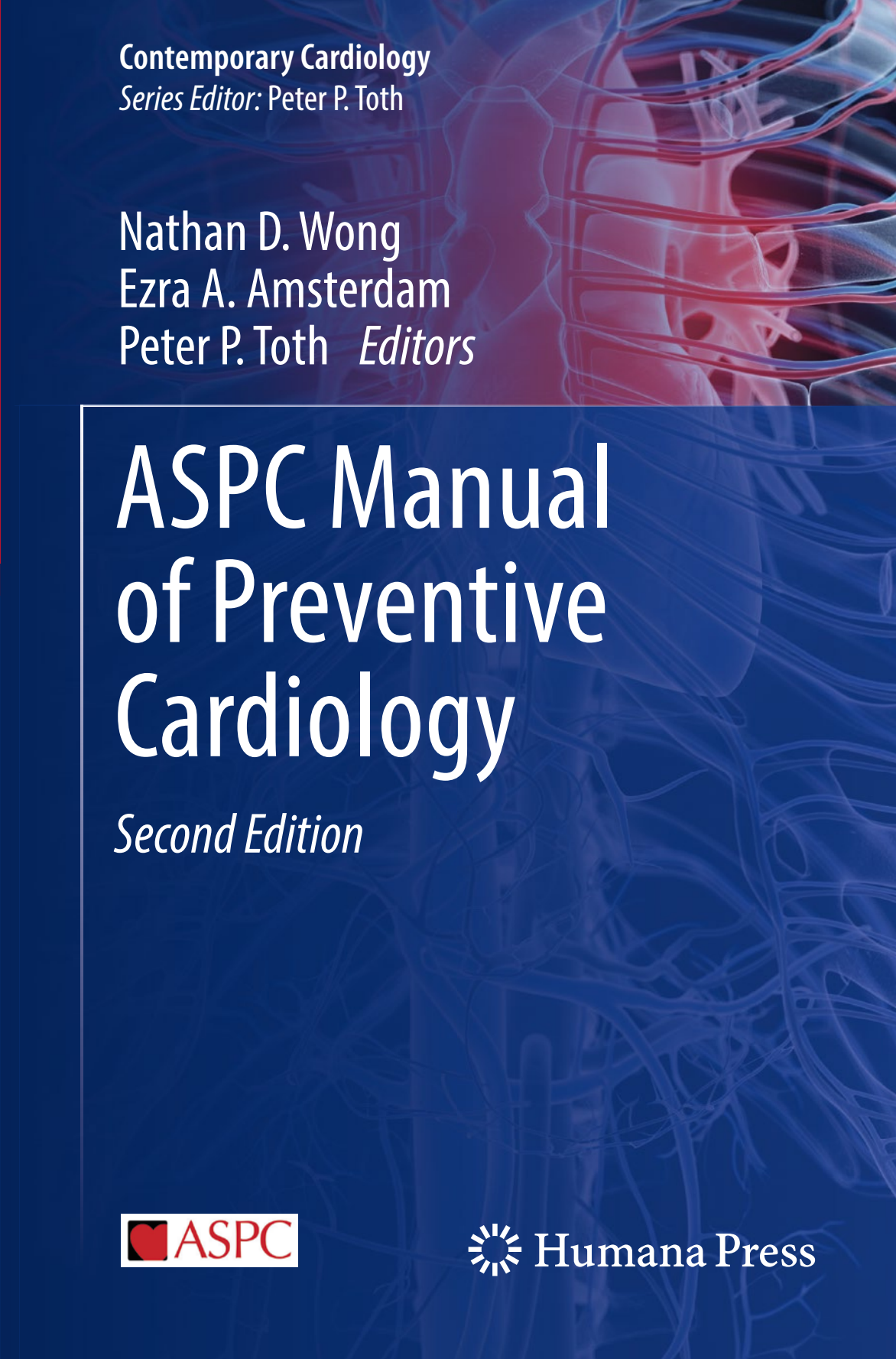
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ASPC Manual of Preventive Cardiology

Second Edition

Humana Press

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Foreword

It is a privilege, albeit a rather daunting one, to follow the great Thomas A. Pearson who wrote the foreword to the previous edition of the *ASPC Manual of Preventive Cardiology*. I would like to think of this as a symbol of increasing recognition that the approach to our greatest cause of death, atherosclerotic cardiovascular disease (ASCVD), should be global. As mortality from ASCVD has declined in the United States, it has risen in developing countries of the world. And even a decline in age-specific mortality may be misleading as deaths may be transferred to older age groups, incident non-fatal cases in younger persons will be missed, and advances in therapy will result in more persons living with ASCVD with consequent accumulating healthcare costs. We are also all concerned about our inability to contain the epidemic of obesity and the specter of unfit, overweight young adults dependent on a cocktail of medications to contain their risks—"chemical salvage" if you will.

Tom Pearson gave due credit to the great Jeremiah Stamler. I would also like to recollect what Geoffrey Rose [1] taught us—firstly, that most cases of ASCVD arise in people at only modestly increased risk, simply because they are far more numerous than high risk people; high-risk *individual*s gain most from preventive measures but a complementary population approach is needed if ASCVD is to be effectively contained. Secondly, "The primary determinants of disease are mainly economic and social, and therefore its remedies must also be economic and social. Medicine and politics cannot and should not be kept apart." It behoves those of us who try to lead in preventive cardiology to be advocates for not only our individual patients but for societal change as well.

Preventive cardiology faces many challenges. The busy healthcare professional is faced with a tsunami of clinical practice guidelines, many very detailed and dense. Many of us were not trained in such aspects as communications, behavior change, or nutrition. The medical system may be hostile to our efforts—we may be reimbursed for treating sick people but not for keeping people healthy. These aspects make the *ASPC Manual of Preventive Cardiology* singularly important, making core principles and key aspects of prevention accessible to the harassed healthcare professional and written by a star-studded cast of authors.

Can we also begin to glimpse the future of prevention? Risk estimation involves applying risk estimates derived from populations to individuals, a very uncertain process. There is much talk about 'personalised' risk estimation. Will genetics help us? It is likely that we have underestimated the impact of the polymorphisms that determine risk, because their effect on 5-year risk is small whereas the impact on true lifetime risk may be great [2]. Also, we will likely see a disentangling of direct genetic effects from indirect effects on lipids and blood pressure. In contrast, the endless quest for new risk factors has been rather disappointing after the effects of the "big three" of smoking, lipids, and blood pressure have been taken onto account.

There is much talk about fashionable topics such as "big data," machine learning, and artificial intelligence. But epidemiologists have always dealt in large numbers, and the harmonisation of data from disparate sources, while exciting, is still challenging. And new methods of data analytics are not inherently magical,- we still have to define clear and answerable questions.

Finally, have we physicians been too paternalistic, too controlling? It is logical and pleasing to see more patient involvement in Guidelines, more development of motivational interviewing skills, and an increase in the teaching of health maintenance skills from childhood on.

In conclusion, I warmly welcome the *ASPC Manual of Preventive Cardiology* as a lucid, comprehensive, and insightful contribution that belongs in the library of every healthcare provider who practices preventive cardiology. It is an indispensable companion for those devoted to state-of-the-art medical practice.

Trinity College, Dublin, Ireland Ian M. Graham, FRCPI, FESC, FTCD

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Preface

Despite significant declines in cardiovascular disease mortality over much of the last half century, rates have begun to rise once again, and annual healthcare costs due to cardiovascular diseases in the United States approach one trillion dollars. Cardiovascular disease has become the leading cause of death in more and more developing countries worldwide, fueled largely by the obesity and diabetes epidemic, which is also driving increases in cardiovascular disease in the United States. While coronary heart disease has traditionally been the focus of preventive cardiology, more comprehensive approaches addressing prevention of peripheral vascular disease, stroke, heart failure, atrial fibrillation, as well as cardiovascular disease related comorbidities including diabetes and chronic kidney disease are needed. Moreover, management limited to traditional risk factors such as cholesterol, blood pressure, and smoking needs to be greatly expanded with the advent of newer therapies to reduce cardiovascular disease risk in diabetes, evidence of benefit from treating inflammation, as well as the role of genetic evaluation to target those most likely to respond to risk reducing therapies.

This new edition of the *American Society for Preventive Cardiology (ASPC) Manual of Preventive Cardiology* features significant updates from newer guidelines of the American College of Cardiology, American Heart Association, and other societies for cardiovascular risk assessment and risk factor management. In just the last 5 years, we have witnessed perhaps a generation of advances in the field of preventive cardiology that have been incorporated into this new edition. The advent of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors has brought low density lipoprotein cholesterol to lower levels than ever before, in many cases below 20 mg/dL, further addressing the problem of "residual risk" in our high-risk patients. This occurred simultaneously with release of key trials of sodium-glucose transport protein 2 (SGLT-2) inhibitors and glucagon-like peptide 1 (GLP1) receptor agonists, the first diabetes therapies to show cardiovascular risk reduction benefits. Moreover, the first two trials to prove the link between inflammation and atherosclerosis and its clinical sequelae have leveraged novel mechanisms to reduce cardiovascular disease risk. The end of the last decade was then topped off by the

first fish oil therapy, icosapent ethyl, to further reduce risk for cardiovascular events beyond statin therapy in high-risk patients.

The contributors of the 29 chapters in this new edition are experts in their respective fields of preventive cardiology and, along with the editors, have dedicated their careers to advancing this field. While each chapter includes much relevant scientific discussion of the latest clinical trials and other research, the goal of the *ASPC Manual of Preventive Cardiology* is to address contemporary, practical therapeutic approaches that enhance the practice of preventive cardiology by the wide range of providers essential for its practice—ranging from lifestyle interventionists, such as dietitians and exercise physiologists, to nurses and nurse practitioners, pharmacists, primary care providers, and specialists including endocrinologists and cardiologists. Guidance is also provided for development of a preventive cardiology center that encompasses this range of healthcare providers essential for optimizing cardiovascular disease prevention in our communities.

It is hoped the *ASPC Manual of Preventive Cardiology* will serve as the authoritative and most up-to-date source of clinically relevant information for healthcare providers, scientists, and trainees in the United States and beyond who have an interest in or who have dedicated their careers to prevent cardiovascular disease in their patients and communities. Moreover, with the ASPC growing from a small group of academic physicians 35 years ago to a multidisciplinary membership of more than 1000 members today, the *ASPC Manual of Preventive Cardiology* is intended to serve an even larger audience of specialists dedicated to the field.

Irvine, CA, USA — Nathan D. Wong
Sacramento, CA, USA — Ezra A. Amsterdam
Baltimore, MD, USA — Peter P. Toth

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This edition of the *ASPC Manual of Preventive Cardiology* is dedicated to:

Drs. William B. Kannel, Jeremiah Stamler, and Nanette Wenger, giants in the field.

Nathan D. Wong: to my wife Mia, son David and parents Donald and Mew Lun Wong

Ezra A. Amsterdam: to my wife, Beulah, and daughters, Elana Amsterdam and Dina Amsterdam

Peter P. Toth: to my most valued and influential teachers: Roger Waltemyer, Louis Bixby, Clarence Suelter, Denton A. Cooley, Paul Seifert, and Barbara Anne Gooding.

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Focus on Cardiovascular Health Promotion and Disease Prevention: Opportunities for Improvement

Devinder S. Dhindsa, Anurag Mehta, and Laurence S. Sperling

Summary

- Prior reductions in cardiovascular mortality have seen stagnation and even a reversal in that trend despite modern and expensive technologies and therapies.
- This trend is due in part to an increase in the prevalence of obesity and diabetes, with resultant impact on other cardiovascular risk factors.
- The need for prevention is imperative and requires a comprehensive approach on a continuum of care from individual patients to large-scale public policy initiatives.

1 Introduction

The latter part of the twentieth century in the United States was notable for an unprecedented reduction in cardiovascular deaths. Importantly, most of the decrease in cardiovascular deaths, particularly between 1980 and 2000, was attributable to preventive efforts through improved awareness and treatment of traditional cardiovascular risk factors (smoking, dyslipidemia, hypertension, diabetes) [1]. Unfortunately, in recent years there has been stagnation in these gains with trends demonstrating a concerning increase in cardiovascular mortality, particularly in younger adults, due in part to a rise in obesity and diabetes in the United States [2–5]. Currently, there are 30 million Americans living with diabetes, 84 million with pre-diabetes, and 75 million with hypertension, and nearly 40% of Americans are obese [6, 7]. Disturbingly, the development of these cardiovascular risk factors

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is largely preventable. Our current healthcare system is inadequate in promoting healthy behaviors and incentivizes disease-focused care, often at advanced stages.

Despite outspending any other country with 18% of our gross domestic product on healthcare, the United States is ranked last among industrialized nations in healthcare value, measured as a composite of care process, access, efficiency, equity, and healthcare outcomes [8]. In 2016, cardiovascular disease spending was estimated at $555 billion [9]. By 2035, this cost is expected to increase to $1.1 trillion [10]. Although spending on technology for cardiovascular care had value in prior decades, the current trends in cardiovascular outcomes suggest this trend may no longer be true [5, 10–12]. As such, a greater focus on primordial and primary prevention is critical for the health and well-being of our communities and our future economy.

2 Defining Cardiovascular Health

A definition of cardiovascular health is useful for guiding efforts geared toward health promotion and disease prevention. In 2010, the Goals and Metrics Committee of the Strategic Planning Task Force of the American Heart Association (AHA) envisioned ideal cardiovascular health as a combination of three key factors: (1) absence of cardiovascular disease (CVD), (2) favorable levels of cardiovascular health factors, and (3) presence of favorable health behaviors [13]. The committee developed objective definitions for "ideal," "intermediate," and "poor" cardiovascular health based on these principles incorporating a combination of seven distinct cardiovascular risk factors and health behaviors [13]. These modifiable cardiovascular risk factors have been colloquially termed Life's Simple 7 and consist of blood pressure, total cholesterol, fasting blood glucose, smoking, physical activity, body mass index, and healthy diet (Table 1) [13]. Ideal cardiovascular health was defined as the presence of ideal levels of all seven metrics, intermediate cardiovascular health as the presence of at least one intermediate metric without any poor metrics, and poor cardiovascular health as the presence of at least one poor health metric [13].

Over the past decade, several studies have reported that individuals with ideal cardiovascular health are rare in American communities. The estimated prevalence of ideal cardiovascular health ranged from 0.5% to 12% in a systematic review conducted in 2016 [14]. A seminal investigation from the National Health and Nutrition Examination Survey (NHANES) revealed that the proportion of American adults meeting all seven ideal cardiovascular health metrics declined over time from 2.0% [95% CI, 1.5–2.5%] in 1988–1994 to 1.2% [95% CI, 0.8–1.9%] in 2005–2010 [15]. Women, non-Hispanic whites, and those with higher education levels were more likely to meet a greater number of these cardiovascular health metrics than their male, ethnic minority, and less educated counterparts. Furthermore, this investigation and several other epidemiologic studies have demonstrated the direct association of ideal cardiovascular health with favorable long-term cardiovascular outcomes [14, 15]. These findings illustrate the urgent need for cardiovascular health

Table 1 Modifiable risk factors and behaviors comprising the definitions of poor, intermediate, and ideal cardiovascular health

Metric	Poor	Intermediate	Ideal
Blood pressure	SBP ≥140 or DBP ≥90 mm Hg	SBP 120–139 or DBP 80–89 mm Hg or treated to goal	SBP <120 or DBP <80 mm Hg
Total cholesterol	≥240 mg/dl	200–239 mg/dl or treated to goal	<200 mg/dl
Fasting glucose	≥126 mg/dl	100–125 mg/dl or treated to goal	<100 mg/dl
Smoking status	Current smoker	Former smoker or quit ≤12 months ago	Never smoker or quit >12 months ago
Physical activity	None	1–149 min/week moderate intensity or 1–74 min/week vigorous intensity or 1–149 min/week moderate + vigorous intensity	≥150 min/week moderate intensity or ≥75 min/week vigorous intensity or ≥150 min/week moderate + vigorous intensity
Body mass index	≥30 kg/m^2	25–29.9 kg/m^2	<25 kg/m^2
Healthy diet score*	0–1 component	2–3 components	4–5 components

Adapted from American Heart Association's Life's Simple 7
*The Goals and Metrics Committee of the Strategic Planning Task Force selected five aspects of diet to define a healthy dietary score, which is detailed in their American Heart Association Special Report [13]
SBP systolic blood pressure, *DBP* diastolic blood pressure, *mm HG* millimeters of mercury, *mg/dl* milligrams per deciliter, *min* minutes, *kg/m^2* kilogram per meter squared

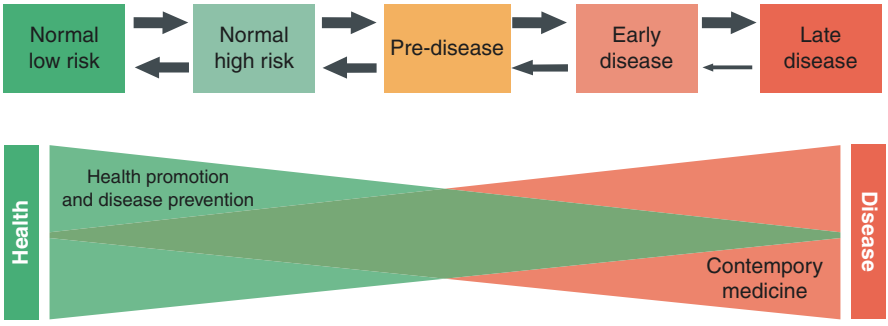

Fig. 1 The cardiovascular health/disease continuum. (Reprinted from Knapper et al. [16]. With permission from Elsevier)

promotion to help shift the cardiovascular health/disease continuum in favor of health (Fig. 1) [16].

A comprehensive, multifaceted approach that involves concerted efforts from key stakeholders is needed for promoting cardiovascular health. We will structure this chapter using the paradigm of the "three buckets of prevention": (1) traditional

clinical prevention, (2) innovative clinical prevention, and (3) community-wide prevention [17]. This framework is a useful means of approaching the continuum of prevention to discuss the challenges and opportunities related to cardiovascular prevention.

3 Bucket 1: Traditional Clinical Prevention

3.1 Improvement in Utilization and Adherence to Guideline-Recommended Therapies

Evidence-based guidelines are designed to guide clinicians and patients toward favorable outcomes for those with, or at risk for, atherosclerotic cardiovascular disease (ASCVD) [18, 19]. Unfortunately, current registries demonstrate inadequate uptake of recommendations, even those with a Class I indication. As an example, 28–36% of patients in the ACC National Cardiovascular Data Registry's (NCDR) Practice Innovation and Clinical Excellence (PINNACLE) Registry who were identified as high-risk benefit groups by current guidelines were not prescribed statins [20]. Additionally, other challenges include clinicians not prescribing the appropriate dose of statins despite supportive evidence for high-intensity statins in high-risk patients [21, 22]. In addition, there is significant lack of adherence among patients. In clinical trials and registries, nonadherence to statins is reported in up to 40% of subjects [23–26]. Together, between patient and clinician-related approaches to care, a large percentage of at-risk patients are not receiving guideline-directed medical therapy [27].

Importantly, lack of adherence poses both short-term and potential long-term risk. Younger patients accrue incremental benefit from early preventive therapy, yet are less likely to have hypertension diagnosed and treated, use statins as recommended, and are more likely to use tobacco [28–30]. Notably, in a high-risk secondary prevention cohort, 20% did not fill at least one of their prescribed cardiac medications within a month of hospital discharge after a myocardial infarction (MI), and of concern, nearly 50% of patients did not fill their antiplatelet therapy afterward [31]. Additionally, although lifestyle management remains the cornerstone of cardiovascular disease risk reduction, implementation remains a challenge, despite guideline recommendations. Americans have high rates of poor diet quality and physical inactivity [15, 28, 32]. Over one-fourth (28%) of US adults aged 35–64 are physically inactive, defined as never getting 10 min or more of leisure-time physical activity per day [28].

