assessment of myocardial viability [8] and its use in the detection of nascent coronary anomalies is also well described [10]. CMR is also well suited to the diagnosis of cardiac and pericardiac tumors [11], hypertrophic cardiomyopathy [12], and arrhythmogenic right ventricular cardiomyopathy [13] and in the overall evaluation of congenital heart disease [14].

With technological advances in both hardware and software, increasing magnet strengths (typically 1.5 or 3 T for cardiac imaging) and novel acquisition sequences, current scan times have been reduced and are typically under 1 h in most clinical cases. Multiple techniques can be performed within a single imaging session to assess myocardial structure and physiology, valvular function, and at rest or stress hemodynamics. In fact, CMR is able to complement or replace a number of existing common imaging modalities. Many quantitative CMR techniques use three-dimensional

P. P. Toth, C. P. Cannon (eds.), *Comprehensive Cardiovascular Medicine in the Primary Care Setting*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-319-97622-8_27

Table 27.1 Indications for CMR

Indication	Class
Congenital heart disease	
General indications	
Initial evaluation and follow-up of adult congenital heart disease	I
Specific indications	
e.g., assessment of shunt size (Qp/Qs)	I
Acquired diseases of the vessels	
e.g., diagnosis and follow-up of thoracic aortic aneurysm including Marfan disease	I
Coronary artery disease	
1. Assessment of global ventricular (left and right) function and mass	I
2. Detection of coronary disease	
e.g., regional left ventricular function at rest and during dobutamine stress	II
Assessment of myocardial perfusion	II
Arterial wall imaging	IV
3. Acute and chronic myocardial infarction	
e.g., detection and assessment	I
Myocardial viability	I
Ventricular thrombus	II
Acute coronary syndromes	IV
In patients with pericardial disease, cardiac tumors, cardiomyopathies, and cardiac transplants	
1. Pericardial effusion	III
2. Constrictive pericarditis	II
3. Detection and characterization of cardiac and pericardiac tumors	I II
4. Ventricular thrombus	I/II
5. Hypertrophic cardiomyopathy: apical/non-apical	I
6. Dilated cardiomyopathy: differentiation from dysfunction related to CAD	I II
7. Arrhythmogenic right ventricular cardiomyopathy (dysplasia)	I II
8. Restrictive cardiomyopathy	IV
9. Siderotic cardiomyopathy (in particular thalassemia)	
10. Noncompaction	
11. Post-cardiac transplantation rejection	
In patients with valvular heart disease	
e.g., quantification of stenosis	I

Adapted from [4, 5]
Class I: provides clinically relevant information and is usually appropriate; may be used as first-line imaging technique; usually supported by substantial literature
Class II: provides clinically relevant information and is frequently useful; other techniques may provide similar information; supported by limited literature
Class III: provides clinically relevant information and is infrequently used because information from other imaging techniques is usually adequate
Class IV: potentially useful, but still investigational

acquisition without the need for geometric assumptions (such as the modified Simpson's equation for calculation of ventricular volumes) and also reduce error attributable to observer bias. In addition, the lack of ionizing radiation use also allows truly noninvasive serial follow-up studies applicable in many clinical settings, as well as creating an opportunity to study patient response to medical therapies.

Current relative contraindications to CMR include patients with non-CMR-compatible permanent pacemakers and automated implantable cardiac defibrillators, although in specific situations the risk benefit might warrant its use. For CMR-compatible devices, scanning protocols with short sequence acquisition time and lower magnet field strength are a must. In the latter part of this chapter, we briefly discuss safety and claustrophobia and the current methods to manage these issues.

27.3 Specific Indications

27.3.1 Discussion of Technique

A magnetic resonance imaging (MRI) system contains three main electromagnetic components [1]: a set of main magnet coils [2], three gradient coils, and [3] an integral radiofrequency transmitter coil. These components each generate a different type of magnetic field. When applied to a patient in combination, they produce spatially encoded magnetic resonance signals that are used to form MR images.

The patient is positioned for imaging within the central bore of the magnet. A strong magnetic field (generated by the main magnet coils) exists inside the magnetic resonance scanner (the scanner is always on), the strength of which is measured in units called Tesla, T. One Tesla is equal to approximately 20,000 times the earth's magnetic field. Nominal field strengths range from 0.2 to 3.0 T for commercially produced clinical MR systems, the most common field strength for cardiac imaging being 1.5 T. Atomic spins align and precess around the axis of this magnetic field.

The primary origin of the MR signal used to generate MR images is either from water or fat within the patient's tissue, hydrogen ions to be precise. CMR utilizes the phenomenon of magnetic resonance of atomic nuclei within such a magnetic field when they are subjected to radiofrequency waves. Because of the predominance of hydrogen atoms and its single nucleus proton, current CMR relies on disrupting and then receiving the signals from protons as they realign themselves after this disruption. The three key parameters that describe this realignment are the T1, T2, and T2* (pronounced T2 star) relaxation times, corresponding to longitudinal, transverse, and translational magnetization, respectively. Living tissues are characterized by their chemical and biochemical compositions and as such have distinct signatures when viewed by CMR. By imaging such tissues through the prism of their distinct relaxation times, CMR enables us to distinguish tissues with extreme precision and resolution. Imaging pulse sequences have been designed to give preferential weight to the different characteristic relaxation times and by doing so allow for unprecedented tissue discrimination.