Multiple factors impact adherence. Out-of-pocket costs are a significant factor, although studies have shown that adherence does not improve substantially when medication copays are eliminated [33]. Additionally, clinicians and their patients, especially younger adults, may hesitate to start a medication regimen that could be lifelong, despite a strong indication to do so [34]. These challenges highlight multiple opportunities to address risk through better understanding and overcoming

barriers to adherence [23]. Whenever possible, clinicians should minimize patient cost, reduce barriers to obtaining medications, and simplify regimens [35]. Prescribing medication electronically reduces risk that a patient may lose a prescription. Pharmacy-initiated text reminders and automated refills are beneficial as well. Additionally, lower dosing frequency (i.e., utilizing long-acting formulations where possible) can improve adherence [36–38].

Evidence suggests that patients are more likely to make a lifestyle modification if their clinician recommends they do so [39]. One readily available lifestyle modification program is the National Diabetes Prevention Program, which enables people at risk for type 2 diabetes to participate in evidence-based lifestyle change programs that have shown significant long-term improvements on cardiovascular risk factors [40]. Registered dieticians, exercise physiologists, or promising community-based programs like Walk With a Doc should be utilized as well [41]. Engaging patients through involvement in shared decision-making, in which clinical guideline-based approaches in the context of individualized care, can strengthen therapeutic relationships, boosting patient engagement and medication adherence [42].

A systems approach to care, using protocols and electronic-medical record alerts, may be useful in overcoming some of the barriers on the part of physicians to implementation of guideline-directed therapy. Treatment protocols can help systematically identify patients who are eligible for intensification of clinical management, reduce variation between patients, simplify medication initiation and intensification, reinforce counselling on lifestyle modifications, and help in scheduling timely follow-up [34, 43]. Protocol implementation has been effective in improvement in performance on chronic disease quality indicators including hypertension control and may serve a critical role in cardiovascular risk reduction in our increasingly electronic and protocolized health system [44, 45].

3.2 Improving Utilization of Cardiac Rehabilitation

As a further example of challenges in implementation of guideline recommendations into clinical practice, cardiac rehabilitation (CR) remains significantly underutilized [46]. Cardiac rehabilitation (CR) services are an integral component in the care of patients with cardiovascular disease [47–49]. Referral to CR is a Class IA recommendation for secondary prevention established by the American Heart Association (AHA) and American College of Cardiology (ACC) after myocardial infarction (MI), percutaneous coronary intervention (PCI), or coronary artery bypass graft surgery (CABG), stable chronic heart failure, stable angina, cardiac transplantation, peripheral arterial disease, and cardiac valve surgery [50]. A meta-analysis of 34 randomized controlled trials showed that exercise-based CR programs in secondary prevention patients are associated with a lower risk of reinfarction (odds ratio [OR] 0.53; 95% confidence interval [CI] 0.38 to 0.76), cardiac mortality (OR 0.64; 95% CI 0.46 to 0.88), and all-cause mortality (OR 0.74, 95% CI 0.58 to 0.95), and CR also leads to improvements in cardiovascular risk

factors (i.e., lipid levels, blood pressure, tobacco use), as compared to usual care [51, 52]. Despite this, only about 60% of patients undergoing PCI are referred for cardiac rehabilitation [53] and even less enroll in CR. The safety and effectiveness of the traditional medically supervised, center-based CR is well established, but unfortunately CR remains substantially underused among eligible patients [54].

Data from several registries and databases indicate patient participation remains low across most demographic groups [49, 55]. Between 2007 and 2011, only 16.3% of Medicare patients and 10.3% of veterans participated in CR after hospitalization for MI, PCI, or CABG [55]. Improving referral rates through education and/or automatic generation of referrals following a hospitalization for a cardiac diagnosis is one possible solution to poor referral rates, but lack of access and other barriers including competing responsibilities, cost/financial viability, and perceived inconvenience for the patient require innovative solutions.

3.3 Improving Identification and Treatment of Familial Hypercholesterolemia

Familial hypercholesterolemia (FH) is the most common autosomal dominant genetic disorder, affecting one in 250 people worldwide in heterozygous form and approximately one in one million in homozygous form [56]. FH is caused by mutations in genes responsible for low-density lipoprotein (LDL) receptor and if left untreated places affected individuals at high risk for premature cardiovascular disease. FH is suggested to account for nearly 20% of myocardial infarctions before the age of 45, and the first presentation of the disease may be MI or sudden death, with homozygous FH resulting in significant ASCVD in childhood [57]. As such, early identification of this disease is critical, as starting therapy with statins and other lipid-lowering medications has been shown to attenuate this risk [58].

Despite the danger presented by this genetic disease, FH remains underdiagnosed and undertreated [59]. Public awareness and implementation of the recommendations from the World Health Organization regarding FH care have lagged substantially behind other advancements made within cardiovascular medicine [60]. Clinicians underestimate the prevalence, high level of risk, importance of treatment initiation within the first two decades of life, and the autosomal dominant inheritance pattern necessitating cascade family screening. Limited understanding by affected individuals of their disease process, economic ramifications of living with and affording lifelong care, and pragmatic concerns surrounding possible genetic discrimination pose additional barriers to care in those who are able to receive an accurate diagnosis [61]. Use of registries, such as the CASCADE FH Registry, and public awareness campaigns are critical to improving detection of this disease estimated to affect 34 million individuals worldwide [62]. Groups such as the FH Foundation have made significant progress in helping increase awareness and identify affected patients [63].

4 Bucket 2: Innovative Clinical Prevention

4.1 New Care Models

The prior discussion on the poor utilization of CR highlights the need for new care models in the modern era. Potential approaches include alternative site-, home-based, or hybrid models of CR, which can be carried out in the home or other non-clinical settings, alleviating access-related barriers for patients. European guidelines on CVD prevention state that "home-based rehabilitation with and without telemonitoring holds promise for increasing participation and supporting behavioral change" [63]. Comparisons of center-based CR and home-based CR show similar effects on quality of life and cost among patients with recent MI or PCI, with low rates of adverse events [49, 64, 65]. Theoretically, these types of programs can be used for other preventive strategies including management of risk factors, increasing physical activity, and maintenance of a healthy dietary pattern.

The increasing use of mobile technology serves as another opportunity to reduce gaps in access to CR through mobile health or "M-health" [66]. Mobile technology is widely utilized in the United States, with approximately 95% of adults owning a cellular device, and smartphone ownership estimated to be at 77%, an increase from 35% in 2011 [67]. This rise in smartphone adoption provides an opportunity to leverage advances in mobile technology, especially in capturing data regarding patient behaviors, physical activity, and enhanced two-way communication. Early research suggests "mCR" may be associated with greater utilization as post-MI patients assigned to a smartphone-based CR program had greater uptake (80% vs 62%), adherence (94% vs 68%), and completion (80% vs 47%) of a CR program compared to those assigned to traditional, center-based CR [68]. Both groups showed similar improvements in physiological and psychological outcomes suggesting equivalent benefits could be achieved with potential reductions in mortality and morbidity commensurate with those observed with center-based programs, with much greater reach [66].

Furthermore, the potential utility of m-health also extends to the promotion of healthy behavior modification beyond CR [69, 70]. A randomized controlled Tobacco, Exercise and Diet Messages (TEXT ME) trial showed that the use of lifestyle-focused text messaging resulted in significant reduction in low-density lipoprotein cholesterol, systolic blood pressure, body mass index, and smoking rates and an increase in physical activity compared to usual care in patients with established cardiovascular disease [71]. Patient education via social media and Internet sources has been shown to increase adherence in patients with non-cardiovascular conditions and could similarly impact cardiovascular care [5, 72, 73].

Systematic reviews indicate benefits of digital health interventions (telemedicine, web-based strategies, e-mail, mobile applications, text messages, remote monitoring) on improving cardiovascular risk [74]. An important area of future investigation will be exploring opportunities to optimize other emerging technologies (i.e., smartphone applications) to improve access, reach, and effectiveness of cardiovascular risk reduction strategies [66].

4.2 Improving Risk Assessment and Treatment of Cardiovascular Disease

Estimation of risk is the first step in cardiovascular disease prevention. In the 2018 ACC/AHA Cholesterol Guidelines, risk calculation guides initiation and intensity of therapy [75]. However, it is important for clinicians to recognize the limitations of population-based risk calculators for individual risk estimation. The 2018 Cholesterol Guideline recommends the identification of risk-enhancing factors beyond traditional cardiovascular risk factors and appropriate consideration of cardiac CT calcium scoring to reclassify risk with the goal of a more accurate and personalized assessment of risk (Table 2) [18]. Advances in genomics and biomarkers may enhance our ability to further assess risk facilitating tailored therapies. Polygenic risk scores may help identify patients at highest cardiovascular risk, even in the absence of traditional cardiovascular risk factors, who may benefit from earlier or more aggressive interventions [76, 77]. Large longitudinal studies, such as the NIH-funded *All of Us Research Program*, which is enrolling one million individuals, can collect the detailed genotypic and phenotypic data needed for this type of research [78]. Initiatives such as this will be invaluable in research and innovation moving forward to usher in an era of precision medicine with refined risk prediction and individualized targeted therapies.

4.3 Improving Partnerships and the Use of Registries

Registries offer clinicians and health systems the capability to evaluate real-world data to monitor practice patterns and trends. Use of the ACC's National Cardiac Data Registry (NCDR) and the Diabetes Collaborative Registry (tracking eight diabetes-related metrics and six either ACC/AHA-endorsed or Physician Quality

Table 2 Risk-enhancing factors in the 2018 ACC/AHA Cholesterol Guidelines

Family history of premature ASCVD (males <55 years; females <65 years)
Primary hypercholesterolemia (LDL-C 160–189 mg/dL; non-HDL-C 190–219 mg/dL)
Metabolic syndrome (three of the following: increased waist circumference, elevated triglycerides ≥150 mg/dL, elevated glucose, low HDL-C)
Chronic kidney disease
Chronic inflammatory conditions
*History of premature menopause (before 40 years) and history of pregnancy-associated conditions (*i.e., *preeclampsia)*
High-risk ethnicities (i.e., South Asian ancestry)
Elevated biomarkers (high-sensitivity C-reactive protein ≥2 mg/L; lipoprotein (a) ≥50 mg/dL or ≥ 125 nmol/L; apo B ≥130 mg/dL)
Ankle-brachial index < 0.9

Based on data from Ref. [75]
ASCVD atherosclerotic cardiovascular disease, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *apoB* apolipoprotein B

Reimbursement System (PQRS) measures) can increase awareness of gaps in care and may lead to improvements in reaching these quality metrics [79, 80]. Similarly, the CASCADE FH Registry provides similar data among FH patients with the goal of improving detection and care of FH patients [62].

5 Bucket 3: Community-Wide Prevention

5.1 Public Policy

Public policy and legislation are perhaps the most powerful tools that can help promote cardiovascular health on the local and national level [81]. A key set of public policies that have an outsized impact on cardiovascular health pertains to taxation of unhealthy consumables, particularly cigarettes [81]. Previous research has shown that higher cigarette taxes are associated with a decrease in consumption, especially among young individuals [82]. Simulation experiments suggest that a 40% tax-induced increase in cigarette prices would reduce smoking prevalence from 21% in 2004 to 15.2% in 2025 [83]. This change would translate into 13 million quality-adjusted life-years gained and $682 billion in total savings [83]. In addition to cigarette taxes, banning public smoking, improving access to healthy affordable foods, taxing sugar-sweetened beverage, restricting trans-fat use, and mandating calorie counts on chain restaurant menus are important public policy avenues that can help promote cardiovascular health.

5.2 Public Health Initiatives

Several public health initiatives geared toward promoting cardiovascular health are operational at the local and national level. Among these, Million Hearts®, a national initiative co-led by the Centers for Disease Control and Prevention (CDC) and the Centers for Medicare and Medicaid Services (CMS), is one of the most ambitious. The initiative has set a goal of preventing one million heart attacks and strokes within 5 years by focusing on a small set of priorities selected for their ability to reduce heart disease, stroke, and related conditions [84]. These priorities include (1) keeping people healthy by reducing daily sodium consumption, prevalence of tobacco use, and physical inactivity; (2) optimizing care by increasing appropriate aspirin use, blood pressure control, cholesterol management, smoking cessation, and cardiac rehabilitation use; and (3) focusing on priority populations such as African Americans with hypertension, people aged 35–64 years, patients with a history of heart attack or stroke, and patients with mental or substance use disorders that consume tobacco [85]. Other publicly focused initiatives like the Let's Move campaign, AHA Go Red for Women, and National Institutes of Health's Heart Truth are focused on promoting cardiovascular health in specific populations.

5.3 Mass Media Campaigns

Mass media campaigns have the ability of promoting cardiovascular health by impacting large population segments. Smoking cessation campaigns are perhaps the best studied and have been associated with increased quitting rates among smokers [86]. Additionally, the Stanford Heart Disease Prevention Program and the Minnesota Heart Health Program were two large studies conducted focused on preventing CVD [86]. The results of these studies suggest that media campaigns can not only promote physical activity and healthy diet but also help increase CVD awareness [86].

5.4 Environmental Interventions

Environmental interventions are important methods for promoting cardiovascular health because building designs and city plans can encourage and facilitate physical activity among residents [81]. For instance, the Task Force on Community Preventive Services has observed that creating or improving access to places where physical activity is feasible results in a 25% increase in the proportion of people who are physically active at least three times a week [87]. Physical activity can be fostered through innovative land use and community design interventions to make it safe and convenient to be physically active [88]. Places for physical activity can be created or developed using existing spaces through enhanced access via shared use agreements [89]. Designing a community to support physical activity through activity-friendly routes to everyday destinations is a critical intervention in a country where over one-fourth (28%) of US adults aged 35–64 state they are not engaging in even 10 min or more of leisure-time physical activity per day [28].

5.5 School-Based Interventions

Schools can play an instrumental role in promoting cardiovascular health at an early age, as nearly 55 million American children spend a majority of their time in schools [81]. The structured framework in schools can be leveraged to provide health education and encourage children to participate in healthy activities on a daily basis. The SPARK (Sports, Play, and Active Recreation for Kids) and CATCH (Coordinated Approach To Child Health) programs are prime examples of such school-based interventions [90, 91]. In addition to promoting physical health, these programs have been shown to improve academic performance and decrease disciplinary problems [92, 93]. The programs are generally cost-effective and lead to an overall improvement in school environment.

5.6 Workplace Interventions

Employee healthcare costs are an important cause of financial strain for employers and improving employee cardiovascular health serves as a significant financial incentive. Several workplace interventions such as smoke-free zones, healthy food and beverage options, worksite wellness programs, and treadmill workstations can be helpful for promoting cardiovascular health at the workplace [94].

6 Conclusion

Improvements in health promotion and disease prevention are critical to turning the tide of rising cardiovascular mortality. Although technological and therapeutic advancements will accelerate, relying on these alone will be inadequate without addressing the main drivers of ASCVD. Despite significant challenges, there is tremendous opportunity for preventive cardiologists and cardiovascular preventive specialists to be at the forefront of new care models, important partnerships, and initiatives. Integrated strategies that encompass each of the three buckets of prevention are essential to the health of individuals and communities and to reducing the burden of cardiovascular diseases on society.

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National and Global Trends of Cardiovascular Disease Mortality, Morbidity, and Risk

Sadiya S. Khan, Stephen Sidney, Donald M. Lloyd-Jones, and Jamal S. Rana

Summary

- Age-adjusted mortality rates demonstrate continued, but slower declines due to heart disease, a plateau related to stroke and diabetes, and persistent increases related to hypertension.
- Among cardiovascular disease subtypes, mortality rates due to heart failure have increased substantially, by a 38% increase in the number of deaths from 2011 to 2017.
- The aging population (≥65 years), which represents the vast majority of all cardiovascular deaths, is projected to increase by 44% between 2017 and 2030 and will likely contribute to a growing burden of cardiovascular mortality in the USA.
- Significant geographic heterogeneity exists in cardiovascular disease mortality rates with the highest age-adjusted mortality rates in the south and in rural counties.
- One in two American adults have some form of cardiovascular disease (coronary heart disease, heart failure, stroke, and hypertension) on the

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basis of nationally representative data from the National Health and Nutrition Examination Survey 2013 to 2016 survey cycles.
- Maintaining better cardiovascular health to middle age is associated with substantially lower risk of developing subclinical or clinical cardiovascular disease or death, indicating important strategies for future prevention efforts.

1 Introduction

The burden of cardiovascular disease (CVD) is rising once again in the USA and worldwide [1, 2]. Nearly 50% of Americans have some form of CVD (coronary heart disease [CHD], heart failure [HF], stroke, and hypertension) with greater rates in non-Hispanic blacks and other disadvantaged populations [3]. When hypertension is excluded, prevalence of CVD is estimated to be 9.0% in the general population. One of the most remarkable and unprecedented public health successes in the last half century has been the dramatic and persistent decline in age-adjusted CVD death rates. Between 1970 and 2010, CVD death rates declined by >50% and CHD death rates declined by >75% [4]. This decline has been attributed to progress in prevention and significant advances in medical and surgical treatments for CVD [5]. Nonetheless, CVD remains the leading cause of US mortality today, and a large proportion of which is preventable (Fig. 1a) [6]. While mortality rates continued to decline after 2000 [7], contemporary data now demonstrate that HD mortality rates plateaued in 2011 (Fig. 1b) [1, 8, 9]. Furthermore, a trend reversal has been observed undoing decades of progress in HD prevention and management with increasing HD death rates in certain population subgroups, such as younger Americans [10]. Increases in midlife mortality, in large part due to CVD, have led to a decrease in life expectancy for the first time in decades [11, 12]. The economic burden of CVD events (CHD, HF, and stroke) related to morbidity and healthcare costs continues to soar, accounting for >6 million hospital discharges and annual direct US costs exceeding $320 billion currently and projected to exceed $800 billion annually by 2030, when >42% of American adults are expected to have some form of CVD [13–15]. Finally, major health disparities in CVD burden persist [13].

At present, it is unclear what factors are contributing to the observed flattening and upward trends observed in CVD death rates, although a number of possible explanations have been posited. We and others have speculated that the worsening trends could be related to the obesity epidemic and consequent adverse changes in risk factors finally becoming manifest in CVD death rates [16]; it could also be due to ceiling effect of gains realized from medical interventions to prevent death among those with acute CVD events. Finally, absolute CVD deaths have increased, in part, due to the aging population. Most likely, the causes are multifactorial and may differ for each sex-race group; and if current trends continue, strategic goals for lowering the burden of CVD set by the American Heart Association (AHA) [17, 18], the

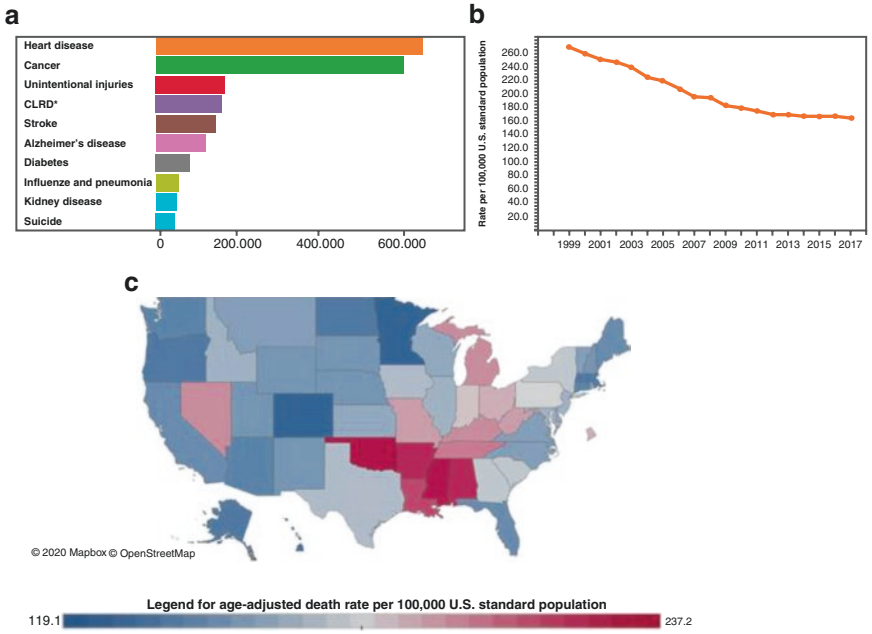

Fig. 1 Number of deaths and age-adjusted mortality rate for heart disease in the USA, overall and by state in 2017 (NCHS Data Visualization Tool). (**a**) Number of deaths for the ten leading causes of the death in the USA. (**b**) Age-adjusted mortality rate due to heart disease in the USA, 1999–2007. (**c**) Age-adjusted mortality rate due to heart disease in the USA by state, 2017

Million Hearts Initiative [19], and the World Health Organization [20] are unlikely to be reached. In the face of this uncertainty, it is now imperative to gain a deeper understanding of past trends in fatal and nonfatal CVD rates and risk factors to inform potential interventions on an individual and population level in the USA and globally.