There are two fundamental CMR sequences from which all others are based, namely, the spin-echo (SE) and gradient-echo (GE) sequences. Spin-echo imaging is often referred to as black-blood imaging with blood appearing black. GE imaging is referred to as white-blood imaging because blood (and fat) appear bright. SE sequences are generally used for static anatomical imaging, while GE and its variants are useful for functional imaging. There are two further noteworthy techniques referred to as "cine" (such as steady-state free precession or SSFP) and inversion recovery imaging which are variants of GE sequences and form the basis of the functional sequences used in perfusion and late gadolinium enhancement (LGE) imaging. CMR images are almost always ECG gated. Advances in cardiac imaging have been in great part due to ECG gating, although more rapid real-time acquisition sequences are currently being developed, which are particularly useful in patients with poor ECG gating or underlying atrial fibrillation.

The strength of CMR as an imaging tool lies in its ability to evaluate global and regional LV and RV function, size, and mass, therefore, relying on a combination of SE and GE sequences, with stress perfusion imaging mainly using "cine" or moving sequences. In recent years edema imaging using T2 SPAIR sequences and T2 mapping has added significantly to the assessment of underlying conditions such as acute myocarditis and acute myocardial infarction [15–18]. Late gadolinium enhancement (LGE) imaging is the current gold-standard technique used in detecting and sizing myocardial fibrosis or scar, as seen in myocardial infarction [19, 20]. LGE imaging is also an important component in the evaluation of potential underlying cardiomyopathy (such as HCM), myocardial inflammation and fibrosis (myocarditis), and myocardial viability in ischemic cardiomyopathy patients. For such patients with coronary artery disease being considered for possible mechanical revascularization, the transmural extent of LGE can stratify the potential benefit from a revascularization procedure by predicting segmental recovery of contractile function [20–22]. In addition, the clinical application of this technique has recently been shown to contribute important prognostic information in patients with ischemic heart disease. For instance, evaluations of unrecognized myocardial scarring and assessments of the peri-infarct zone in patients with recognized or unrecognized MI have suggested a high cardiac risk with the potential of providing novel methods of patient risk stratification [23–25]. This growing body of evidence indicates that the prognostic information provided by CMR is capable of independent and robust prediction of patient adverse events (ref prior chapter).

T1 mapping is an emerging CMR imaging technique, which has shown early clinical promise particularly in the setting of diffuse myocardial fibrosis in conditions such as hypertensive heart disease, hypertrophic cardiomyopathy (HCM), cardiac amyloidosis (CA), and dilated cardiomyopathy (DCM). Routine use of T1 mapping sequences are in clinical use in many large centers and offer useful additional information in the initial evaluation of patients with potential underlying cardiomyopathy.

CMR is proving to be a robust imaging modality for evaluation of myocardial iron overload with T2* sequences having been validated in the evaluation of disorders such as thalassemia and hemachromatosis. These sequences are currently used to detect myocardial involvement both qualitatively and quantitatively and have in effect become the reference noninvasive standard for evaluation of myocardial iron in these conditions. The T2* relaxation parameter has the characteristic of being most shortened in tissues containing particulate iron. In a study of 32 patients, measurements of myocardial T2* using a single breath-hold multiecho constant repetition (TR) technique were compared with the standard multiple breath-hold variable TR technique which showed good agreement of values between both methods paving the way for more rapid acquisition times [26]. This has recently allowed the non-invasive monitoring of patients suffering from thalassemia or asymptomatic myocardial siderosis undergoing iron-chelating therapy [27, 28].

Other techniques visualizing atrial and pulmonary venous anatomy using three-dimensional (3D) acquisition sequences have become part of routine clinical practice in aiding pre-procedural planning of electrophysiological RF ablations of atrial [29] or ventricular arrhythmias [30], and recent data suggests that CMR may obliterate the role of pre-procedural TEE in AF patients undergoing pulmonary vein isolation (PVI) [31].

27.3.2 Imaging Cases

The CMR techniques described above allow the comprehensive evaluation of underlying cardiac conditions as will be outlined in the form of clinical cases below. Areas of particular clinical interest and therefore routine clinical scans performed in our institution include:

- Pericardial assessment in cases of pericardial constriction or masses
- Myocardial perfusion and stress CMR to detect ischemia
- The assessment of myocardial viability in cases of ischemic cardiomyopathy, with consideration to planned revascularization
- Characterization of heart valve disease and shunt assessment (Qp/Qs)
- Evaluation of cardiac masses and tumors
- Evaluation of inherited cardiomyopathies such as ARVC, HCM, and LNVC

Other cardiovascular diseases to which CMR greatly contributes include adult congenital heart disease, Takotsubo cardiomyopathy, and infiltrative disease such as cardiac amyloidosis and cardiac sarcoidosis.

Through chosen cases, the following figures illustrate the practical application of CMR in routine clinical practice.

Case 1 Figure 27.1a–d: Case of a 65-year-old man with worsening dyspnea and clinical evidence of heart failure. He had a longstanding history of uncontrolled hypertension, and severe LVH detected on echocardiography was initially felt to be potentially due to longstanding hypertension. His EKG revealed atrial fibrillation with small complexes, and the clinical suspicion was raised for potential underlying cardiac amyloidosis following an abnormal renal profile and light chains result.

Case 2 A 39-year-old man with a family history of sudden cardiac death and recently detected nonsustained ventricular tachycardia (NSVT) on a Holter monitor presents for a cardiac MRI for further risk stratification following an abnormal echocardiogram which revealed asymmetrical LVH with a hyperdynamic left ventricle and a significant left ventricular outflow tract gradient with Valsalva. The echo findings were highly suggestive of hypertrophic cardiomyopathy. Figure 27.2 LGE images of right (RV) and left ventricle (LV) taken 10 min post iv gadolinium administration.

Following the MRI, given the family history of SCD, the extent of LGE and the NSVT the patient underwent ICD implantation.

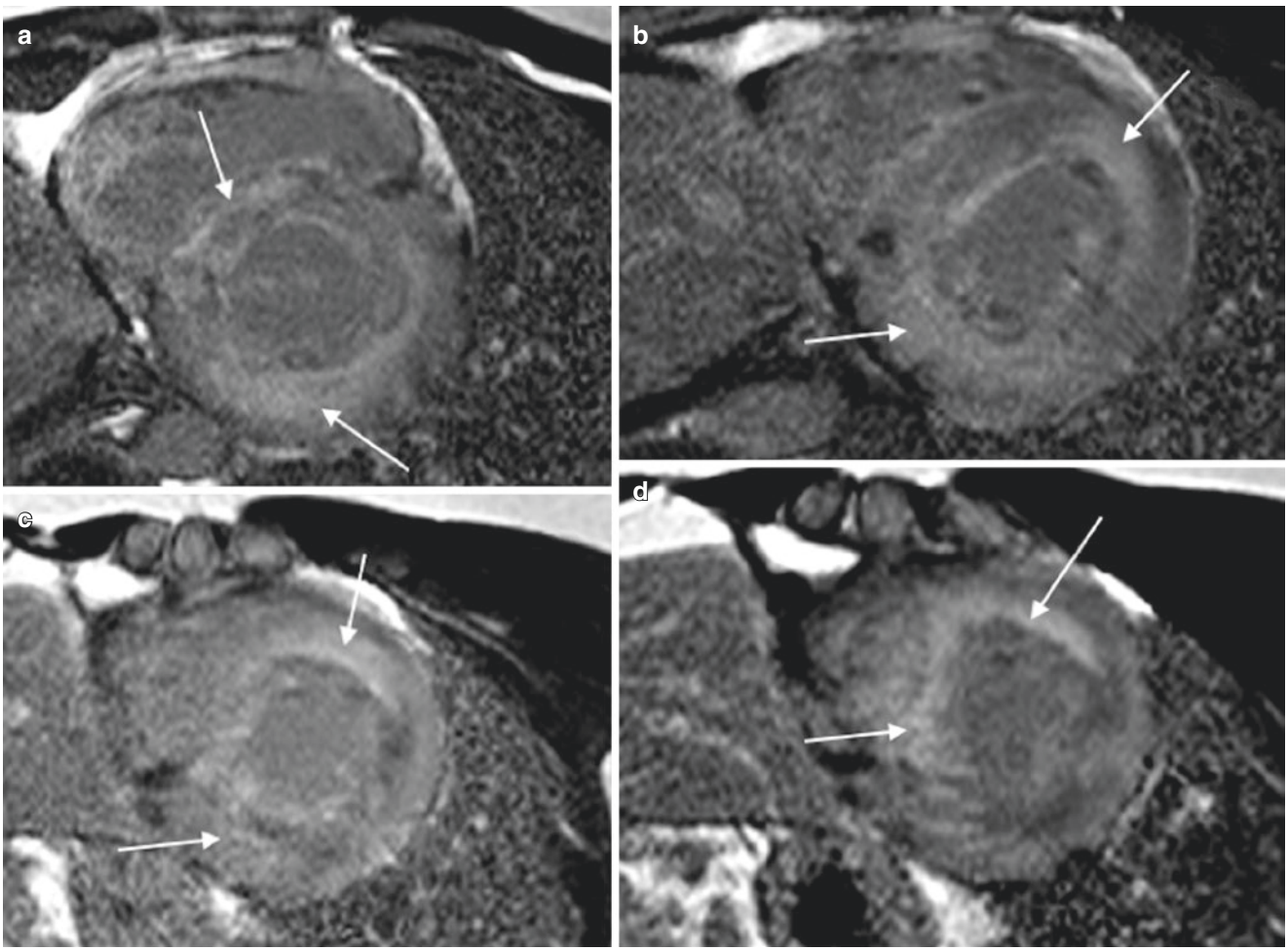

Fig. 27.1 The images in (**a**–**d**) above reveal short-axis slices through the RV and LV starting at the base (**a** and **b**) and moving toward the mid-ventricle and apex (**c** and **d**). Image quality is marginally affected by underlying atrial fibrillation and gating issues, but we clearly see the classic pattern of LGE seen in cardiac amyloidosis cases with almost global subendocardial LGE (arrows) affecting all myocardial slices from base through apex and with relative sparing of the epicardium. There is extensive replacement fibrosis as indicated by extensive LGE affecting all segments. Also classical for amyloidosis is the nulling of blood and mid-/epimyocardium together