2 Overall Cardiovascular Disease Mortality and Morbidity

2.1 Cardiovascular Disease Mortality

Total deaths in the USA attributed to major CVD (*International Classification of Diseases, Tenth Revision* [*ICD-10*] codes I00-I78) in 2018 were 863,834 (an 11% increase compared with 2011) [21]. Deceleration in the decline of age-adjusted mortality rate (AAMR) due to CVD was first observed and reported by examining data from 1999 to 2014 by Sidney et al. [9] and was confirmed in a recent time-trend analysis incorporating mortality data through 2017 by Shah et al. [1] using the Joinpoint Regression Program (National Cancer Institute) [22]. Specifically, the rate

of AAMR declines for heart disease was −8.3 (95% confidence interval [CI] −8.8, −7.8) indicating that 8.3 fewer deaths per 100,000 population occurred per year between 1999 and 2010. This substantially slowed subsequently with a rate of decline of −1.8 (−2.5, −1.0) between 2010 and 2017.

Significant heterogeneity in CVD mortality exists across states (Fig. 1c); observed declines between 1999 and 2016 varied widely and were largely attributable to cardiovascular risk factors [23]. Disparities in CVD mortality also exist on a county level, and rural counties in the "US heartland" in southeastern Oklahoma, the Mississippi River Valley, and Eastern Kentucky bore a disproportionate burden of counties at >90th percentile for CVD mortality, whereas the lowest CVD mortality rates were observed in counties in California, Colorado, Nebraska, Minnesota, Virginia, and Florida [24].

Marked disparities persist in CVD mortality in that non-Hispanic blacks (NHB) compared with NH whites have higher AAMR for CVD with the highest CVD AAMR occurring in NHB men (Fig. 2) [3, 25, 26]. Further, these disparities have remained largely unchanged over time and are likely attributable to multiple factors, such as access to healthcare, disease management, and delivery of care as well as general societal and structural contributors to health and disease (e.g., income, education, safe housing, racism) [27]. Limited data on American Indians/Alaska Natives likely obscure the burden of CVD mortality in this population subgroup and lack of mortality data on disaggregated Hispanic and Asian subgroups makes it challenging to interpret mortality differences.

Of note, the burden of CVD mortality is greatest among older adults aged 65 years and older who represented over 80% of all CVD deaths in 2018 [2]. The total US population of older adults has increased significantly with 50.9 million adults aged 65 years and older in 2017 (22.9% total increase between 2011 and 2017). Despite declines in AAMR, the growth of the aging population accounts for a significant increase in total CVD deaths. Given projections of the population of older adults to increase to 73.1 million by 2030 (44% increase estimated between 2017 and 2030), innovative strategies to prevent and manage CVD are needed that target the morbidity and mortality in this growing "baby boomer" subgroup.

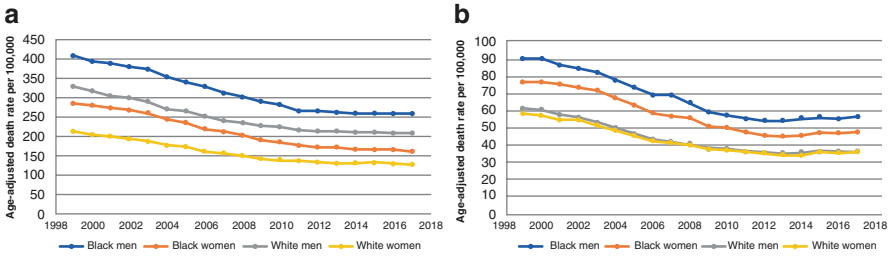

Fig. 2 Trends in cardiovascular mortality by race-sex subgroups due to heart disease and stroke in the USA from vital statistics using the centers for disease control wide-ranging online data for epidemiologic research data source, 1999–2017. (**a**) Heart diseases. (**b**) Cerebrovascular diseases

2.2 Cardiovascular Disease Morbidity

Prevalence of CVD (comprising of CHD, stroke, HF, and hypertension) in adults aged ≥20 years and older is estimated to be 48.0% overall (representing 121.5 million adults in 2016) based on data from the National Health and Nutrition Examination Survey 2013 to 2016 data [3]. Excluding hypertension, CVD prevalence is 9.0% representing 24.3 million adults in 2016. Age-adjusted prevalence of heart disease varied by race/ethnicity (11.0%, 9.7%, 7.4%, and 6.1% among whites, blacks, Hispanics, and Asians, respectively). Healthcare utilization for CVD remains high with increases in the number of hospital discharges from 1993 to 2016 with approximately 4,840,000 inpatient discharges with CVD as a principal diagnosis in 2016 based on the Healthcare Cost and Utilization Project (HCUP) data [3]. In addition, there were 4,774,000 visits to the emergency department (ED) and 72,128,000 physician office visits with a primary diagnosis of CVD in 2016 based on National Ambulatory Medical Care Survey (NAMCS) data [3].

3 Mortality and Morbidity Attributable to CVD Subtypes in the USA

Subtypes of HD, such as CHD, stroke, heart failure (HF), and hypertension, are heterogeneous in their pathophysiology and contribution toward preventable fatal and nonfatal CVD events. Therefore, in order to facilitate targeted efforts to reduce the national burden of CVD, it is important to delineate cause-specific patterns in CVD morbidity and mortality that have significant variability.

3.1 Coronary Heart Disease

Total deaths attributed to CHD (*ICD 10* codes I20-I28) in 2018 were 365,744 (a 3% decrease compared with 2011), which represents the largest subgroup of deaths due to CVD [21]. Rates of decline in CHD followed similar patterns to overall CVD trends with deceleration in decline of ischemic heart disease (IHD) AAMR (mean annual rate of change −2.7% per year between 2011 and 2015 compared with −5.0% per year between 2000 and 2011) [28]. This inflection point in 2011 was statistically significant in the overall population as well as in men and women and among NH whites, NH blacks, and Hispanic adults. As for total CVD, NH blacks had the highest AAMR due to CHD.

An estimated 18.2 million American adults have CHD based on self-reported data from the 2013–2016 NHANES survey cycles with an overall prevalence of 6.7% [3]. Based on data from the 2017 National Health Interview Survey, prevalence of CHD is estimated to be highest among blacks (5.9%) compared with whites

(5.6%), Asians (4.3%), and American Indian/Alaska Natives (2.7%) [3]. While the overall body of literature identifies a decline in the incidence of CHD over time, emerging data from the Atherosclerosis Risk in Communities Study identified an increase in the proportion of hospitalizations for acute myocardial infarction (MI) occurring among younger adults (35–54 years) from 25% to 32% of all hospitalizations for MIs between 1995 and 2014 [29].

There are multiple factors that may contribute to both the decline and now the overall deceleration in the decline in CHD deaths in the USA over the past several decades, including heterogeneous changes in cardiovascular risk factor burden as well as remarkable advances in medical, surgical, and device treatments for CVD. When applying the widely validated IMPACT model to CHD mortality data between 1980 and 2000, reductions in major cardiovascular risk factors (total cholesterol, systolic blood pressures, rates of cigarette smoking) accounted for approximately 61% of the decrease in CHD deaths [5]. However, this was offset, in part, by increases in body mass index and prevalence of diabetes, which resulted in approximately 25,905 and 33,465 additional deaths, respectively. Approximately 47% of deaths prevented were explained by changes in medical treatments, predominantly secondary prevention. This highlights that prior to 2000, even before the deceleration observed in 2011, increases in the rates of obesity and diabetes were beginning to contribute to excess CHD mortality. These data inform future individual-level and population-based prevention strategies targeting prevention of risk factors as well as dissemination and implementation to enhance uptake of evidence-based medical therapies for CHD.

3.2 Stroke and Transient Ischemic Attack

Total deaths attributed to cerebrovascular diseases or stroke (*ICD 10* codes I60-I69) in 2018 were 147,810 (a 15% increase compared with 2011) [21]. When separated from aggregate CVD mortality, stroke ranks fifth among all causes of death, behind heart disease, cancer, respiratory diseases, and unintentional injuries/accidents [3]. AAMR from 1999 to 2017 experienced an inflection point in 2011, similar to overall CVD with the rate of AAMR decline between 1999 and 2011 of −2.3 deaths per 100,000/year with no significant change in AAMR between 2011 and 2017 [1]. Similar disparities were observed in mortality due to stroke with stroke AAMR for NH black adults compared with NH white, NH Asian, NH Indian or Alaska Native, and adults in the USA [3]. There are also significant disparities geographically for stroke mortality with the approximately 30 to 40% higher rates in the southeastern USA, termed the “stroke belt,” that have persisted since 1940 [24].

Based on data from NHANES 2013 to 2016, stroke prevalence was estimated to be 2.5% representing 7.0 million American adults [3]. Projections predict a 21% increase in prevalence of stroke by 2030 [30]. Stroke events annually exceed 790,000, of which 30% are recurrent stroke events, approximately 87% are ischemic, and 13% are hemorrhagic [3]. Prevalence of transient ischemic attacks is

limited based on awareness, but is estimated to be at least 2.3% or five million adults in the USA. Hospitalization rates for acute ischemic stroke have largely remained stable or increased over time in younger adults (25–59 years), but have declined for older adults (≥60 years) [31, 32]. Black-white disparities in stroke are greater among younger adults with incidence rate ratio (IRR) of 4.02 for those aged 45–54 years, whereas overall age- and sex-adjusted IRR was 1.51 [33, 34]. In 2016, 874,000 inpatient discharges, 590,000 ED visits, and 2,155,000 physician office visits with stroke as the principal or first-listed diagnosis occurred [3].

3.3 Heart Failure

Total deaths attributed to HF (*ICD 10* codes I50) in 2018 as an underlying cause of death and multiple cause of death (i.e., any mention on the death certificate) were 83,616 (a 43% increase compared with 2011) and 366,464 (a 29% increase compared with 2011), respectively [21]. Surveillance statistics measuring mortality related to HF are fraught with coding issues in that HF is not considered an underlying cause of death by nosologists, but a mode of death, and the underlying cause of death should be listed as the disease process leading to HF (e.g., CHD) [35]. As a result of coding recommendations for death certificates to discourage the recording of HF as the underlying cause of death, any mention of HF on the death certificate represents a more comprehensive burden of mortality related to HF. However, this still does not allow distinction between the two major subtypes of HF that share similar case fatality rates: HF with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF). Between 2000 and 2011, the AAMR of HF as any mention decreased and reversed with increasing AAMR subsequently [28]. Relative increases in HF AAMR were greatest among younger adults (<65 years), but the absolute burden of HF deaths was greatest among older adults (≥65 years) [2, 36]. Numerous studies have outlined the adverse consequences of a national policy, the Hospital Readmissions Reduction Program established by the Centers for Medicare and Medicaid Services to impose financial penalties on hospitals with higher-than-expected 30-day readmission rates in patients with HF that may also be contributing, in part, to increasing mortality trends [37–39].

Prevalence of HF is estimated to be 6.2 million among American adults based on NHANES 2013 to 2016 with projections estimating the prevalence will increase to >8 million (a 46% increase) by 2030 based on the aging population [3, 40]. Decrease in the incidence of HF was reported in data from Olmsted County between 2000 and 2010 (315.8 vs. 219.3 per 100,000) [41]. Despite these promising data, overall remaining lifetime risk for HF remains high and is estimated to range from 20 to 45% at age 45 years in data from the Cardiovascular Lifetime Risk Pooling project [42]. Burden of hospitalized HF remains high with 809,000 discharges in 2016. In addition, 1,932,000 physician office visits and 414,000 ED visits for HF occurred in 2016 [3]. Heterogeneous trends within HF for HFrEF and HFpEF are even more challenging to account for in the absence of a national surveillance system. Registry,

electronic health record, and cohort data suggest that HFpEF is now the predominant cause of HF and is expected to increase in the context of the aging population and increasing rates of obesity and diabetes [43, 44]. Contemporary data from Get With the Guidelines that was linked to Medicare identify from a total of 39,982 patients from 254 hospitals between 2005 and 2019 that 46% had HFpEF (≥50%), 8.2% had borderline EF (40–49%), and 46% had HFrEF (<40%) with median survival of 2.1 years. All three types of HF had similar 5-year mortality rates [45, 46]. Patients with HFpEF had the greatest risk of all-cause readmission, but HF with borderline EF and HFrEF had higher rates of cardiovascular and HF readmissions.

3.4 Hypertension

Total deaths attributed to hypertension (*ICD 10* codes I10-I15) in 2018 as an underlying cause of death and multiple cause of death (or any mention) were 95,876 (a 123% increase compared with 1999) and 494,873 (a 323% increase compared with 1999), respectively [21]. Significant race disparities in hypertension-related mortality exist with age-adjusted mortality rates for hypertension as an underlying cause of death in 2017 estimated to be twice as high for NH black compared with NH white men and women (54.1 vs. 23.0 and 37.8 vs. 18.6 per 100,000, respectively) [3]. Since hypertension is relatively infrequently the direct cause of death, examining any mention of hypertension on the death certificate provides a broader and more comprehensive burden of mortality related to HTN. Age-adjusted mortality rate for hypertension as any mention was similarly higher in 2017 for NH black compared with NH white men and women (224.9 vs. 132.9 and 155.3 vs. 99.8 per 100,000, respectively). It is also important to note that these mortality estimates are based on ICD coding for hypertension and not threshold values of blood pressure.

Changing definitions of hypertension have led to widely different published prevalence rates in the literature. Hypertension is also further complicated by different subtypes, including white-coat hypertension and masked hypertension that are harder to identify based on ambulatory clinic blood pressure readings alone. Overall prevalence of hypertension in the USA is high and estimated to be 46.0% based on data from NHANES 2013 to 2016 representing 116.4 million adults based on systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 or on antihypertensive medication using the latest 2017 definition [3]. Estimates across the spectrum of BP categories include approximately 42.3%, 12.1%, 13.7%, and 7.7% with BP readings <120/80, 120 to 129/<80, 130 to 139/80 to 89, and ≥140/90 mm Hg for those not on treatment based on data from NHANES 2011–2014 [47]. Treatment-resistant hypertension is also an important form of hypertension that is associated with high rates of CVD morbidity and mortality and is estimated to complicate approximately 13.7% of cases and increases to 40.4% in a high-risk population of chronic kidney disease [48]. In 2016, hospital discharges with hypertension as the principal diagnosis and any listing were 486,000 and 16,676,000, respectively. Eliminating hypertension is likely to have the most significant impact on reducing

CVD mortality compared with elimination of all other risk factors in women and all other risk factors except smoking in men and is estimated to potentially reduce CVD mortality by 30.4% and 38.0% among men and women, respectively [49].

3.5 Other Cardiovascular Disease

Burden of CVD can also be attributed to additional subtypes of heart disease, such as valvular heart disease, congenital heart disease, and arrhythmias.

Total deaths attributed to valvular heart disease (*ICD 10* codes I34-I38) in 2017 as an underlying cause of death and multiple cause of death (or any mention) were 24,811 and 52,939, respectively. In 2016, 120,000 hospital discharges were for valvular heart disease. Overall prevalence of undiagnosed moderate or severe valvular disease in a primary care population in Europe that was screened with echocardiography was 6.4% [50].

Congenital heart disease is a common form of CVD that represents a growing proportion of adults with CVD given improvement in health outcomes and survival into adulthood. In 2017, mortality related to congenital heart disease was estimated to contribute to 2906 deaths or 0.9 per 100,000 population. In 2010, the estimated prevalence of congenital heart disease was 2.4 million and, in 2016, accounted for 45,000 total hospital discharges. The annual birth prevalence ranges from 2.4 to 13.7 per 1000 live births.

Overall arrhythmias with any mention of disorder of heart rhythm contributed to 558,408 deaths in 2017. The most common disordered heart rhythm is atrial fibrillation and atrial flutter. In 2017, atrial fibrillation was listed as an underlying cause of death in 26,077 and any-mention mortality on 166,793 death certificates. Prevalence of atrial fibrillation in the USA was estimated to be 5.2 million in 2010 with projections increasing to 12.1 million by 2030.

4 Prevalence of Ideal Cardiovascular Health Factor Levels

CVD develops across the life span as the cumulative product of early life and chronic exposures from the environment and health behaviors (e.g., adverse diet, low physical activity, smoking) and the development of risk factors (overweight/obesity, elevated blood pressure, dyslipidemia, dysglycemia) leading to clinical CVD events. However, this progression to CVD during the life course is eminently preventable through individual and population *primordial prevention* strategies, focused from birth on lifestyle and environment to maintain higher stock of health and prevent the development of causal risk factors, and *primary prevention* strategies that identify individuals at risk for incident CVD and attempt to intervene with lifestyle or drug therapies (e.g., weight loss, smoking cessation, statins, antihypertensive therapy. In 2010, the AHA developed and defined a new construct of

Table 1 American Heart Association definition of poor, intermediate, and ideal cardiovascular health for each metric

	Level of cardiovascular health for each metric		
	Poor	Intermediate	Ideal
Current smoking	Yes	Former <12 months	Never or quit ≥12 months
Body mass index	≥30 kg/m^2	25–29.9 kg/m^2	<25 kg/m^2
Physical activity	None	1–149 min/week moderate or 1–74 min/week vigorous or combination	≥150 min/week moderate or ≥75 min/week vigorous or combination
Diet pattern[a], no of components	0–1	2–3	4–5
Total cholesterol	≥240	200–239 or treated to goal	<200
Blood pressure	SBP ≥140 or DBP ≥90	SBP 120–139 mm Hg or DBP 80–89 mm Hg or treated to goal	<120 mm Hg/ <80 mm Hg
Fasting plasma glucose, mg/dL	≥126	100–125 or treated to goal	<100

Adapted from Lloyd-Jones et al. [17] with permission from Wolters Kluwer Health, Inc.
[a]In the context of a healthy dietary pattern that is consistent with a Dietary Approaches to Stop Hypertension-type eating pattern, to consume ≥4.5 cups/day of fruits and vegetables, ≥2 servings/wk of fish, and ≥3 servings/day of whole grains and no more than 36 oz/week of sugar-sweetened beverages and 1500 mg/day of sodium

"cardiovascular health" (CVH), to help quantify CVH in individuals and the population, monitor it over time, and potentially modify it to prevent CVD (Table 1).

In 2010, the AHA developed and defined a new construct of "cardiovascular health" (CVH), to help quantify CVH in individuals and the population, monitor it over time, and potentially modify it to prevent CVD [17]. The full spectrum of CVH can be assessed through the presence and levels of health behaviors and factors: smoking status, physical activity, diet, body mass index, cholesterol, blood pressure, and fasting glucose.

Unfortunately, CV health typically declines from childhood through adolescence to young adulthood and into middle age [51–54]. In a recent study describing trajectories of CVH from young adulthood to midlife using pooled data from five prospective cohorts (the Cardiovascular Risk in Young Finns Study (YFS), Bogalusa Heart Study (BHS), Project Heartbeat, the Special Turku Coronary Risk Factor Intervention Project (STRIP), and the Coronary Artery Risk Development in Young Adults (CARDIA) study), levels of intermediate CVH were present in 25% of the cohort as early as 8 years of age with subsequent declines in CVH. Further, long-term trajectories of CVH were shown to be associated with subclinical atherosclerosis in midlife (carotid intima-media thickness) [55]. These data are consistent with numerous other studies linking favorable CVH with reduction of CVD and non-CVD morbidity, compression of morbidity toward the end of life, and lengthening of health span in multiple population-based cohort studies as well as lower risk

of atherosclerotic CVD in an electronic health record cohort [56–62]. However, few US adults maintain this ideal CV health profile into middle age, and cumulative exposure to intermediate or poor CVH over the lifetime is associated with adverse outcomes highlighting the importance of prevention efforts earlier in the life course [63, 64]. In fact, NHANES data from 2013 to 2016 estimate that <1% of adults meet criteria for ideal levels of five or more CVH metrics.

Despite major health promotion efforts by organizations such as the AHA to improve CVH of all Americans by 2020, the 2012 forecast of only a 6% improvement in population CVH by 2020 is on track to be accurate [63]. However, deterioration of CVH is not an inevitable consequence of aging; it is highly preventable. Behavioral and environmental factors, including policies, play a powerful role in preservation or loss of optimal health factor levels with aging, while genetic factors account for <20% of the variance in maintenance of ideal CV health into middle age [65, 66]. A recent study demonstrated that 60% of young adults who follow five healthy lifestyles (body mass index <25 kg/m^2, no or moderate alcohol intake, healthy diet pattern, healthy physical activity levels, and no smoking) achieve ideal CV health into middle age compared with just 3% of those with no healthy lifestyles [67]. Finally, race disparities in CVH metrics persist [64].

It remains critically important to identify and provide the evidence basis for optimal population-wide strategies that will preserve ideal CVH status from younger life into middle age and beyond and restore greater CVH when possible in middle and older ages. One potential target for CVH promotion that can enhance prevention efforts is 50 × 50 × 50 representing a bold goal to achieve a prevalence of ideal CVH ≥50% in all segments of the population less than age 50 years by 2050 in order to equitably achieve the CVD endgame for all [68].

5 Global Burden of Cardiovascular Disease

Approximately 18 million deaths worldwide annually are due to CVD, a number estimated to increase to 23.6 million by 2030 [69, 70]. Data from the World Economic Forum highlights that CVD now represents 50% of noncommunicable disease and preventable deaths and represents 37% of noncommunicable disease deaths in individuals <70 years [71]. Within Europe, estimates from the European Society of Cardiology in 2017 highlighted that AAMR per 100,000 population were higher in men compared with women in both high-income (410 vs. 283) and middle-income (1019 vs. 790) countries, and in general, AAMR for both men and women are higher in middle-income compared with high-income countries [72]. While AAMR have declined since 1990, there is suggestion of a plateau similar to the US CVD mortality trends. In terms of years of life lost due to CVD, estimates are 38 million and 28 million for men and women, respectively, which accounts for a greater proportion of life lost within middle-income compared with high-income countries. However, patterns of CVD, including CHD, stroke, rheumatic heart disease, and other heart disease, are heterogeneous, globally. For example, in China,

prevalence of CHD is lower, but stroke prevalence is much higher compared with Western countries [73].

Overall, a large proportion of the global CVD burden is estimated to be borne by low- and middle-income countries (~70% of CVD deaths, Fig. 3) [74]. The Global Burden of Disease (GBD) 2017 Study, which utilizes statistical models and available national data on nonfatal and fatal CVD events for 359 diseases and injuries in 195 countries and territories, estimated that the highest mortality rates attributable to CVD were in Central Asia and Eastern Europe. In a recent sub-study from GBD focusing on countries that constitute approximately 50% of the global population and are undergoing rapid economic development (Brazil, Russia, India, China, and South Africa), a time trend analysis between 1992 and 2016 described that the AAMR decline was only −17%, approximately half of that reported in North America during this same period (−39%) [75]. Within countries, Brazil had the largest decline in AAMR, India had very little decline, and South Africa was the only country where the AAMR for CVD actually increased. In addition to reporting AAMR statistics, the GBD program has also estimated that within the USA and worldwide, a large proportion of preventable CVD deaths are due to poor dietary quality, hypertension, obesity, hyperlipidemia, diabetes, smoking, and physical inactivity [76].

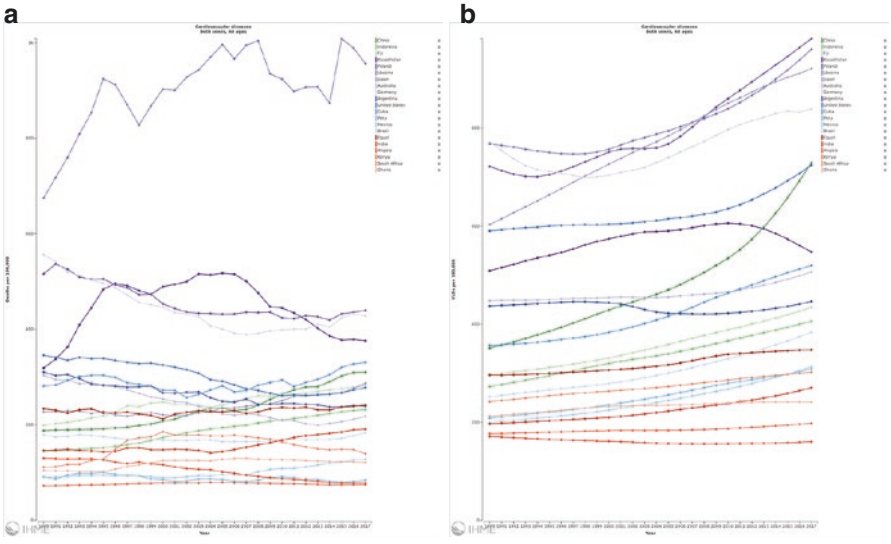

Fig. 3 Global deaths due to cardiovascular disease and years of life lost in all ages and both sexes by country from the Institute for Health Metrics and Evaluation/Global Burden of Disease Collaboration. (**a**) Total cardiovascular disease deaths per 100,000. (**b**) Years of life lost per 100,000

6 Conclusion

In summary, concerning trends in HF and hypertension-related mortality have offset gains achieved in CHD mortality over the past several decades. Increasing prevalence of CVD morbidity is likely in part related to higher rates of obesity, diabetes, and the growth of the aging population. Promotion of CVH across the life course is necessary to focus on primordial and primary prevention strategies and optimization and maintenance of CVH into older adulthood to achieve relative and absolute compression of morbidity. Efforts such as the Million Hearts Initiative can be strengthened by bold and disruptive goals that offer an explicit target and timeline such as 50x50x50 (e.g., achieve a prevalence of ≥50% of all segments of the population less than age 50 years by 2050) to equitably achieve the CVD endgame for all [68, 77]. Multilevel interventions are needed focused on dissemination and implementation of evidence-based therapies at the individual level as well as policy changes at the population level (e.g., smoking bans) to reverse these concerning trends in CVD disease morbidity and mortality in the USA and worldwide.

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Cardiovascular Risk Assessment: From Global Risk Scoring to Risk Enhancing Factors

Rina Mauricio and Amit Khera

Summary

- Primary prevention should begin with assessing ~~for~~ healthy lifestyle habits and determining the patient's absolute risk for developing ASCVD.
- Risk assessment entails determining absolute, global, short-term (i.e., 10 years) risk using validated risk assessment equations. Guidelines support the use of the Pooled Cohort Equations for estimating 10-year global ASCVD risk.
- The currently available risk assessment tools may overestimate or underestimate risk in certain populations. Being cognizant of the strengths and weaknesses of these tools is important when determining an individual patient's risk.
- Risk enhancing factors and, when needed, coronary calcium scores should be taken into consideration for patients at borderline or intermediate risk.
- Guidelines support routine risk assessment in asymptomatic individuals 40 to 75 years old. In individuals 20–39 years old, or those over the age of 75, there is limited evidence for routine risk assessment.
- Risk factors such as diet, physical activity, and obesity, while not included in current risk assessment tools, should still be taken into account when assessing a patient's overall global cardiovascular risk.
- Preventive interventions, such as statin therapy or blood pressure management, should be targeted at high-risk individuals to maximize the benefits of these interventions and minimize harm or overtreatment.

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1 Introduction

Cardiovascular disease (CVD) remains the number 1 cause of death in the United States [1]. Rates of death attributable to CVD had been on the decline. However, despite advances in prevention and treatment, there has been a noticeable increase in CVD mortality in men and women in recent years [1]. Redoubling efforts to reverse this trend requires continued identification of individuals at increased risk for developing CVD. This practice, termed CVD risk assessment, remains a cornerstone of prevention efforts.

Our understanding of risk assessment has greatly evolved from focusing on individual risk factors to determining global cardiovascular risk. Risk assessment aims to find those individuals who are at the highest absolute risk and target primary prevention therapies at this cohort [2]. Risk assessment currently focuses on short-term risk (i.e., 10-year risk). Assessing long-term or lifetime risk may be beneficial for certain individuals. This chapter focuses on methods to determine short-term cardiovascular risk, the rationale for doing so, and potential pitfalls to current risk assessment tools.

2 The High-Risk Approach and Shifting Toward Risk Assessment Equations

When assessing an individual's short-term risk for cardiovascular disease, the focus should be on absolute risk, rather than relative risk [3, 4]. Relative risk is an exposed individual's risk for a given outcome relative to nonexposed individuals. For example, an individual smoker will have a higher relative risk for developing lung cancer compared to a nonsmoker. The shortcomings of this type of risk assessment are that it is always in reference to the baseline population and is dependent on heterogeneity of the exposure. If a population was comprised entirely of smokers, relative risk would be the same between each individual, despite the fact that absolute risk for disease is high. Further, Fig. 1 shows the effect of treatment on low, absolute risk individuals (without a history of vascular disease, i.e., primary prevention) versus high, absolute risk individuals (prior history of vascular disease, i.e., secondary prevention). After treatment, both groups had a 24% relative risk reduction but marked differences in absolute risk reduction: 2.0% in the low, absolute risk group vs. 3.4% in the high, absolute risk group. Thus, the greatest clinical benefit is in those at high, absolute risk. Preventive interventions, such as statin therapy or blood pressure management, should be targeted at individuals at high, absolute risk to maximize the benefits of these interventions and minimize harm or overtreatment.

There are two different but complementary strategies for CVD preventions, termed the high-risk and population-based approaches [2]. The population-based strategy aims to lower the mean level of risk factors in the population with the goal of favorably shifting the overall prevalence of the disease, largely through public

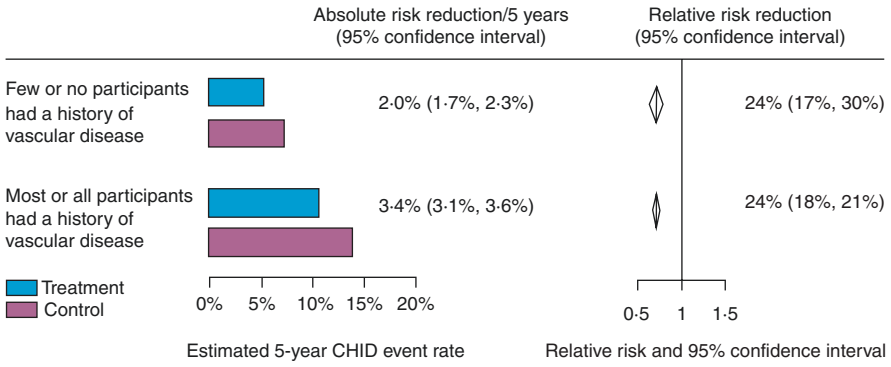

Fig. 1 Absolute and relative treatment effects on coronary heart disease in cholesterol-lowering trials by history of vascular disease. (Reprinted from Jackson et al. [101]. With permission from Elsevier)

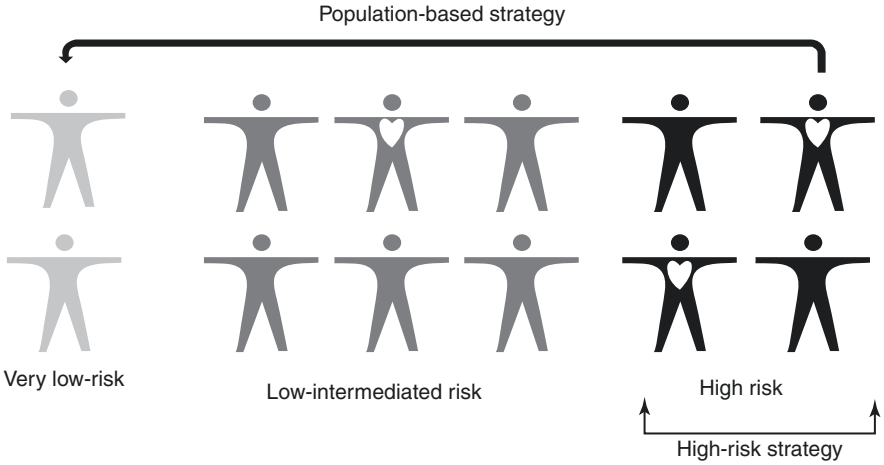

Fig. 2 Population-based strategy versus high-risk strategy. (Reprinted from Khera [102]. With permission from Springer Nature)

health measures. This is a powerful strategy with potential for large effects on population health, but it can also lead to overtreatment of a sizeable number of individuals. For example, population-wide efforts to discourage vaping may meaningfully reduce the number of individuals who vape, but these initiatives will also target individuals who do not vape, offering them little direct benefit.

In the population as a whole, only a select group of individuals are high risk for developing CVD and merit high intensity intervention. This high-risk or "medical" approach is more commonly encountered in office-based practice and involves setting a threshold of risk and focusing treatment strategies on individuals who exceed this risk (Fig. 2). Here, interventions are more targeted to the individual, maximizing

the risk-benefit ratio of any intervention and optimizing cost-effectiveness. A shortcoming is that lower-risk patients who cumulatively have large numbers of cardiovascular events are not treated. A goal of primary prevention, therefore, is to identify those at high, absolute risk and target preventive therapies to these individuals, with the intensity of treatment matching the individual's absolute risk of disease.

2.1 Shifting from Risk Factors to Multivariable Risk Assessment Models

The term cardiovascular "risk factors" originated from the Framingham Heart Study and involves factors whose presence is associated with an increased likelihood that disease will develop at a later time [5, 6]. Since the publication of the seminal paper from the Framingham Heart Study [6], our understanding of cardiac risk factors and cardiovascular risk has grown considerably. Previous assessment of CVD risk relied on assessing and treating each risk factor individually, with lack of a formal integrated method to assess risk [7]. However, individual risk factors poorly discriminate CVD risk, as evidenced by the fact that half of all patients with myocardial infarction have average cholesterol levels for the population. Over time, multivariable risk prediction models were developed, integrating multiple CVD risk factors and demographic data, to more accurately pinpoint an individual's CVD risk into a single score.

The Framingham Heart Study developed one of the first such multivariable risk calculators, which included a model to assess 10-year risk of coronary heart disease (CHD) [8]. The Framingham 10-Year Risk Score for global CHD risk was recommended by the Third Report of the National Cholesterol Education Program Expert Work Group on Diagnosis, Evaluation, and Treatment of High Blood Cholesterol In Adults (ATP III) for the assessment of risk of hard CHD events (myocardial infarction or coronary death) in individuals free of CHD [4]. Over time, Framingham risk assessment models expanded to predict absolute global CVD risk, defined as CHD plus stroke, peripheral arterial disease, and heart failure [9]. The 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk recommended against using the Framingham Risk Score for CHD due to concerns regarding its limited scope and generalizability [10]. The Working Group then developed the Pooled Cohort Equations (PCE), which are now widely incorporated in clinical practice for assessment of global CV risk and to guide initiation of preventive therapy.

3 Using the Pooled Cohort Equations to Assess Cardiovascular Risk

The Working Group of the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk identified two reasons for developing the PCE. First, the Framingham Risk Score was derived in an exclusively white population, limiting its

generalizability, and second, it focused only on CHD events, missing an opportunity for stroke prevention. Moreover, the initial Framingham baseline exams began in 1968, now half a century old, at a time when risk factor prevalence and prevention strategies were markedly different from contemporary patient populations. Therefore, the goal was to develop a new risk score that expanded to hard ASCVD events (defined as first occurrence of nonfatal myocardial infarction, CHD death, or fatal or nonfatal stroke) and in more contemporary, multiethnic populations.

The PCE were derived from several large, racially diverse cohort studies, including the Atherosclerosis Risk in Communities (ARIC) study, the Cardiovascular Health Study (CHS), the Coronary Artery Risk Development in Young Adults (CARDIA) study, and the Framingham Original and Offspring Cohort [10]. ARIC, CHS, CARDIA, and the Framingham Offspring Cohort started recruitment in the 1970s–1990s, reflecting more modern cohorts compared to the original Framingham Study, though still lagging in time relative to modern practice. The majority of participants were middle-aged (mean age of 54.7 years old), and all participants were white or African-American. The Working Group specifically chose cohorts with more than 10 years of follow-up.

Similar to the Framingham Risk Score, the PCE incorporates recognized traditional risk factors for CVD: age, sex, race, total cholesterol, high-density lipoprotein cholesterol (HDL-C), systolic blood pressure, antihypertensive treatment, diabetes mellitus, and smoking. At the time of the development of the PCE, several risk scores had been developed including novel risk factors such as high-sensitivity C-reactive protein (hs-CRP) [11, 12], family history, and body mass index (BMI) [13]. Diastolic blood pressure, family history, moderate or severe chronic kidney disease (defined as estimated glomerular filtration rate [GFR] of <60 mL/min/1.73m^2), and BMI were all considered as additional risk factors for inclusion in the final PCE equation, but they did not improve model discrimination. Other potential risk factors, specifically hs-CRP, apolipoprotein B (ApoB), coronary artery calcium (CAC) score, carotid artery intima-media thickness (CIMT), and ankle-brachial index (ABI), could not be evaluated for inclusion in the model as they were not systematically assessed in the included studies.

The result was two risk calculators, one for white and another for African-American individuals, which provide sex- and race-specific estimates of 10-year ASCVD risk for individuals aged 40–79 years. The PCE are recommended for use in non-Hispanic blacks and non-Hispanic whites, reflective of the populations from which it was derived. It also provides estimation of lifetime ASCVD risk for those aged 20–59 years of age.

The Working Group externally validated the PCE in a combined cohort from the Multi-Ethnic Study of Atherosclerosis (MESA) and the REasons for Geographic And Racial Differences in Stroke (REGARDS) studies, as well as contemporary data from the derivation cohorts (ARIC visit 4, Framingham Original Cohort cycle 22 and 23, and Framingham Offspring Cohort cycle 5 or 6). The validation cohort included 13,652 white and African-American individuals 40–79 years old. Although the PCE overpredicted events in the validation group, this was more pronounced in higher-risk rather than lower-risk individuals. Practically, higher-risk individuals would

have met the threshold for treatment, so overestimation of risk in this group would not lead to unnecessary treatment. Since the publication of the PCE, several studies have expanded on shortcomings and additional considerations in their application.