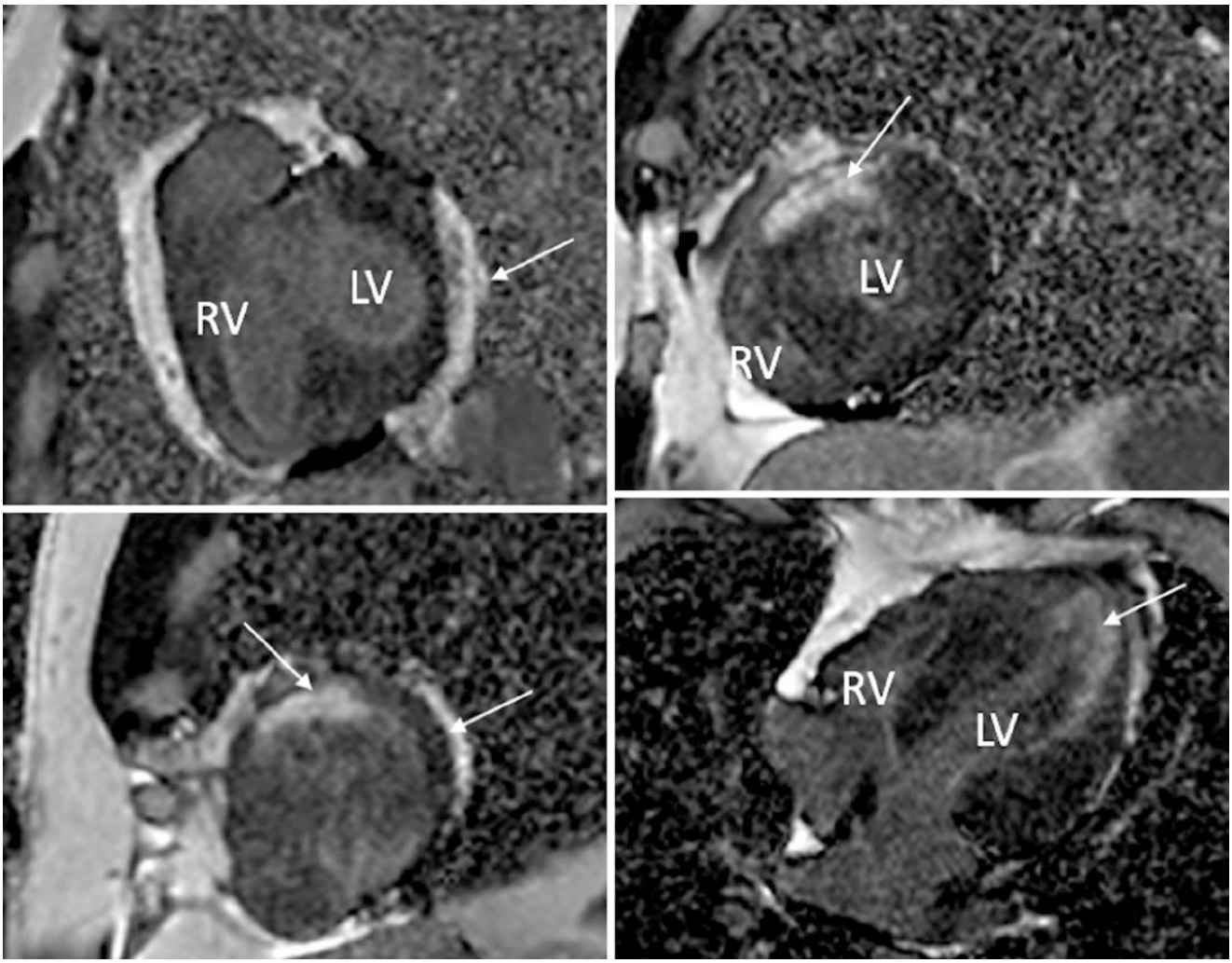

Fig. 27.2 RV, right ventricle; LV, left ventricle. The images reveal (clockwise from top left) short-axis RV and LV slices from base through apex and a four-chamber view (bottom right). There is extensive late gadolinium enhancement (arrows) involving the epi- and midmyocardium at the LV base (anterolateral and inferolateral segments) and midslices (anteroseptum). At the LV apex (bottom left and indicated by arrow in the four chamber) the LGE affects both the anterior wall and the lateral wall

Case 3 A 54-year-old male presented to our institution with increasing dyspnea and 20 lb weight gain. He was found to have biventricular enlargement with severely impaired LV function on TTE. A cardiac MRI was requested to exclude possible underlying causes such as cardiac infiltration or myocardial inflammation as a potential cause. Coronary angiography revealed patent epicardial vessels. Two-, three-, and four-chamber cine images (Video 27.1) reveal a globular LV with severely reduced LV systolic function and a dilated RV with mildly reduced RV systolic function. The calculated LVEF was 20% (Fig. 27.3).

Cases of DCM can also be found to have no LGE as indicated by Fig. 27.4.

Case 4 A 43-year-old female with no prior cardiac history who presented to the ED with atypical chest pain after playing tennis. Chest X-ray at that time was notable for an enlarged right atrium. Echocardiogram revealed preserved EF 65% with a round, well-circumscribed echodensity measuring 5 × 5 cm behind the aortic valve apparatus. She was referred for cardiac MRI for improved characterization of the mass (Fig. 27.5a–h). The following movie files highlight the use of CMR in characterization of cardiac masses (Videos 27.2, 27.3, 27.4, and 27.5).