4 Limitations of the Pooled Cohort Equation

Even the earliest tool for global risk assessment, the Framingham Risk Score, noted that their model was limited in individuals with very low CHD incidence rates, such as younger individuals, and in populations that varied from the source population, including those from other countries or ethnic groups. The PCE limited the derivation populations exclusively to white and African-American individuals from cohorts with a 10-year rate of ASCVD ranging from 1.0 to 28.5%, with a median rate of 9.5% [10]. Therefore, its ability to predict risk in other races/ethnicities with event rates dissimilar to these is limited. Although there is no separate equation for Asian-Americans, application of PCE for whites is recommended. However, the PCE can underestimate risk in South Asians and overestimate risk in East Asians [14]. Hispanic and Latino-Americans are a heterogeneous group in terms of ancestry, country of origin, and ASCVD risk. The PCE for whites is the default risk calculator, although the PCE for African-Americans can be used if there is also African ancestry. Additionally, without a large number of older persons in the derivation cohorts, the PCE does not predict risk beyond age 75. Finally, the PCE only estimates hard ASCVD and does not include the risk of softer events or procedures such as unstable angina, bypass surgery, or percutaneous interventions.

4.1 Populations with Lower or Higher CVD Incidence Rates

Subsequent assessments of the PCE outside of the Working Group using modern cohorts demonstrated moderate to good discrimination in some studies [15, 16] and overestimated short-term risk in others [17–20]. Using data from MESA, the PCE overestimated risk by 86% in men and 67% in women [20]. Increased use of preventive therapies in modern cohorts, such as aspirin, lipid-lowering medications, and antihypertensive therapies, did not appear to explain the overestimation of risk [20].

Outside of the United States, in a large, modern, multiethnic cohort, the PCE overestimated risk of ASCVD [21]. Furthermore, degrees of risk were different when comparing individuals of European vs. Chinese or other Asian vs. Indian, Maori, or Pacific Islander ancestry [21]. The PCE also overestimate or underestimate risk in other racial and ethnic groups [22–24]. Indeed, alternative risk prediction models have been developed for non-US populations and are better calibrated for the population from which they were derived [21, 22]. Socioeconomic status also appears to affect the performance of the PCE. The PCE overestimates risk in individuals of higher socioeconomic status [25] and underestimates risk in patients from lower socioeconomic classes [26]. Risk scores that incorporate social

determinants of health more accurately identify high-risk individuals and predict future events [27].

4.2 Young Populations and When to Assess Long-Term or Lifetime Risk

Assessing for the presence of traditional cardiovascular risk factors should begin in young adults starting at age 20–39 years old [28]. However, incorporating these individual risk factors into a global 10-year risk estimate for younger individuals is challenging. First, 20- to 39-year-old individuals were excluded from the PCE derivation cohort. Additionally, using short-term risk calculators such as the PCE or the Framingham Risk Score in younger individuals is limited by the calculators' reliance on age as the dominant risk determinant resulting in low estimated event rates. Determining 30-year (long-term) or lifetime risk may be more applicable in younger individuals.

Studies have shown that optimal risk factor control at middle age confers lower lifetime risk of CVD compared to individuals with two or more major cardiac risk factors in middle age [29–31]. In another study (average age, 40–50 years), low 10-year risk but high lifetime risk has been associated with greater carotid intima media thickness, higher CAC scores, and greater progression of coronary artery calcium [32].

There are few models for estimating 30-year risk of CVD. A model for assessing 30-year risk of hard CVD (coronary death, MI, fatal and nonfatal stroke) events was developed in the Framingham Offspring Cohort [33] and adjusted for the competing risk of non-cardiovascular death. However, this tool is limited given its derivation in an exclusively white cohort that was recruited at a time when risk factor prevalence and treatment differed from today. These characteristics likely result in overestimation of 30-year risk when using this tool in a younger, modern population.

Lifetime risk can be estimated using the ACC/AHA ASCVD Risk Estimator (https://tools.acc.org/ldl/ascvd_risk_estimator). This long-term calculator was based on a prior study that divided participants into five mutually exclusive sex-specific groups based on number of optimally controlled risk factors [29]. Thus, when one calculates lifetime risk using this tool, there are only five potential risk estimates that can be provided. Although a helpful construct for shared decision-making in patient care, lifetime risk estimation is somewhat limited in precision.

4.3 Risk Assessment in Elderly Populations

As life expectancy increases, there will be more opportunities for primary prevention in individuals greater than 75 years old. Unfortunately, the PCE has poor calibration and discrimination in this population and does not apply to individuals >79 years old. One study showed that in individuals >75 years old, the PCE

overestimates risk in the highest risk individuals, driven in part by competing risk of non-cardiovascular death [34]. Furthermore, the PCE does not address the risk of heart failure, and individuals >75 years old comprise 53% of heart failure hospitalizations [35]. A model developed for 4-year global CVD (incident CHD, stroke, and heart failure hospitalization) risk assessment that incorporated hs-cardiac troponin T, N-terminal pro-B-type natriuretic peptide, and hs-CRP was better able to discriminate high-risk from low-risk individuals compared to the standard PCE in an older population (mean age, 75.4 ± 5.1 years) [36]. Thus, the authors suggest that determining 35-year risk, as opposed to 10-year risk, and incorporating biomarkers indicative of subclinical injury, may provide more accurate risk assessment in elderly individuals.

5 Using Risk Enhancing Factors to Calibrate Risk Assessment

Calculating the Pooled Cohort Equations is the starting point of risk assessment. However, due to its limitations, additional factors can help guide the clinician patient risk discussion when treatment decisions are uncertain. These risk enhancing factors help inform risk prediction at the individual level and identify individuals at higher risk, who might otherwise not be captured by the PCE. The risk enhancing factors identified by the 2018 ACC/AHA Multi-society Guideline on the Management of Blood Cholesterol and the 2016 European Guidelines on Cardiovascular Disease Prevention in Clinical Practice are outlined in Table 1. Conceptually, risk enhancing factors can be divided into several categories: additional patient history, comorbid conditions, laboratory biomarkers, and imaging tests.

Several risk enhancing factors can be obtained from taking additional patient history. Family history of premature ASCVD (<55 years old in men, <65 years old in women) is readily ascertained in a patient visit and is associated with a higher risk of developing CVD [37, 38]. Offspring with at least one parent with premature CVD have an almost twofold increased risk of cardiovascular events, independent of traditional cardiovascular risk factors [38]. Family history of premature ASCVD improves risk prediction most in intermediate-risk individuals [38]. Several studies have demonstrated the incremental value of a positive family history of CVD, even in individuals with a CAC score of zero [39, 40].

South Asian ancestry is also a risk enhancing factor as studies have shown an increased risk for ASCVD in South Asians compared with other racial or ethnic groups [41, 42]. In a large study examining US death records from 2003 to 2010, Asian Indian men and women had a higher proportionate mortality burden for ischemic heart disease compared to non-Hispanic whites [42]. While the reasons for this increased risk are not completely elucidated, increased prevalence of insulin resistance and diabetes likely play a role. Further, the INTERHEART study

Table 1 Risk enhancing factors according to the 2018 ACC/AHA cholesterol guidelines and the 2016 European Guidelines on Cardiovascular Disease Prevention

	ACC/AHA[a]	ESC[b]
Family history of premature ASCVD	Males, age <55yo; females, age <65yo	Males, age <55yo; females, age <65yo
Metabolic syndrome	Increased waist circumference,[c] elevated triglycerides (>150 mg/dL, nonfasting), elevated BP, elevated glucose, low HDL-C (<40 mg/dL men, <50 mg/dL women). Tally of 3 makes the diagnosis.	Waist circumference >94 cm (men) or >80 cm (women); BMI target >20–25 kg/m^2
Primary hypercholesterolemia	LDL-C, 160–189 mg/dL, non-HDL 190–210 mg/dL	
Chronic kidney disease	eGFR 15–59 mL/min/1.73m^2, +/− albuminuria, not on dialysis or post kidney transplantation	
Chronic inflammatory conditions	For example, psoriasis, lupus, rheumatoid arthritis, HIV/AIDS	
Female-specific risk factors	Premature menopause (age <40 yo), pregnancy-associated condition that increases later ASCVD risk, such as preeclampsia	
High-risk race/ethnicity	For example, South Asian ancestry	
Biomarkers Triglycerides If measured: hs-CRP Lp(a) apo(B) ABI	Persistent elevated,[d] primary hypertriglyceridemia (≥175 mg/dL, nonfasting) ≥2.0 mg/L ≥50 mg/dL or ≥125 nmol/L[e] ≥130 mg/dL (corresponds to LDL-C >160 mg/dL) <0.9	Consider obtaining (IIb recommendation)
Socioeconomic status		Low socioeconomic status, lack of social support, stress, hostility, depression/anxiety
Atherosclerotic plaques determined by carotid artery screening		Consider obtaining (IIB recommendation)
Coronary artery calcium score		Consider obtaining (IIb recommendation)

[a]Adapted from the 2018 ACC/AHA Multi-society Guidelines on the Management of Blood Cholesterol

[b]Adapted from the 2016 European Guidelines on Cardiovascular Disease Prevention in Clinical Practice. The ESC guidelines recommend only six risk enhancing factors: family history, BMI/central obesity, ABI, socioeconomic status, carotid artery plaque, and coronary artery calcium score

[c]By ethnically appropriate cutoffs

[d]Optimally, three determinations

[e]Preferred units of measurement

demonstrated a similar importance of traditional risk factors for CHD in South Asians compared to other groups, but there was an increased prevalence of these risk factors at a younger age in the South Asian population [41, 43].

Risk enhancing factors specific to women include a history of premature menopause (<40 years old) and pregnancy complications known to increase ASCVD risk, such as preeclampsia [44–46]. The average age of menopause in the United States is approximately 50 years old. Both natural and surgical premature menopause are associated with an approximately two-fold increased risk of CHD after adjusting for traditional cardiovascular risk factors [47]. In a meta-analysis looking across a continuum of age of menopause, women younger than 45 years old at the onset had an almost 20% increased relative risk of CVD mortality compared to women who experienced menopause at 50 years old or older; this signal was not present for women 45–49 years at the age of menopause [48]. Recent literature has highlighted the association between pregnancy complications and future cardiovascular risk. Preeclampsia affects approximately 5 to 7% of all pregnancies in the United States [49]. Though there are variable findings between cohorts, overall, preeclampsia is associated with an almost twofold increase in CVD and an approximately threefold increased risk for developing hypertension [14, 50]. Other pregnancy complications such as preterm delivery (delivery at <32 weeks) also portend an increased risk of myocardial infarction and stroke [51]. Given the depth of evidence relating reproductive history and CVD, multiple society guidelines have emphasized the importance of taking a thorough reproductive history when assessing cardiovascular risk in women [14, 28, 52].

Comorbid inflammatory conditions such as psoriasis, rheumatoid arthritis, systemic lupus erythematosus (SLE), and HIV/AIDS are accompanied by an increased risk for CVD [53–55]. Rheumatologic conditions have been associated with increased cardiometabolic risk (defined as CHD, stroke, peripheral arterial disease, venous thromboembolism, and type 2 diabetes) as well as an increased risk of subclinical atherosclerosis [56]. This increased risk may be greater for SLE compared with psoriasis [57]. HIV-infected individuals have a 1.5–2-fold greater risk of myocardial infarction compared to noninfected individuals [58, 59]. This may be due to ~~an~~ more frequent hypertension, diabetes, and dyslipidemia in this population, some of which are known side effects of antiretroviral medications, or to adverse effects of the viremia itself [59]. Multivariable risk functions such as the Framingham Risk Score and PCE are poorly calibrated and underestimate risk in those with HIV [53].

Both the metabolic syndrome and chronic kidney disease are considered risk enhancing factors. The metabolic syndrome is defined as having three or more of the following: increased waist circumference, elevated triglycerides, low HDL, elevated blood pressure, and elevated fasting glucose. In a meta-analysis, metabolic syndrome is associated with an approximately 1.5–2-fold increase in CVD and CV mortality [60, 61]. Coronary artery disease is the leading cause of morbidity and mortality in individuals with chronic kidney disease, and risk for CVD mortality increases progressively with declining eGFR (HR 1.38, 95% CI 1.16–1.65, HR 2.42, 95% CI 1.92–3.05, and HR 3.29, 95% CI 1.72–6.31 for eGFR 45–59 mL/min/1.73 m^2, 30–44 mL/min/1.73 m^2, and 15–29 mL/min/1.73 m^2, respectively) [62, 63].

Several lipid parameters and biomarkers have also been identified as risk enhancing factors. C-reactive protein is an acute-phase reactant protein predominantly produced by the liver that is a nonspecific marker of systemic inflammation. Elevated levels of hs-CRP have consistently been associated with a range of CVD endpoints including an increased risk of CHD, ischemic stroke, and vascular death [64]. In the JUPITER trial of; individuals without CVD or hyperlipidemia (median LDL, 108 mg/dL), but elevated hs-CRP (median, 4.2 mg/L), rosuvastatin significantly reduced the incidence of major cardiovascular events compared with placebo [65]. Although interpretation of this trial is limited due to the lack of inclusion of individuals with normal hs-CRP levels, the results of this study and others suggest elevated hs-CRP may help identify those who derive benefit from statin therapy.

Lipoprotein(a) [Lp(a)] has a wealth of evidence regarding its role in identifying individuals at higher risk of CVD. Lp(a) is a low-density lipoprotein-like particle with an apolipoprotein-B100 (apoB_{100}) molecule linked to a large apolipoprotein(a) protein. Epidemiological [66], Mendelian randomization [67], and genome-wide association studies [68] have confirmed the causal association of elevated Lp(a) with a higher risk of CVD. Lp(a) is more atherogenic than LDL through its proatherogenic, pro-inflammatory, and antifibrinolytic properties [69]. The 2016 European Guidelines on Cardiovascular Disease Prevention and 2018 ACC/AHA Multi-society Guideline on the Management of Blood Cholesterol recommend an Lp(a) level ≥50 mg/dL (or ≥125 nmol/L) as the cutoff value for identifying individuals at greater risk for CVD.

Apolipoprotein(b) [apo(b)], persistently elevated triglycerides, and an ankle-brachial index (ABI) of <0.9 are additional parameters conveying ASCVD risk. Apolipoprotein(b)-100 is an apolipoprotein contained in atherogenic lipoprotein particles: LDL, IDL (intermediate-density lipoprotein), and VLDL (very-low-density lipoprotein). It is therefore an aggregate measure of these particles that has compared favorably to LDL-C in several studies. A large meta-analysis showed that apo(b) was a more potent marker of cardiovascular risk compared to both non-HDL-C and LDL-C [70]. Triglycerides persistently above 150 mg/dL are associated with increased risk for CHD and ischemic stroke, though this association is attenuated after adjusting for additional cardiac risk factors, specifically for HDL-C and non-HDL-C [71, 72]. Although less commonly measured in asymptomatic individuals, an ABI <0.9 is associated with a two-fold increase in MI and CV death and improves risk assessment beyond the Framingham Risk Score [73].

6 Alternative Tools for Risk Assessment

Although the Framingham Risk Score and Pooled Cohort Equations have been the most commonly used risk assessment tools in the United States, there are several other available risk calculators. These include models incorporating novel risk factors, those that have been developed in cohorts of different race/ethnicities and in cohorts outside of the United States. A summary of risk prediction tools, including the PCE, is presented in Table 2.

Table 2 Alternative tools for risk assessment

	Framingham	Pooled Cohort Equations (PCE)	Reynolds Risk Score	SCORE	ASSIGN	QRISK3	MESA Risk Score	Astro-CHARM
Population	Framingham, MA, USA. Baselines: 1968–71, 1971–75, 1984–87	ARIC, 1987–89; CHS 1990, 1992–1993 CARDIA, 1985–1986; FHS, 1968–1975, 1984–1987	WHS 1992–2004; PHS II 1995–2008	12 prospective studies from 11 European countries, 1972–1991	SHHEC Prospective Study, Scotland, 1984–1987	QRESEARCH database, UK, 1998–2015	MESA	MESA, DHS, PACC
Sample size	3969 men and 4522 women	11,240 white women, 9098 white men, 2641 African-American women, 1647 African-American men	10,724 men and 16,400 women	117,098 men and 88,080 women	6540 men and 6757 women	3.9 million men and 4.0 million women	3176 men and 3550 women	4060 men and 3322 women
Ethnicities represented	White	White, black	White, black, Hispanic, Asian (nonwhite <5%)	Not reported. 11/12 participating cohorts from Western Europe	White	White, black-Caribbean, black-African, South Asian, other Asian (nonwhite ~11%)	White, black, Hispanic, Chinese (nonwhite ~62%)	White, black, Hispanic
Calculates	10-year risk of CVD (2008) and 10-year risk of CHD (1998)	10-year risk for first atherosclerotic CVD event	10-year risk of CVD	10-year risk of CVD mortality (two versions for high- or low-risk countries)	10-year risk of CVD	10-year risk of CVD	10-year risk of CHD	10-year risk of ASCVD

Included endpoints	CVD: CHD, stroke, PAD, heart failure CHD: angina, MI, coronary insufficiency, CHD death	CHD death, nonfatal MI, fatal or nonfatal stroke	MI, stroke, coronary revascularization, CV death	CV mortality	CV death, CHD, cerebrovascular disease, CABG or PCI	CHD, ischemic stroke, TIA	MI, CHD death, resuscitated cardiac arrest, revascularization due to angina	CHD death, stroke death, nonfatal MI, nonfatal stroke
Age range (years)	30–75	40–79	48–58 (women); median 63 (men)	40–65	30–74	25–84	45–84	Mean age 51
Variables	Age, sex, total cholesterol, HDL-C, SBP, smoking, DM, hypertensive treatment	Age, sex, race (white/ African-American/other), total cholesterol, HDL-C, SBP, antihypertensive treatment, DM, smoking	Age, sex, total cholesterol, HDL-C, SBP, smoking, family history, hs-CRP	Age, sex, total cholesterol or total cholesterol/ HDL-C ratio, SBP, smoking	Age, sex, total cholesterol, HDL-C, SBP, quantitative smoking, DM, socioeconomic status, family history	Age, sex, ethnicity, total cholesterol/ HDL-C ratio, SBP, smoking, DM, socioeconomic status, family history, BMI, BP treatment and variability, chronic diseases	Age, sex, race (white, black, Hispanic, Chinese), total cholesterol, HDL-C, SBP, lipid-lowering med, BP medication, DM, smoking, family history, CAC	Age, sex, race (black/ Hispanic/ other), total cholesterol, HDL-C, SBP, BP medication, smoking, DM, family history, hs-CRP, CAC score

Based on data from the ESC 2016 Primary Prevention of Cardiovascular Disease Guidelines

ARIC Atherosclerosis Risk in Communities, *CARDIA* Coronary Artery Risk Development in Young Adults, *FHS* Framingham Heart Study, *WHS* Women's Health Study, *PHS II* Physician's Health Study II, *SHHEC* Scottish Heart Health Extended Cohort, *MESA* Multi-Ethnic Study of Atherosclerosis, *DHS* Dallas Heart Study, *PACC* Prospective Army Coronary Calcium Project, *CVD* cardiovascular disease, *CHD* coronary heart disease, *TIA* transient ischemic attack, *DM* diabetes mellitus, *BMI* body mass index

Utilizing a tool derived from a population most representative of the patient being assessed will provide more accurate risk assessment. The Systematic COronary Risk Evaluation (SCORE) project was undertaken to develop a risk assessment tool specifically for use in European clinical practice [74]. SCORE was derived from 12 cohorts from Western Europe and Russia. Unlike other risk assessment tools, its defined endpoint is total cardiovascular mortality. This departure is notable for only CVD mortality instead of including nonfatal events. This decision was based on the lack of ascertainment of nonfatal CVD endpoints in the derivation cohorts. A multiplier has been recommended to estimate risk of nonfatal CVD events [52]. SCORE data indicate that the rate of total CVD is three times higher than fatal CVD for men, four times higher for women, and somewhat lower than 3 for the elderly [52]. Compared to other risk assessment tools, SCORE includes a relatively narrow list of risk factors in its model: cholesterol and HDL levels, sex, smoking status, and systolic blood pressure. Importantly, it does include diabetes as a factor and defines all such persons at high or very high risk. However, the guidelines recommend considering other cardiovascular risk factors, such as premature family history and an elevated CAC score, when using this tool in clinical practice [52]. SCORE is ~~to~~ recommended for use throughout Europe. As such, there are two SCORE calculators – one for use in countries with baseline low risk of CVD and another for countries with a baseline high risk of CVD.

Several risk scores have been developed which incorporate novel risk factors, some of which are risk enhancing factors, into their models. The Reynolds Risk Score incorporates hs-CRP as well as family history into its risk assessment algorithms. The Reynolds Risk Score for women was derived and validated using data from the Women's Health Study, and a similar score for men, the Reynolds Risk Score for men, was derived and validated using data from the Physicians Health Study [11, 12]. The Reynolds Risk Score for women has improved calibration and discrimination compared to the Framingham Risk Score for CHD [11]. While family history is readily ascertained in a standard patient visit, the Reynolds Risk Score is limited by its reliance on hs-CRP, which is not routinely obtained.

The ASSIGN score was developed in 2006 from the Scottish Heart Health Extended Cohort (SHHEC) [27]. In addition to traditional cardiovascular risk factors, ASSIGN incorporates family history, quantitative measures of cigarette smoking (i.e., amount smoked), and social deprivation according to the Scottish Index of Multiple Deprivation. The ASSIGN score had marginally better discrimination and improved calibration compared to the Framingham Risk Score. However, it is limited by the homogenous population in which it was derived and its incorporation of additional risk factors such as social deprivation which vary in ascertainment between regions.

QRISK, initially developed in 2007, built off these previous scores by incorporating additional novel risk factors. The QRISK score was developed using the QRESEARCH database, consisting exclusively of practices in the United Kingdom [13]. Similar to ASSIGN, it added social deprivation and family history into its model, as well as body mass index (BMI). Since the initial development of QRISK, there have been two additional iterations of the model: QRISK2 and QRISK3.

QRISK2 added self-described ethnicity (divided into nine possible groups), rheumatoid arthritis, chronic renal disease, type 2 diabetes, and atrial fibrillation to the model [75]. The latest version, QRISK3, added systolic blood pressure variability, migraine history, steroid and antipsychotic use, severe mental illness, history of lupus, and erectile dysfunction [76]. The original QRISK score has improved discrimination and calibration compared to the Framingham Risk Score and ASSIGN and has been validated in another UK cohort [77]. However, QRISK scores have not been validated in a non-European cohort. Though ethnicity factored into QRISK2 and QRISK3, >95% of the derivation and validation cohorts were white. The QRISK scores also require inputting multiple risk factors, some of which may not be readily available in routine clinical practice, hindering their ease of use. Lastly, there was no formal adjudication of events in the QRISK cohort, possibly limiting its accuracy. A QRISK lifetime risk calculator is also available [52, 78].

Since a difference in baseline cardiovascular risk exists between countries and individuals of different ethnicity and race, the GLOBORISK score was developed as a tool for risk assessment that could be calibrated to many different countries worldwide [79]. The score was derived using eight cohorts (ARIC, CHS, FHS Original and Offspring, WHI, Honolulu Heart Program, Multiple Risk Factor Intervention Trial, Puerto Rico Heart Health Program), with six out of the eight cohorts being from the United States, one of Japanese Americans from Hawaii (Honolulu Heart Program), and the last consisting of Puerto Rican men. It was then validated in cohorts outside of the United States: the Scottish Heart Health Extended Cohort, Tehran Lipid and Glucose Study, and the Australian Diabetes, Obesity, and Lifestyle cohort. The resulting tool is a series of charts, similar to the SCORE model, that are specific for a given country, with primary outcome of fatal ASCVD. The model showed good discrimination in internal and external validation and also demonstrated that risk varied substantially between high-, middle-, and low-income countries. To facilitate use, in addition to risk assessment charts that use lab-based information (i.e., total cholesterol), there are also ones using only data that can be obtained in the office (i.e., blood pressure and BMI). While the authors focused on fatal ASCVD (i.e., CHD and stroke), they also developed scores for fatal and nonfatal ASCVD but only for those countries that had high-quality data for those outcomes. There are currently 182 country risk charts available for use and may be beneficial for those practicing in other countries or populations without representative risk equations (www.globorisk.org).

Coronary artery calcium scores are perhaps the strongest predictors of ASCVD risk [80–82]. A simplified approach to incorporating CAC scores in risk assessment is using low or elevated (i.e., >0 vs. ≥100) scores to dichotomously identify individuals at lower or higher risk. However, CAC scores, and thereby associated risk, exist on a continuum and simplified methods using categorical thresholds result in imprecise risk prediction. Novel risk calculators include continuous CAC scores and are potentially valuable tools to help refine risk assessment.

The MESA risk score incorporates CAC scores, as well as family history, to estimate 10-year CHD risk, including myocardial infarction, resuscitated cardiac arrest, fatal CHD, and revascularization for angina [83]. It was derived from a

multiethnic cohort including Chinese-, African-, and Hispanic-Americans and was validated in two external cohorts, the Heinz Nixdorf Recall Study (HNR) and the Dallas Heart Study (DHS). Compared to the score without CAC, the addition of CAC showed improved discrimination and calibration.

The Astro-CHARM risk prediction tool expands from the MESA findings and incorporates CAC scores to estimate 10-year hard ASCVD risk, similar to the PCE endpoint [84]. Astro-CHARM was developed using the MESA, DHS, and Prospective Army Coronary Calcium Project (PACC) cohorts, all of which comprise of black, white, and Hispanic participants, and was externally validated in the Framingham Heart Study cohorts. In addition to CAC and family history, hs-CRP was also added to the final risk prediction model. Similar to the MESA risk score, the final model improved discrimination, calibration, and risk classification compared to the one comprising only ~~of~~ traditional risk factors. Both the MESA (www.mesa-nhlbi.org/MESACHDRisk) and Astro-CHARM (www.astrocharm.org) models are available as online tools.

7 Risk Factors Not Represented in Risk Assessment Tools

Other risk factors have not been incorporated into risk prediction tools, despite their known contribution to the development of ASCVD, due to difficulty with quantification or lack of improvement in discrimination when they were added to traditional risk assessment models, including the PCE [10]. These risk factors include diet, physical activity, and obesity [8].

Optimal dietary patterns, such as the DASH or Mediterranean diet, include high intake of fruits, vegetables, and whole grains and are low in saturated fats, meats, and higher fat dairy products. Poor dietary patterns have been associated with an increased risk of developing cardiovascular risk factors and myocardial infarction [85, 86]. Similarly, physical inactivity and poor cardiorespiratory fitness correlate with a worse cardiometabolic biomarker profile and increased risk for CVD [87–91]. Nevertheless, despite independent association of diet and physical activity with CVD outcomes, these parameters do not seem to add incremental information to risk prediction beyond PCE factors [92].

Obesity is independently associated with an increased risk of cardiovascular disease [93, 94]. However, the concept of "metabolically healthy obesity" (MHO) has emerged. Debate exists on whether these individuals who are obese but do not have features of the metabolic syndrome have increased risk of CVD [95]. These individuals tend to be younger, of non-Hispanic or black ethnicity, physically active, have higher cardiorespiratory fitness levels, and have lower levels of abdominal visceral adipose tissue or ectopic fat [96]. Different studies use varying combinations of elevated blood pressure, low HDL, high triglycerides, and elevated fasting glucose to define MHO. This has led to conflicting results in the literature. However, large meta-analyses show that compared to metabolically healthy, normal BMI individuals, those who are overweight, obese, or metabolically unhealthy regardless of

their weight had a higher risk of CVD especially in the long term, suggesting that MHO exists on a spectrum and these individuals are on the path for developing CVD risk factors [96, 97]. When evaluating obesity parameters, waist circumference is a better measure of metabolically active intra-abdominal adipose tissue and should be assessed to identify those at higher cardiometabolic risk [28]. Interestingly, addition of BMI to the model did not improve risk prediction in PCE model development. Notably, BMI and waist circumference have been incorporated into the QRISK scores [76].

Across the entire spectrum of age, those who have optimal lifestyle habits have a lower risk for CVD [98–100]. While lifestyle factors may not incrementally inform ASCVD risk estimates, they remain important modifiable targets to lower the risk of developing ASCVD. Assessing for the presence of a healthy lifestyle pattern should be included in routine risk assessment.

8 Summary of the ACC/AHA and ESC Guidelines

The American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC) have each made recommendations on risk assessment for primary prevention.

8.1 ACC/AHA 2019 Primary Prevention Guidelines

The starting point for primary prevention begins with global risk scoring. Foundational to this is assessment for a heart-healthy lifestyle and counseling the patient on lifestyle interventions as needed, as part of the clinician-patient discussion on the best ways to reduce CVD risk. The guidelines recommend routine assessment for 10-year risk of ASCVD in asymptomatic 40–75-year-olds free of CVD using the PCE [28]. No specific time interval was provided for the frequency of this assessment. Risk assessment should be the starting point for the physician-patient conversation and not the sole factor in the decision to initiate preventive therapies. For blood pressure management, individuals with blood pressure of 130–139/80–89 mmHg with 10-year ASCVD risk estimated to be ≥10% would benefit from therapies to reduce their blood pressure to a goal of <130/80 mmHg. Similarly, those with blood pressure ≥140/90 mmHg are recommended antihypertensive therapy regardless of ASCVD risk. With regards to blood cholesterol management, individuals whose 10-year risk is greater than 20% are deemed high risk and aggressive risk modification is recommended, including reduction in LDL-C levels by 50% or more. Those whose risk is between 7.5 and 20% are at intermediate risk, and individuals whose 10-year risk is between 5 and <7.5% are borderline risk. For individuals at borderline or intermediate risk, the presence of risk enhancing factors favors initiation or intensification of statin therapy. If the patient's overall risk

still remains in question and/or the physician or patient is uncertain about initiating preventive therapies, CAC scanning can further guide the risk discussion, with scores of 0 favoring deferral of statin therapy (as long as diabetes, cigarette smoking, or a premature family history of ASCVD is not present) and scores of ≥100 or ≥75th percentile favoring initiation. Both the MESA CAC risk score and Astro-CHARM are mentioned as options to integrate CAC values with traditional risk factors for quantitative risk estimates in the 2019 ACC/AHA Prevention Guidelines. A statin treatment algorithm according to the 2018 ACC/AHA cholesterol guidelines is outlined in Fig. 3.

For younger individuals (20–39 years old), assessment of traditional ASCVD risk factors every 4–6 years is recommended. Global risk prediction in this population using either 30-year or lifetime risk assessment tools can be considered. For individuals >75 years old, a patient-physician discussion on the risks and benefits of preventive therapies in the context of possible other comorbidities and life expectancy is an appropriate starting point.

8.2 ESC 2016 Cardiovascular Disease Prevention Guidelines

While the European guidelines agree that assessment of global cardiovascular risk is indicated, and that treatment should be commensurate to the degree of risk, it differs from the American recommendations in whom and when to assess risk. The ESC guidelines recommend risk assessment in individuals with risk factors or comorbidities increasing cardiovascular risk (i.e., family history of premature disease or the presence of major cardiovascular risk factors) [52]. Furthermore, risk assessment is recommended every 5 years though can be more frequent in those individuals nearing the higher-risk thresholds. Lastly, risk assessment in younger individuals (men <40 and women <50 years old) with no known cardiovascular risk factors is not recommended.

For those in whom risk assessment is recommended, the European guidelines recommend using SCORE to assess risk of cardiovascular death. Practitioners in Europe should use either the low- or high-cardiovascular risk calculator depending on the country in which he or she practices. Similar to the ACC/AHA guidelines, the European guidelines recommend that risk calculation should start the physician-patient discussion regarding preventive therapies but not be the absolute determinant of medication initiation.

Notably, the ESC cutoffs for the definition of high-, moderate-, and low-risk individuals vary from those of the ACC/AHA, since the ESC SCORE endpoint is CVD mortality. Very high-risk individuals have an absolute 10-year risk of >10% and drug therapies are recommended. For high-risk (5–10%) individuals, drug therapy can be considered but focus should be paid to intensifying lifestyle interventions. Low- to moderate-risk (<5%) individuals should be counseled on lifestyle interventions. For individuals at the borderline of risk (>5%), the presence of risk modifiers can be considered to classify a patient's risk upward. It is worth noting that risk modifiers in the European guidelines differ slightly from those in the ACC/AHA guidelines (Table 1).

For younger individuals (defined as <50 years old) with a family history of premature CVD, assessing for familial hypercholesterolemia or the presence of cardiovascular risk factors is recommended. Assessment of relative risk or lifetime risk can be considered, but the guidelines conclude that in the absence of very high individual risk factors, cholesterol-lowering or blood pressure therapy is rarely indicated in a younger population. Global risk assessment in elderly individuals is not recommended due to the lack of definitive evidence for primary prevention in this group, as well as the competing risk for non-cardiovascular disease. As with the ACC/AHA guidelines, a physician-patient discussion regarding risks/benefits of therapy, quality of life, and burden of drug treatment is recommended in this population.

9 Conclusion

Primary prevention of cardiovascular disease begins with determining an individual's global, absolute, short-term (10-year) risk for atherosclerotic CVD. Risk enhancing factors should also be considered to calibrate a patient's risk either upward or downward. Global risk assessment, supplemented by the consideration

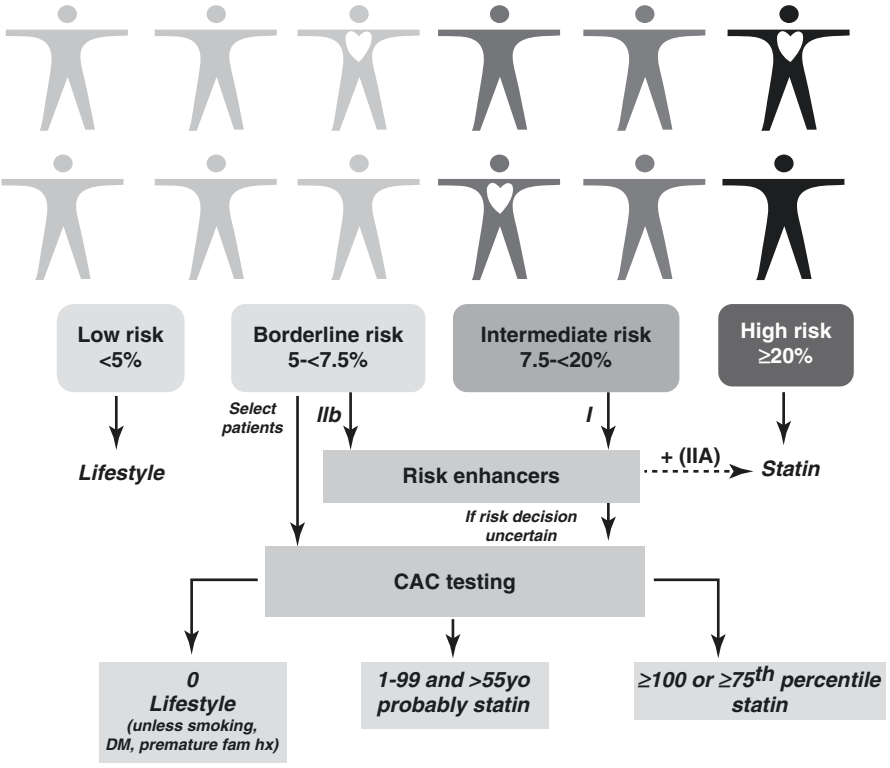

Fig. 3 Statin treatment algorithm according to the 2018 ACC/AHA cholesterol guidelines

of risk enhancing factors and where necessary coronary calcium measures, should inform the physician-patient discussion on the risks and benefits of starting preventive therapies. The intensity of preventive therapies should be commensurate to the degree of risk, with the highest-risk individuals receiving the most intensive treatment. Finally, practitioners should be aware of the shortcomings of all risk assessment tools and factor these into their final conclusions or recommendations.

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Assessment and Management of Psychosocial Risk Factors Within Preventive Cardiology Practice

Alan Rozanski

Summary

- Traditional psychosocial factors associated with cardiovascular disease (CVD) include depression, anxiety, social isolation or poor social support, hostility, and chronic stress.
- Increasing data also points to a significant association between CVD and pessimism, low sense of life purpose, and vital exhaustion.
- A gradient relationship has been demonstrated between the magnitude of these negative risk factors and CVD risk.
- Positive factors, such as optimism and high sense of life purpose, appear to be associated with enhanced survival and decreased CVD risk.
- Two general pathophysiological mechanisms may link psychosocial risk factors to CVD: direct pathophysiological effects and their negative impact on health behaviors (e.g., more likely to smoke, be sedentary, and eat poorly).
- Cardiologists can help manage psychosocial risk factors by screening for their presence and then either managing these factors in some cases, referring patients to hospital- or community-based programs, or referring patients with more severe psychosocial dysfunction to mental health professionals.

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1 Introduction

Over recent decades, a plethora of epidemiological studies have demonstrated a strong association between a variety of psychosocial risk factors and incident cardiovascular disease (CVD) and/or risk for adverse cardiac events. Initial studies focused on five major psychosocial factors: depression, anxiety, work stress, social isolation, and anger/hostility [1]. Since then, additional factors have been linked to cardiovascular disease, including pessimism [2], vital exhaustion [3, 4], and a low sense of life purpose [5, 6]. The association of these risk factors and cardiovascular disease is now supported by extensive epidemiological data, and various pathophysiological mechanisms have been identified by which these factors may cause or contribute to progression of CVD or development of adverse clinical outcomes. This chapter will provide a topical overview of those psychosocial risk factors linked to cardiovascular disease by growing epidemiological evidence. The material herein is designed to provide the practitioner with a general overview of these psychosocial factors, provide a general outline of pathophysiological mechanisms that link psychosocial risk factors to CVD, and review basic principles related to the management of psychosocial factors in clinical practice.

2 Psychosocial Risk Factors

The factors which will be reviewed in this chapter are listed in Table 1. It is important to note that each of these factors lies along a continuum from health-promoting to disease-producing. The health promoting aspects of the negative risk factors have been more recently recognized and highlighted since the advent of the field of positive psychology.

2.1 Depression

Depression has been the most extensively studied of the risk factors listed in Table 1. Depression occurs along a continuum from mild depressive symptoms to major depressive disorder, a DSM-V psychiatric condition. Major depressive disorder is characterized by a markedly depressed mood or the lack of interest in nearly all of

Table 1 Psychosocial risk factors

Depression
Anxiety
Lack of social connectivity
Pessimism
Hostility
Other negative cognitive states
Lack of life purpose
Vital exhaustion
Chronic stress

one's activities in life for at least 2 consecutive weeks, in conjunction with other symptoms, such as loss of or increase in appetite, fatigue, insomnia, and feelings of guilt. When depression is chronic in nature, it can lead to marked pathophysiological dysfunction and a heightened risk of many illnesses. Various meta-analyses have demonstrated a particularly strong link between depressive symptoms and cardiovascular disease (CVD). The largest of these is a meta-analysis of 52 studies, involving 146,538 subjects [7]. In this study, depression was associated with an approximately twofold increased risk of myocardial infarction and/or cardiac death in community cohorts and comparable risk for adverse clinical events among patients with known coronary artery disease (CAD). Of note, early studies demonstrated a "dose-response"-like relationship between the magnitude of depressive symptoms and CVD outcomes [8, 9]. Even mild depressive symptoms were noted to increase clinical risk compared to patients without depressive symptoms.