This case highlights the use of CMR in tissue characterization for cardiac masses, a common indication in our institution. The protocol for a cardiac mass takes 50–60 min;

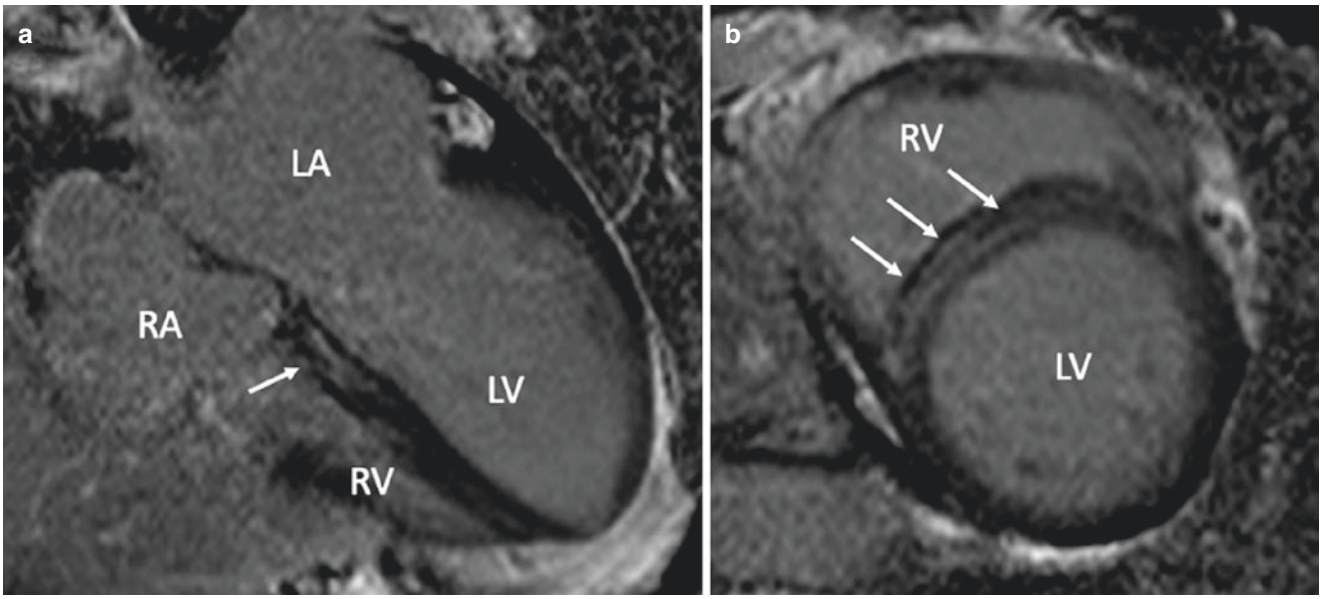

Fig. 27.3 Panel (**a**) reveals a four-chamber view obtained 15 min post iv gadolinium administration (PSIR image) with the four cardiac chambers labeled. The white arrow points to upper septal midwall LGE which is also seen more clearly in the basal short axis image (**b**), also represented by white arrows. The LGE is in a linear pattern, a pattern often described in DCM. The subendocardium is typically spared in DCM, as seen in this case

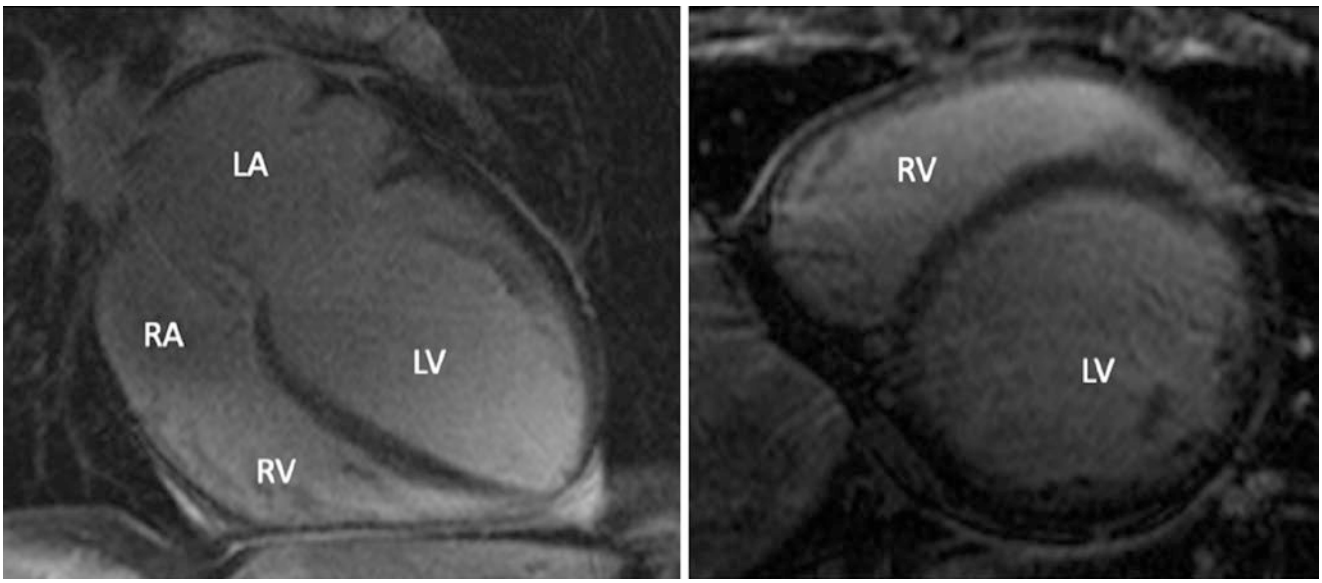

Fig. 27.4 The four-chamber LGE image (left panel) and short-axis LV and RV image (right panel) reveal a globular severely dilated LV, a mildly dilated RV, a dilated LA, and no definitive LGE which is also a pattern seen in up to 59% of patients [32]

however it can yield extremely important information for the clinician. In this case a subsequent biopsy revealed tissue consistent with cardiac paraganglioma.