2.2 Anxiety Syndromes

As with depression, anxiety can present along a continuum, ranging from mild anxiety symptoms to major anxiety disorders. Four major anxiety disorders show a strong association with CVD risk: generalized anxiety disorder, panic disorder, phobias, and post-traumatic stress disorder (PTSD). Generalized anxiety disorder consists of excessive and generally uncontrollable anxiety or worry that is present for most days for at least 6 months. It is characteristically associated with occupational and social dysfunction. Panic disorder is considered present when individuals experience recurrent panic attacks. Part of its debilitation is a common worry that more panic attacks will follow. Phobias are characterized by a marked and persistent fear of objects or situations, which, upon exposure, commonly provoke anxiety and/or fear of acting in a dysfunctional manner. In one early study of 33,999 males, investigators found a graded relationship between the presence of phobic anxiety syndromes and cardiovascular death [10], with patients having the highest levels of phobic anxiety having a threefold increase in cardiac death compared to the patients with no phobic anxiety. A strong relationship has also been noted between PTSD and CVD [11]. The disorder consists of a characteristic triad of symptoms: flashback memories or other persistent re-experiencing persistent avoidance of stimuli related to the original trauma, and symptoms of hyperarousal that continue for >1 month after a traumatic event. As with other anxiety disorders, PTSD can lead to significant impairment of daily life functioning. As with milder forms of depression, an association has been noted between subsyndromal degrees of anxiety and the risk for adverse CVD events [12, 13].

2.3 Lack of Social Connectivity

Social connectivity is a profound psychosocial factor that emerges from a basic human need to be connected to others. This need varies widely in intensity. Some individuals are comfortable with a small social circle and are comfortable to be

alone without feeling lonely. Others experience a need for strong social connectivity. Unmet social needs and feelings of loneliness have emerged as a strong risk factor for CVD. The first major study to link social factors to CVD was the Alameda County Study [14]. This study found an inverse relationship between the size of one's social network and mortality among both men and women. Since then, the relationship between social factors and CVD has been repeatedly demonstrated. This arena of study has grown to include many aspects of social connectivity, including the size and structure of one's social network, the quality of one's social relationships, and the value of structural or functional social support. In a large meta-analysis of 148 studies, involving 308,849 participants, a significant relationship was noted between both measures of functional support and/or structural support and longevity [15]. A composite measure of social integration was found to be associated with a 1.91-fold (95% CI 1.63–2.23) increase in survival. As noted by the investigators of this study, this large effect size is comparable to that noted for many therapeutic interventions, such as smoking cessation and participation in cardiac rehabilitation programs.

2.4 Pessimism

The health- and life-promoting benefits of optimism versus pessimism have been touted for decades, but the study of this mind-set with respect to CVD risk has only been assessed recently. Initial studies regarding optimism versus pessimism followed a model developed by Seligman which examined individuals "explanatory style." According to this model, pessimists have an explanatory style of invoking self-blame for negative events, as well as a tendency to view negative events as persistent and affecting many aspects of their lives. By contrast, optimists are less likely to be self-blaming and more likely to view negative events as temporary setbacks and non-global in nature. More recently, the study of optimism versus pessimism has tended to examine this mind-set as a dispositional trait. According to this paradigm, optimists have a general tendency to expect positive outcomes in the future and to interpret life events in a positive way. Pessimists are more likely to expect negative outcomes in the future. A simple six-item scale (with four filler questions), called the Life Orientation Test-Revised, has gained wide traction for assessing optimism versus pessimism [16], as listed in Table 2. A recent meta-analysis of 15 studies, involving 229,391 participants, found a dose-response relationship between the measured levels of pessimism/optimism and risk of cardiac events. Within this pooled analysis, optimism was associated with 35% lower risk of cardiac events. Results were similar when the results were adjusted for gender, depression, and other potential confounders.

Table 2 Life orientation test-revised

1. In uncertain times, I usually expect the best
2. *It's easy for me to relax*
3. If something can go wrong for me, it will
4. I'm always optimistic about my future
5. *I enjoy my friends a lot*
6. *It's important for me to keep busy*
7. I hardly ever expect things to go my way
8. *I don't get upset too easily*
9. I rarely count on good things happening to me
10. Overall I expect more good things to happen to me than bad

Each question is answered on a five-point scale: A = I agree a lot; B = I agree a little; C = I neither agree nor disagree; D = I disagree a little; E = I disagree a lot
Questions 3, 7, and 9 are reverse scored
Questions in italics are fillers and are not scored

2.5 Hostility

Another mind-set that has long been studied relative to CVD risk is hostility. Investigators have proposed hostility as a construct that encompasses the traits of anger, cynicism, and mistrust. Interest in hostility initially derived from its overlap with "Type A" behavior pattern, a personality complex characterized by competitiveness, time urgency, and easily provoked impatience. Although Type A was ultimately not found to be a reliable predictor of CVD, particularly when assessed by questionnaire data, epidemiological investigation of hostility has been more consistent. In a meta-analysis of 25 studies, Chida et al. reported that the presence of anger or hostility was associated with an approximately 20% increased risk of CVD among community cohorts and 25% increased risk of CVD events among another 19 studies involving the investigation of patients with known CVD [17]. Overall, however, hostility is not as strong a predictor of CVD risk versus other psychosocial factors noted in this review. Of note, the epidemiological study of hostility may be more challenging than the study of other psychological constructs since many patients with hostility manifest lack of self-awareness or some degree of self-denial about their anger and hostility.

2.6 Other Negative Cognitive States

Isolated studies have also examined the relationship between other negative mind-sets or cognitive patterns and cardiovascular indices, including worry, rumination, perfectionism, and resentment (the last mostly studied through its opposite, the

analysis of the trait or state of forgiveness). Preliminary data suggests that the study of such cognitive states may merit further exploration as to their potential link to health outcomes, but there is currently insufficient data to link these factors to CVD risk.

2.7 Lack of Life Purpose

Intrinsic to human behavior is a basic psychological need to pursue a life of meaning and purpose. An expanding evidence base has found a strong association between individuals' sense of life purpose and a variety of physical and psychological health indices. A meta-analysis of ten prospective longitudinal studies, involving more than 136,000 subjects, found that having a high sense of life purpose was associated with both a lower risk for cardiovascular events (adjusted relative risk of 0.83, 95% CI 0.75–0.92) and all-cause mortality (adjusted relative risk of 0.83, 95% CI 0.75–0.91) [5]. Similarly, a recent analysis of 6985 participants in the Health and Retirement Study found a graded relationship between individuals' reported sense of life purpose and survival [6].

2.8 Vitality Exhaustion

Based on early clinical observations regarding the study of fatigue, Appels et al. delineate a triad of symptoms that may be related to CVD: excessive fatigue, feelings of demoralization, and increased irritability [18]. They termed this triad as "vital exhaustion." Since then, a variety of longitudinal studies have examined the relationship between this construct and CVD risk. A meta-analysis of 17 studies involving over 100,000 participants found a significant relationship between vital exhaustion and CVD events [3]. This relationship persisted among those studies which adjusted CVD risk for depression.

2.9 Chronic Stress

There is a widespread assumption that chronic stress is associated with CVD risk, but this relationship is not straightforward. Because of the basic human need to engage in life with a sense of purpose, individuals tend to pursue various levels of life challenge, with acceptance of the stress that accompanies active goal pursuit. Interestingly in this regard is data that suggests a U-shaped relationship between one's perceived level of life stress and adverse clinical outcomes, with some level of stress being associated with better physical and mental well-being versus either no or very high stress levels. For instance, in a study of 2398 individuals reporting

lifetime exposure to negative events, those reporting moderate versus either very high or very low stress exposure had the least magnitude of psychosocial dysfunction and highest level of life satisfaction [19].

Investigators have studied how both objective life circumstances and perceived stress levels are related to CVD risk. Among objective stressors, various models of job stress, chronic unemployment, marital stress, and the long-term effects of childhood abuse or trauma have all been linked to CVD. However, the assessment of perceived stress is important because it is the interpretation or experience associated with objective life stressors, rather than objective stressors per se, that may be linked most closely to negative health consequences. With respect to perceived stress, "bad" or "toxic" stressors are those which are experienced as overwhelming, uncontrollable, and/or meaningless.

3 Positive Psychosocial Functioning

Each of the psychosocial domains discussed above exists according to a spectrum that ranges from positive to negative psychosocial functioning (Fig. 1). Each domain of positive psychosocial functioning may contribute to "vitality," which may be defined as a pleasurable sense of feeling energetic. Since vitality is a function of both physical and psychological well-being, it has been proposed as an integrative variable for assessing optimal biopsychosocial functioning. The beneficial value of positive psychosocial functioning is

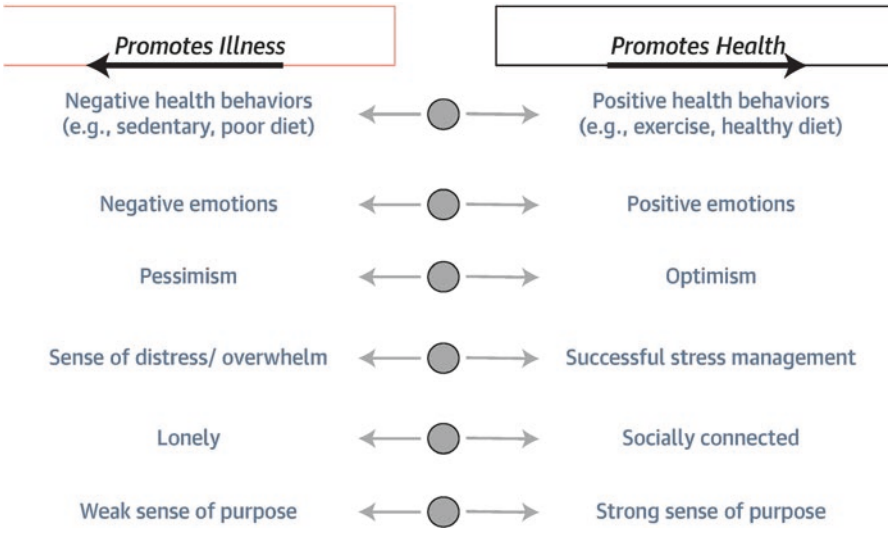

Fig. 1 Psychosocial factors generally exist along a continuum, ranging from positive factors that promote physiological functioning and reduce health risks to negative factors, which promote pathophysiological dysfunction and increase health risks, including the risk for cardiovascular disease. (Reprinted from Rozanski [24], with permission from Elsevier)

supported by a meta-analysis of 35 studies demonstrating increased longevity in association with positive emotions [20] and data indicating an inverse relationship between levels of emotional vitality and CVD [21, 22].

4 Pathophysiological Mechanisms

Psychosocial risk factors are linked to CVD through two broad mechanisms: their impact on health behaviors and their impact on pathophysiologic functioning. With respect to health behaviors, consistent data has linked negative psychosocial risk factors to a higher frequency of smoking, poor nutrition, obesity, and physical inactivity. In addition, the presence of negative psychological factors is associated with poorer patient adherence to recommended behavioral changes among patients with known CAD. It is important to recognize that the relationship between health behavioral and psychological functioning is bidirectional since the presence of poor health habits, such as physical inactivity and lack of sleep, can increase patients' vulnerability to psychosocial stressors.

The direct pathogenic effects of psychosocial risk factors upon physical functioning have been best studied for depression. Chronic depression may lead to persistent activation of the hypothalamic-pituitary-adrenal axis and dysregulation of the sympathetic nervous system.

The resultant elevation in serum cortisol levels and enhanced sympathetic stimulation, and interplay between the neuroendocrine and immune systems, can lead to widespread systemic dysfunction, including endocrine abnormalities (insulin resistance, diabetes, and central obesity), autonomic dysfunction, inflammation, increased cardiovascular reactivity (i.e., exaggerated heart rate and blood pressure responses to stress and delayed recovery), endothelial dysfunction, multiple platelet abnormalities, and unfavorable alterations in brain plasticity [1, 23, 24]. Different psychosocial factors may cause various patterns of pathophysiological dysfunction, which vary according to both the type and magnitude of individual stressors.

5 Management of Psychosocial Risk Factors in Preventive Cardiology

Healthcare professionals in general and specifically in the field of preventive cardiology can and should play an important role in the assessment and management of psychosocial risk factors in clinical practice. Whereas a full review of management techniques is beyond the scope of this chapter, clinicians can play an important role in screening for psychosocial dysfunction and then consider managing these risk factors according to a tiered approach.

5.1 Screening

Physicians should not underestimate the utility of adding a few questions to their standard review of symptoms when attending to their patients. With practice, such a review can be accomplished quickly and is effective because many patients welcome inquiry into their sense of well-being. These screening questions can take the form of short open-ended questions such as the following: (1) How has your energy level been? (2) How has your sleeping been recently? (3) What kind of pressure have you been under at work or at home? (4) How has your mood been recently? (5) Who do you turn to for support these days? (6) Do you find that you are able/unable to unwind after work or at the end of the day?

In medical settings involving the collection of questionnaire data, very short screening questions regarding depression and anxiety may be useful, given their common occurrence among medical patients and the attendant risk that may be associated with high levels of these two risk factors. A multidisciplinary council from the American Heart Association has recommended screening for depression using a two-item subscale of the Patient Health Questionnaire which asks patients how often over the last 2 weeks they have you been bothered by (i) little interest in or pleasure in doing things and (ii) feeling down, depressed, or hopeless. Responses are recorded to a four-point scale: 0, not at all; 1, several days; 2, more than half the days; and 3, nearly every day [25]. For those indicating a positive answer to either question, considered to be a score of >2 (reflecting the occurrence of these feelings on more than half of days), a nine-item version of the PHQ may be used to further query patients regarding other symptoms, such as sleeping difficulties, fatigue, poor appetite or overeating, and suicide risk. In patients with high depressive scores, referral to a qualified professional is indicated. Similarly, anxiety can be screened for by using a two-item subscale of the Generalized Anxiety Disorder 7-item (GAD-7) scale which queries patients to what extent they have been feeling nervous, anxious, or on edge or an inability to stop or control worrying over the past 2 weeks.

5.2 Tiered Management of Patients

The management of psychosocial risk factors in medical practice can be quite challenging due to limited time and resources and/or limited training in such management. Beyond screening for psychosocial risk factors according to some open questions, as suggested above, physicians can best augment their management of identified risk factors by adopting a tiered approach: (1) personal physician management of simple psychosocial issues; (2) referral of patients with mild psychosocial needs to either designated office personnel or to community or hospital programs, and (3) the referral of patients with severe psychosocial dysfunction to qualified professionals. Each of these tiers of care is briefly described below.

5.3 First Tier: Personal Physician Management

Medical practitioners should not underestimate the outsized role that they may *sometimes* exert by making practical life enhancing suggestions to their patients. For example, upon observing patients who are undergoing undue stress, physicians can make practical suggestions regarding rest and relaxation or stress reduction practices, such as breathing exercises and progressive relaxation techniques, or even simply recommend increased downtime at nights and weekends or the use of apps that may provide stress reduction instruction and practices. In addition, physicians should not underestimate the considerable psychological benefit which may be derived when patients adopt improved health behaviors. This has been particularly well shown with respect to exercise. A now considerable evidence base involving cross-sectional studies and longitudinal epidemiological studies has demonstrated a strong association between higher levels of physical activity and lower rates of depression [26]. In addition, a series of prospective randomized studies have compared the effectiveness of antidepressant medications versus exercise for reducing depressive symptoms [27–29]. In each of these studies, exercise was found to be comparable to antidepressant medication in alleviating depressive symptoms.

5.4 Second Tier: Invoking Office Personnel, Community Programs, or Hospital-Based Programs

For many patients, the management of psychosocial risk factors requires more than directed physician guidance. Fortunately, community- and hospital-based programs have become more commonplace, and physicians can also designate specific office personnel to assist patients when so desired within practice settings. For example, in further reference to patients experiencing undue stress or an increased sense of physical or mental tension, physicians may refer such patients to structured programs such as mindfulness-based stress reduction classes, yoga or tai chi. Similarly, if a patient is suffering from loneliness or poor emotional or tangible social support, the physician may recommend patients to community- or hospital-based programs that can provide the opportunity for social interaction or social support. Of if a patient is suffering from poor sleep or insomnia, they may benefit from referral to a sleep hygiene program. Thus, at a minimum, it behooves physicians to be aware of community- or hospital-based programs that provide these forms of psychosocial management.

5.5 Third Tier: Referral to Qualified Mental Health Professionals

Patients who are noted to have excessive worry, rumination, or pessimism may benefit from referral to trained mental health professionals as a preventive strategy to ward off more serious emotional sequelae, such as the development of clinical

depression or anxiety. Once present, depression and anxiety can be managed by use of psychotherapy and, when indicated, psychotropic medications. The use of psychotherapy for treating depression may include either cognitive behavioral therapy or interpersonal psychotherapy. Selective serotonin reuptake inhibitors (SSRIs) are the first-line medication for treating depression when pharmacologic agents are required. Similarly, various treatment options may be used to manage anxiety. For mild transient forms of anxiety, relaxation techniques and problem-solving counseling may be useful. With more severe symptoms, a mainstay for treatment includes the use of cognitive behavioral therapy, with modifications for specific forms of anxiety such as phobias and post-traumatic stress disorder. Pharmacological interventions for anxiety include the use of SSRIs and benzodiazepines.

6 Conclusion

Over the past 40 years, epidemiological studies have repeatedly demonstrated a strong association between psychosocial risk factors and CVD. While initial studies showed a relationship between CVD outcomes and depression, anxiety, social factors, work stress, and hostility, more recently, evidence has emerged that links such factors as pessimism, lack of life purpose, and vital exhaustion to CVD as well. Both direct pathophysiological effects and adverse health behaviors form the basis for this linkage between psychosocial risk factors and adverse clinical outcomes. Clinicians can play an important role in aiding the management of psychosocial risk factors by screening for these factors in clinical practice, providing simple advice or directives when indicated, and referring appropriate patients to either designated office staff or community- or hospital-based programs or to mental health professionals when psychosocial dysfunction is severe.

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Dietary Strategies for Atherosclerotic Cardiovascular Risk Reduction

Geeta Sikand

Summary

- The most important way to prevent atherosclerotic cardiovascular disease (ASCVD), heart failure, and atrial fibrillation is to promote an ongoing healthy lifestyle. All adults should consume a healthy dietary pattern that emphasizes the intake of vegetables, fruits, nuts, legumes, whole grains, low-fat or nonfat dairy, lean sources of vegetable or animal protein, and fish and minimize the intake of *trans* fats, processed meats, refined carbohydrates, and sweetened beverages.
- Include dietary adjuncts viscous fiber, plant sterols/stanols, soy, and long-chain omega-3 fatty acids.
- For overweight or obese adults, dietary counseling and caloric restriction with a registered dietitian-nutritionist (RDN) are recommended for achieving and maintaining weight loss.
- Referral to an RDN helps to personalize the individual's dietary pattern with personal and cultural food preferences to optimize treatment for dyslipidemia, high blood pressure, overweight/obesity, and hyperglycemia and to prevent or reverse metabolic syndrome and type 2 diabetes. Multiple visits with an RDN help target behavior change by providing accountability and support.
- Multidisciplinary clinic-based strategies that include on-site RDNs can also facilitate personalized nutrition counseling that targets patient behavior change for ASCVD risk reduction. RDNs help patients identify and personalize their heart-healthy dietary patterns per their self-efficacy as well as personal and cultural food preferences.

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1 Introduction

Despite significant improvement in atherosclerotic cardiovascular disease (ASCVD) outcomes, it still remains the leading cause of morbidity and mortality in the United States and globally [1–3]. In recent years, deaths from cardiovascular disease (CVD) have increased in the middle age (45–64 years) cohort in the United States. This is mainly due to increased incidence of overweight/obesity, high blood pressure, and increases in glucose and lipids that are attributed to a poor dietary lifestyle [4].

ASCVD also remains the leading cause of death among most racial/ethnic groups in the United States, with an estimated cost of >$200 billion annually in healthcare services, medications, and lost productivity. This increased cost is mostly attributable to suboptimal implementation of prevention strategies and uncontrolled ASCVD risk factors in many adults [1–3].

Due to the high global burden of disease, the American Heart Association (AHA) [5] has recently shifted the focus of its 2030 goals from managing heart disease to one of embracing and incorporating health promotion and disease prevention. This renewed focus on AHA prevention aims to ensure that prevention-related interventions for heart disease and stroke events effectively reach the vulnerable populations, communities, and the healthcare and public health systems [5]. It will require an emphasis on health behaviors, in particular diet and physical activity beyond the identification and treatment of cardiovascular risk factors, including tobacco use, obesity, diabetes mellitus, hypertension, and hyperlipidemia [5].