Case 5 Figure 27.6a–f: A 37-year-old man presented to hospital complaining of presyncope and palpitations, and subsequent telemetry revealed periods of intermittent 2:1 heart block and five and six beat runs of NSVT. He underwent cardiac MRI to evaluate for possible underlying cardiomyopathy following an unrevealing echocardiogram.

These cases underscore the importance of using specific CMR protocols, tailoring them to the clinical question at hand. Protocols have been carefully planned, and a consensus

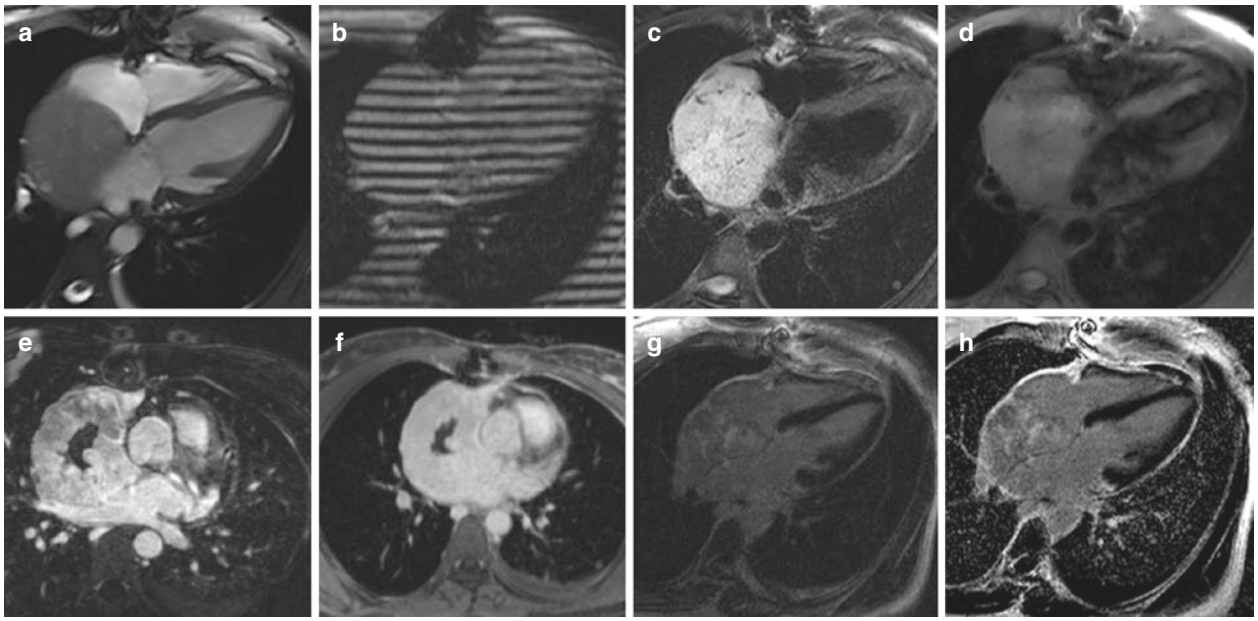

Fig. 27.5 (**a–h**) Four-chamber SSFP still frame reveals a large mass encroaching upon the right and left atria (**a**); the same view (**b**) with tag lines indicate the mass is malignant and infiltrating as evidenced by no line break in the moving file (see separate movie file); T2- and T1-weighted images (**c**, **d,** respectively) indicate that the mass is hyperintense on T2 with a central scar; a still frame from a navigator sequence in (**e**) reveals central necrosis in the mass (central black area). A navigator sequence was very helpful in this case to determine the extent of the mass. It revealed a 7.9 × 5.1 × 5.7 cm (AP × trans × CC) mass, centered immediately superior to the right atrium. The mass was seen to invade the superior right atrial wall, extending into the right atrial lumen inferiorly. Anteriorly, the mass invaded into the SVC, completely obliterating the SVC lumen, with consequent severe dilatation of the azygos vein. The mass extended anteromedially to the epicardial fat in the right atrioventricular groove, but did not involve the RCA. Posteriorly, there was extrinsic compression of the anterior wall of the left atrium, causing severe stenosis of the right superior pulmonary vein. Medially, the mass extended to the aortic root, surrounding the non-coronary sinus of Valsalva, but was separated from the aortic wall by a small rim of fat. Superiorly, it extends to the inferior surface of the right main pulmonary artery; long TI navigator in (**f**) confirms the presence of central necrosis and thrombotic material; the LGE images in (**g**) and (**h**) reveal patchy LGE within the mass, consistent with a heterogeneous mass lesion. This information was particularly helpful to the surgeon in planning this case

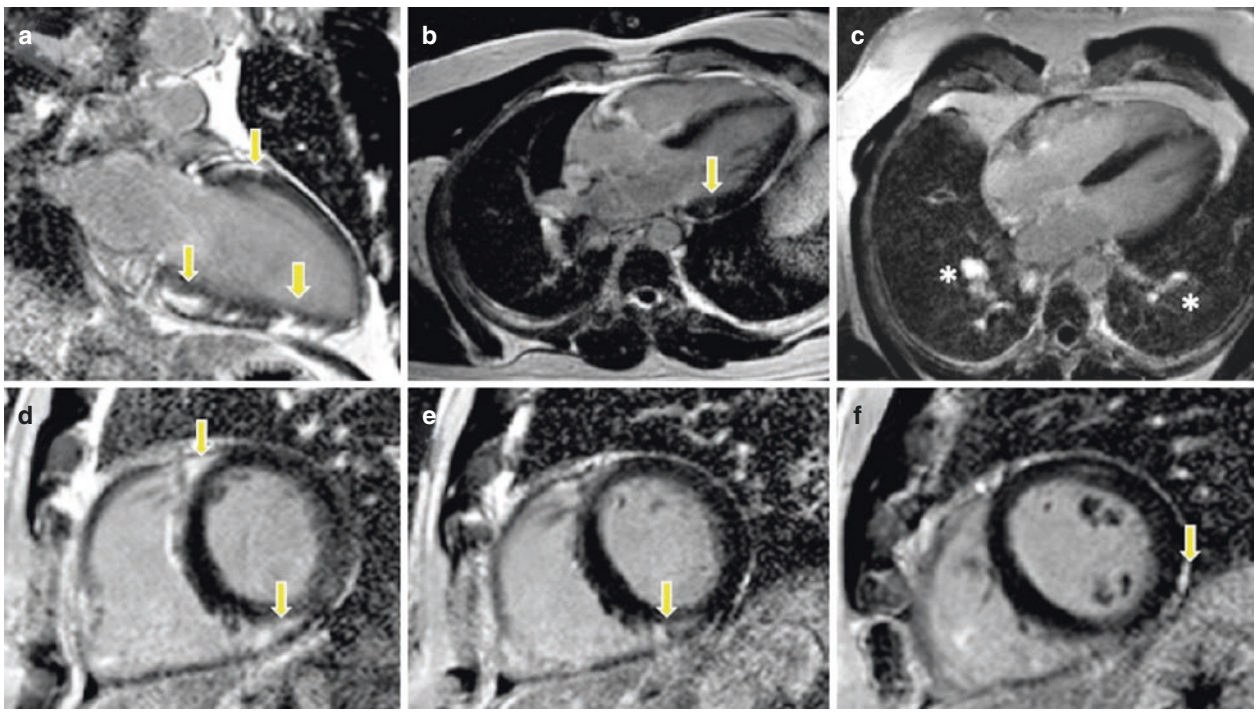

Fig. 27.6 (**a–f**) Late gadolinium enhancement images reveal the presence of midwall and epicardial LGE affecting the basal anteroseptum and inferoseptum at the RV insertion points, as well as the midinferolateral wall (yellow arrows), and panel c reveals the presence of pulmonary adenopathy (marked by white asterisk). *Note*: Yellow arrows indicate areas of LGE or late gadolinium enhancement

approach to standard protocols is available through the Society of Cardiovascular Magnetic Resonance (SCMR) [33]. The value of knowing the patients clinical information and performing the correct protocol cannot be overemphasized. Additionally, with respect to myocardial perfusion and stress CMR to detect ischemia, a protocol commonly performed in our institution, a recent multicenter trial suggested that CMR stress perfusion imaging was a valuable alternative to the more widely available single-photon emission computed tomography (SPECT) for CAD detection, showing equal performance in head-to-head comparisons in all patient groups [34]. In fact CMR stress perfusion imaging performed better than SPECT in patients with two or more vessel CAD in this study [34]. This does not come as a surprise given that the current CMR perfusion technique typically operates at a substantially higher in-plane spatial resolution (1.5–2.0 mm as compared to 10–12 mm for SPECT) and at high contrast-noise ratio. CMR stress cine function has been shown to have a sensitivity of 83% and a specificity of 86% [35], whereas CMR stress perfusion imaging has a sensitivity of 91% and a specificity of 81%, in detecting significant coronary artery disease [35].

A common indication for CMR in our institution is the assessment of myocardial viability and the detection of previous myocardial necrosis. LGE is a marker of tissue necrosis and fibrosis in the assessment of both ischemic and nonischemic cardiomyopathies. In patients with CAD, our group has shown that unrecognized myocardial scarring and peri-infarct tissue heterogeneity identified by LGE imaging are markers of high cardiac risk beyond patient demographical, ECG, and left ventricular function variables [23, 25, 36].

27.4 Safety Considerations

CMR (including 1.5 and 3 T) has proven safe in routine clinical practice in the vast majority of clinical settings including common situations involving cardiac patients with previously placed coronary stents and bioprosthetic valves [37, 38]. Gadolinium-based contrast agents (GBCA) are the most common contrast agents used in magnetic resonance imaging and have demonstrated a very low incidence of serious adverse side effects. The total incidence of adverse reactions to contrast agents in magnetic resonance imaging ranges between 2% and 4% [39, 40]. Fortunately, cases of severe acute reactions to gadolinium, such as laryngospasm and anaphylactic shock, are rare. It is also possible for chronic complications secondary to the use of gadolinium to occur. Recently an association between its use and a rare dermatologic disease occurring in patients with renal failure has been reported. Nephrogenic systemic fibrosis (NSF) was the subject of an official health notification issued by the American Food and Drug Administration. This progressive disease is characterized by hardened skin with fibrotic nodules and plaques which may involve other parts of the body [41]. Patients who have been affected by this disorder had a history of chronic renal failure, with metabolic acidosis, and had undergone magnetic resonance angiography, likely with exposure to large amounts of intravenous paramagnetic contrast. NSF was first identified in 1997 and its incidence linked to gadolinium use in the literature in 2006 [42]. While initially observed to remain isolated to skin, it is now known that there may be involvement of lungs, skeletal muscle, heart, and renal tubules and is associated with an increased frequency of thrombotic events. The name of the entity has therefore been expanded to describe its systemic manifestations. The median time between GBCA exposure and onset of symptoms is 25 days, with a range of 2–75 days [41]. Worldwide, there have been over 200 cases of NSF reported [43]. At the time of preparation of this article, there has been no report of NSF in patients with normal renal function.

Unfortunately, there is no established treatment for NSF, but there may be some benefit of rapid correction of renal dysfunction by either hemodialysis or kidney transplantation. It is our practice in our institution not to administer gadolinium-based contrast agents to patients with an EGFR < 30.

27.5 Training in CMR and Other Practical Issues

The Society of Cardiovascular Magnetic Resonance (SCMR) has been pivotal in establishing training guidelines for physicians with a strong interest in learning CMR [44]. The current recommendation for each of the three levels of training in CMR is detailed in Table 27.2. Information about current certified training centers can be found on the website www.scmr.org.

In the clinical setting, certain practical aspects of CMR need to be considered before proceeding with the scan and merit a directed discussion with each patient. These include,

Table 27.2 Current (2008) training guideline endorsed by the Society of Cardiovascular Magnetic Resonance (SCMR)

Level	Duration of training in months	Number of cases
1	1	25 mentored interpretations (by a Level 2- or Level 3-trained physician)
2	3–6	150 mentored interpretations (by a certified Level 2- or Level 3 (preferred)-qualified CMR physician, including at least 50 as primary interpreter (and operator, if possible))
3	At least 12	300 mentored interpretations by a Level 3-qualified CMR physician including 100 as primary interpreter (and operator, if possible)

for instance, the total duration of the CMR scan and the duration of patient breath-holding during sequence acquisition. The latter can in some cases be reduced using parallel imaging techniques.

The management of patients suffering from claustrophobia is also of particular importance. Usually patient reassurance and sometimes the use of single-dose anxiolytics are sufficient to allow the scan to proceed. The need for conscious sedation is relatively uncommon, in less than 1% of all clinical cases. The introduction of larger borehole magnets has rendered the scan less challenging and problematic for those suffering from claustrophobia.

As is the case with other imaging modalities, a careful appreciation of artifacts is necessary for correct image interpretation. This becomes even more important when image quality is suboptimal. Special consideration and adequate training are needed to discern artifacts related to the more commonly encountered artifacts such as motion, metallic and magnetic field susceptibility, wrap-around effects linked to relatively small fields of view, shimming artifacts related to magnetic field inhomogeneities, chemical shift artifacts appearing at specific tissue interfaces, and partial volume artifacts related to image resolution.

In planning a CMR scan, a systematic approach should be adopted in order to ensure the best patient care and most efficient use of the technical hardware. This may involve several steps which include:

1. Defining the clinical question to be answered
2. Considering which CMR pulse sequence is best suited to characterizing a given cardiac abnormality
3. Checking for CMR safety contraindications (e.g., presence of ferromagnetic foreign bodies, pace setting medical devices, and severe renal dysfunction)
4. Planning the specific CMR protocol

27.6 Future Prospects

As the cases above illustrate, be it in the differentiation of ischemic and nonischemic cardiomyopathies, in the identification of CAD, myocardial ischemia, and prior infarction or in the evaluation of specific cardiomyopathies, the information provided by CMR not only enhances the understanding of the underlying condition but also contributes to patient management. The advent of novel techniques such as T1 and T2 mapping in recent years has been the latest great addition to the field, with the prospect of detecting underlying myocardial disease processes at a much earlier stage. What started out as a research tool has been used more recently in routine clinical practice, in particular at our institution and other large teaching centers. Indeed exciting research is being presented at annual cardiology meetings and the SCMR annual congress to validate their use in routine clinical practice. For certain there will be more exciting developments in this field in coming years.

CMR hardware and novel pulse sequences are continuously being developed and refined. Areas of promise include real-time and three-dimensional acquisition sequences that may improve current interpretation and herald the next generation of images paving the way for improved coronary artery visualization, an area where to date cardiac CT has proved superior. Improved postprocessing techniques allow CMR experts to gain as much information from the sequences as possible. Beyond the quality of the images, however, the central goal is improved patient care through enhanced diagnostic accuracy and ultimately improved outcomes. The CMR community continues to work toward this goal and hopes to continue to provide more advances and exciting research toward improved patient care and outcomes in coming years.

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Index

P. P. Toth, C. P. Cannon (eds.), *Comprehensive Cardiovascular Medicine in the Primary Care Setting*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-319-97622-8

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