The AHA 2020 goals are to improve the cardiovascular health of all Americans to reduce CVD morbidity and mortality by 20%. To attain this goal, the AHA released a tool, "Life's Simple 7 ™," that focuses on adherence to seven key metrics of cardiovascular health [6]:

1. Get active.
2. Control cholesterol.
3. Eat better.
4. Manage blood pressure.
5. Lose weight.
6. Reduce blood sugar.
7. Stop smoking.

The cornerstone of preventing ASCVD, heart failure, and atrial fibrillation is to promote a healthy lifestyle throughout life [1]. It is noteworthy that 6 out of the top 10 take-home messages listed below from the recent 2019 American College of Cardiology (ACC) and AHA primary prevention guidelines are within the context of nutrition, diet, and physical activity [1].

- A team-based care approach is an effective strategy for the prevention of cardiovascular disease. Clinicians should evaluate the social determinants of health that affect individuals to inform treatment decisions.
- All adults should consume a healthy diet that emphasizes the intake of vegetables, fruits, nuts, whole grains, lean vegetable or animal protein, and fish

and minimize the intake of *trans* fats, processed meats, refined carbohydrates, and sweetened beverages. For overweight or obese adults, counseling and caloric restriction are recommended for achieving and maintaining weight loss.

- For adults with type 2 diabetes mellitus (T2DM), lifestyle changes, such as improving dietary habits and achieving exercise recommendations, are crucial. If medication is indicated, metformin is first-line therapy, followed by consideration of a sodium-glucose cotransporter 2 inhibitor or a glucagon-like peptide-1 receptor agonist.
- Nonpharmacological interventions are recommended for all adults with elevated blood pressure or hypertension. For those requiring pharmacological therapy, the target blood pressure should generally be <130/80 mm Hg (although "normal BP" is now considered <120/80 mmHg by ACC/AHA 2017 BP Guideline).
- Adults should engage in at least 150 min per week of accumulated moderate-intensity physical activity or 75 min per week of vigorous-intensity physical activity.

2 ACC/AHA Nutrition and Diet Recommendations for ASCVD Prevention

The ACC/AHA nutrition and diet recommendations for ASCVD prevention are summarized below (Table 1) [1].

Other factors that affect ASCVD risk include overweight/obesity and type 2 diabetes mellitus (T2DM) [1].

Table 1 ACC/AHA nutrition and diet recommendations for ASCVD prevention [1]

COR	LOE	Recommendations
I (strong)	B-R	1. A diet emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish is recommended to decrease ASCVD risk factors
IIa (moderate)	B-NR	2. Replacement of saturated fat with dietary monounsaturated and polyunsaturated fats can be beneficial to reduce ASCVD risk
IIa (moderate)	B-NR	3. A diet containing reduced amounts of cholesterol and sodium can be beneficial to decrease ASCVD risk
IIa (moderate)	B-NR	4. As a part of a healthy diet, it is reasonable to minimize the intake of processed meats, refined carbohydrates, and sweetened beverages to reduce ASCVD risk
III-harm	B-NR	5. As part of a healthy diet, the intake of *trans* fats should be avoided to reduce ASCVD risk

Abbreviations: *COR* class (strength) of recommendation, *LOE* level (quality) of evidence, *R* randomized, *NR* nonrandomized, *B* moderate quality

3 ACC/AHA Nutrition and Diet Recommendations for Adults with Overweight and Obesity

The ACC/AHA Nutrition and Diet Recommendations for Adults with Overweight and Obesity are summarized (Table 2) [1]. Adults diagnosed with obesity (BMI ≥ 30 kg/m^2) or overweight (BMI = 25–29.9 kg/m^2) are at an increased risk of ASCVD, heart failure, and atrial fibrillation versus normal-weight individuals. The nutritional aspects of obesity revolve around the principle of balancing caloric intake with caloric expenditure. Weight loss of 5–10% of initial weight, achieved through comprehensive lifestyle intervention, has been shown to improve BP, delay the onset of T2DM, improve glycemic control in T2DM, and improve the lipid profile. Waist circumference measurement is recommended in all patients with a BMI <35 kg/m^2. Ethnic differences are reported in waist circumference thresholds associated with cardiometabolic risk [1].

Cheong et al. estimated optimal BMI cutoffs in a multiethnic Malaysian population that included people of Malay, Chinese, and Indian origins and recommended cutoffs of 23.0 and 24.0 kg/m^2 for Asian men and women, respectively [7]. The International Diabetes Federation has established different cut points for populations of European (>94 cm for men and >80 cm for women) and Asian (>90 cm for men and >80 cm for women) origin [8, 9]. In Asian ethnic groups, waist circumference may be more useful than BMI in persons with abdominal obesity [1, 10, 11].

Counseling by a registered dietitian-nutritionist (RDN) or referral to a multidisciplinary lifestyle intervention program, including calorie restriction and adjunctive therapies (e.g., nutrition and lifestyle counseling by a RDN, FDA-approved drugs, bariatric surgery), is associated with significant reductions in waist circumference, lipids, A1c, and blood pressure [1, 2, 12]. The ACC/AHA nutrition recommendations for adults with overweight and obesity are summarized below (Table 2).

Table 2 ACC/AHA nutrition recommendations for adults with overweight and obesity [1]

COR	LOE	Recommendations
I (strong)	B-R	1. In individuals with overweight and obesity, weight loss is recommended to improve the ASCVD risk factor profile
I (strong)	B-R	2. Counseling and comprehensive lifestyle interventions, including calorie restriction, are recommended for achieving and maintaining weight loss in adults with overweight and obesity
I (strong)	C-EO	3. Calculating body mass index (BMI) is recommended annually or more frequently to identify adults with overweight and obesity for weight loss considerations
IIa	B-NR	4. It is reasonable to measure waist circumference to identify those at higher cardiometabolic risk

Abbreviations: *COR* class (strength) of recommendation, *LOE* level (quality) of evidence, *R* randomized, *NR* nonrandomized, *B* moderate quality, *EO* expert opinion

4 ACC/AHA Nutrition Recommendations for Adults with Type 2 Diabetes

The ACC/AHA Nutrition and Diet Recommendations for Adults with T2DM are summarized below (Table 3) [1]. A heart-healthy dietary pattern is a key intervention in the treatment of T2DM. The Mediterranean, DASH, and vegetarian/vegan diets have all been shown to achieve weight loss and improve glycemic control in T2DM. Weight loss is an essential treatment component for T2DM, and dietary recommendations should be adjusted to achieve meaningful weight loss, if needed. Establishing an appropriate nutrition plan requires time and effort and is best accomplished with assistance from a registered dietitian-nutritionist or a multidisciplinary diabetes education program [1].

5 Nutrition Recommendations for the Prevention and Treatment of Hypertension

A summary of the most supported nutritional interventions for hypertension and their impact on the prevention and treatment of hypertension is listed (Table 4) [1].

6 ACC, AHA, and National Lipid Association (NLA) Nutrition Goals for Optimizing LDL-C and Non-HDL-C and Reducing ASCVD Risk

The ACC/AHA and NLA nutrition goals for optimizing LDL-C and non-HDL-C and reducing ASCVD risk are as follows [1–3]:

- Achieve weight loss of 5–10% of body weight if overweight.
- Reduce saturated fat intake to <7% of energy and dietary cholesterol to <200 mg/day.
- Avoid trans fats.

Table 3 ACC/AHA nutrition recommendation for adults with type 2 diabetes [1]

COR	LOE	Recommendations
I (strong)	A	1. For all adults with T2DM, a tailored nutrition plan focusing on a heart-healthy dietary pattern is recommended to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors

Abbreviations: *COR* class (strength) of recommendation, *LOE* level (quality) of evidence, *A* high-quality evidence

Table 4 Most strongly supported nutritional interventions and their impact on prevention and treatment of hypertension[1]

Type of nutrition intervention	Goals	Approximate impact on SBP (hypertensives)	Approximate impact on SBP (normotensives)
Weight loss	Best goal is ideal body weight, but aim for at least a 1 kg reduction in body weight for most adults who are overweight Expect about 1 mm Hg for every 1 kg reduction in body weight	−5 mm Hg	−2/3 mm Hg
DASH dietary pattern[a]	Consume a diet rich in fruits, vegetables, whole grains, and low-fat dairy products, with reduced content of saturated and total fat	−11 mm Hg	−3 mm Hg
Reduced intake of dietary sodium	Optimal goal is <1500 mg/d, but aim for at least a 1000 mg/d reduction in most adults	−5/6 mm Hg	−2/3 mm Hg
Enhanced intake of dietary potassium	Aim for 3500–5000 mg/d, preferably by consumption of a diet rich in potassium	−4/5 mm Hg	−2 mm Hg
Moderation in alcohol intake	Alcohol consumption in individuals who drink alcohol, reduce alcohol[b] to: Men: ≤2 drinks daily Women: ≤1 drink daily	−4 mm Hg	−3 mm Hg

Type, dose, and expected impact on blood pressure (BP) in adults with a normal BP and with hypertension

BP blood pressure, *DASH* Dietary Approaches to Stop Hypertension, *NHLBI* National Heart, Lung, and Blood Institute, *SBP* systolic blood pressure

[a]Detailed information about the DASH diet is available via the NHLBI (S4.4–81) and Dashdiet.org

[b]In the United States, one "standard" drink contains roughly 14 g of pure alcohol, which is typically found in 12 oz of regular beer (usually about 5% alcohol), 5 oz of wine (usually about 12% alcohol), and 1.5 oz of distilled spirits (usually about 40% alcohol)

- Reduce intake of added sugars (<10% of total energy).
- Follow a heart-healthy dietary pattern with a focus on plant-based protein.
- Increase intake of viscous fiber to 5–10 g/day and plant sterols/stanols to 2 g/day.

7 Criteria for Nutritional Indicators for Dyslipidemia and Cardiometabolic Risk Factors

The criteria for nutritional indicators for dyslipidemia and cardiometabolic risk factors are [13, 14]:

- Abnormal low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), and non-high-density lipoprotein cholesterol (non-HDL-C)
- Overweight (body mass index) BMI 24.9–29.9
- BMI Class 1 obesity 30–34.9, Class II obesity 35–39.9, and Class III obesity >40
- Dietary intake of saturated fat >7% of total daily energy or especially if >10% of total daily energy
- Poorly controlled diabetes, defined by HbA1c >7 mg/dL
- Sedentary lifestyle
- Abdominal obesity: waist circumference >35 inches in men, >32 inches in women
- Fasting glucose ≥100 mg/dL
- High intake of refined carbohydrate >10% of energy intake
- Alcohol intake coupled with high TG or overweight or obesity

8 Heart-Healthy Dietary Patterns for Reducing LDL-C, Non-HDL-C, and ASCVD Risk

Dietary guidance to achieve cardiovascular health should remain focused on adopting a heart-healthy dietary pattern. Guidance focused on heart-healthy dietary patterns is more likely to improve diet quality and promote cardiovascular health. Scientific evidence from randomized controlled trials revealed that each reduction of 1% in LDL-C or non-HDL-C is associated with a 1% decrease in coronary heart disease (CHD) event risk over 5 years [1–3]. Weight loss of 5–8 kg if sustained results in mean LDL-C reduction of 5 mg/dL and an increase in HDL-C of 2–3 mg/dL. A 3 kg weight loss reduces TG by 15 mg/dL [1–3]. Diet and lifestyle patterns are also associated with nontraditional risk factors including markers of inflammation, insulin resistance, oxidative stress, and thrombogenicity [1–3].

Heart-healthy dietary patterns are low in saturated fat and dietary cholesterol. These patterns are high in fruits, vegetables, whole grains, low-fat or fat-free dairy products, lean protein sources, legumes, nuts, seeds, and liquid vegetable oils; low in red and processed meats; and low in refined grains, sugar-sweetened foods, and beverages [1–3, 6, 15–18].

8.1 DASH Dietary Pattern

The original Dietary Approaches to Stop Hypertension (DASH) dietary pattern, as well as the higher unsaturated fat-DASH pattern, improved blood pressure, blood lipids, and ASCVD risk. The DASH dietary patterns (Appendix A) are high in

vegetables, fruits, whole grains, low- or nonfat dairy, seafood, skinless poultry, legumes, and nuts; moderate in alcohol (for adults); low in red and processed meats; and low in refined grains, sugar-sweetened foods, and beverages [1–17].

8.2 *Mediterranean-Style Dietary Pattern (Healthy US-Style Food Pattern)*

Like DASH, the Mediterranean diet is high in fruits, vegetables, whole grains, legumes, unsalted nuts and seeds, and olive oil; low to moderate in red wine (in individuals consuming alcohol), fish, skinless poultry, and low-fat dairy products; and low in red meat. This diet is also high in monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA), polyphenols, flavonoids, phytosterols, and fiber which contribute to reduced risk of CVD and DM [1–3, 18]. In the recently republished PREDIMED study [19], 5859 adults, ages 55–80 years with T2D or at least three major risk factors without CVD, showed significantly lower rates of major CV events with an energy-unrestricted Mediterranean diet *plus* extra-virgin olive oil *or* mixed unsalted nuts versus a reduced fat diet (control group). Median follow-up was 4.8 years [19]. Results were similar after the omission of 1588 participants whose study-group assignments were known or suspected to have departed from the protocol. A primary endpoint event occurred in 288 participants; there were 96 events in the group assigned to a Mediterranean diet with extra-virgin olive oil (3.8%), 83 in the group assigned to a Mediterranean diet with mixed nuts (3.4%), and 109 in the control group (4.4%). In the intention-to-treat analysis including all the participants and adjusting for baseline characteristics and propensity scores, the hazard ratio was 0.69 (95% confidence interval [CI], 0.53–0.91) for a Mediterranean diet with extra-virgin olive oil and 0.72 (95% CI, 0.54–0.95) for a Mediterranean diet with nuts, as compared with the control diet [19]. A higher adherence to a Mediterranean diet in 25,994 US women followed for 12 years showed a 28% relative risk reduction in CVD events due to improved inflammation, glycemic status, insulin resistance, and adiposity [20].

8.3 *Vegetarian/Vegan Dietary Pattern (Plant-Based Dietary Patterns)*

A large meta-analysis [21] of 130,000 vegetarians (86 cross-sectional and 10 prospective cohorts) and 15,000 vegans (24 cross-sectional and 4 prospective cohort) examined the association between vegetarian, vegan diets, and risk factors for chronic diseases. The cross-sectional studies reported significant reductions in BMI, LDL-C, and glucose in vegetarians and vegans vs. omnivores. The cohort prospective studies reported a 25% risk reduction in incidence and/or mortality from

ischemic heart disease (RR 0.75; 95% CI, 0.68–0.82) in vegans and vegetarians versus omnivores although total cardiovascular and cerebrovascular diseases were not reduced [21].

A nonlinear association between adherence scores above the median to a healthy plant-based diet and all-cause mortality was observed in US adults. Healthy plant-based diet scores above the median were associated with a lower risk of all-cause mortality in US adults. Future research exploring the impact of quality of plant-based diets on long-term health outcomes is needed [22]. Vegetarians typically have a higher intake of fiber, carbohydrate, potassium, magnesium, folate, n-6 fatty acids, nonheme iron, and vitamin C [15].

A recent RCT in the United States evaluated the effects of a vegan diet vs. American Heart Association (AHA)-recommended diet for 8 weeks in adults (n = 100) with coronary artery disease (CAD) and elevated hs CRP [23]. Both groups received the same number of dietician visits, support tools, and groceries except the vegan group received substitution of animal-based protein for plant-based protein. Overall the vegan diet resulted in a significant 32% lower high-sensitivity C-reactive protein (b, 0.68, 95% confidence interval [0.49–0.94]; P = 0.02) when compared with the AHA diet. Results were consistent after adjustment for age, race, baseline waist circumference, diabetes mellitus, and prior myocardial infarction (adjusted b, 0.67 [0.47–0.94], P = 0.02). Both diet groups reported significant improvement in weight loss, glycemic control, lipid profile, and quality of life (QOL). The vegan diet group (n = 48) reduced hs CRP by 28% (range = −47–0%) versus AHA diet group (n = 49) by 7% (range = −29–+40%) (P = 0.026 between groups). The degree of reduction in body mass index and waist circumference did not significantly differ between the two diet groups (adjusted β, 0.99 [0.97–1.00], P = 0.10, and adjusted β, 1.00 [0.98–1.01], P = 0.66, respectively). There were also no significant differences in markers of glycemic control between both diet groups. There was a nonsignificant 13% reduction in LDL-C with the vegan diet versus the American Heart Association diet (adjusted β, 0.87 [0.78–0.97], P = 0.01). There were no significant differences in other lipid parameters. However, the results are not generalizable as only 14% of screened participants joined the study [23].

9 Low Fat Versus Low Carbohydrate and Very Low Carbohydrate (Including Ketogenic Diets for Overweight/Obesity, Dyslipidemia, Metabolic Syndrome, Diabetes, Inflammation, and ASCVD Risk)

Diet affects the inflammatory response which affects ASCVD risk and mortality. A high-glycemic load diet coupled with insulin resistance and overweight status is associated with chronic systemic inflammation [24]. Systematic reviews report that weight loss of at least 2.5 kg or 3% of body weight led to improved LDL-C and

triglycerides (TG) in the general population. A 3 kg weight loss reduced TG by at least 15 mg/dL [1–3].

Restricting carbohydrates for weight reduction could be beneficial for some, while a high-quality moderate-carbohydrate low-fat diet may work better for others. People with overweight/obesity who also have diabetes and/or elevated TG may benefit from following a very-low-carbohydrate diet for 2–6 months [25, 26]. It could lower TG, blood glucose, and body weight. However, a very-low-carbohydrate diet (including a ketogenic diet) is rigid and not nutritionally adequate. It is not consistent with nutrition recommendations by the ACC/AHA dietary guidelines and other professional organizations. It may restrict foods associated with cardioprotective benefits. Compliance (>6 months) may be difficult and long-term benefits are unproven. It may increase LDL-C in some individuals as it may encourage foods high in saturated fat and dietary cholesterol that increase ASCVD risk. Low-carbohydrate diets result in a greater short-term reduction in HbA1c versus high-carbohydrate low-fat diets, but results were not sustained after 1 year [25].

Low-carbohydrate diets resulted in a reduction in the use of diabetes medications even at carbohydrate intake levels that did not induce ketosis. The Mediterranean dietary pattern also produced improvements in TG, HDL-C, and HbA1c levels in individuals with T2D compared to low-carbohydrate diets. Patients' personal preference and self-efficacy should be considered when counseling patients on selecting a weight loss diet [25].

Kirkpatrick et al. [25] concluded that for the short term (≤6 months), hypocaloric low-carbohydrate and very-low-carbohydrate diets may result in greater weight loss than hypocaloric high-carbohydrate, low-fat diets. However, for the long term (>6 months), these results are not sustained and are similar to the results of a higher-carbohydrate, low-fat hypocaloric diet. Furthermore, very-low-carbohydrate diets are difficult to maintain and are not clearly superior for weight loss compared to diets that allow a higher amount of carbohydrate in adults with overweight and obesity with or without diabetes. Long-term participation in any weight loss intervention can be challenging. However, adherence can be lower in patients trying to follow a rigid low-carbohydrate diet and especially very-low-carbohydrate diet [25].

Furthermore, long-term dietary patterns with low carbohydrate intake along with high animal-derived fat/protein intake are associated with increased cardiac and noncardiac mortality. Mazidi et al. [27] examined the association between low-carbohydrate diets and overall or cause-specific mortality from National Health and Nutrition Examination Survey data ($n = 24{,}825$) and found that participants with the lowest carbohydrate intake (<39% of daily energy intake) based on 24-h recall assessment had the highest risk of overall (32%), CVD (50%), cerebrovascular (51%), and cancer (36%) mortality. Another analysis of pooled data from nine prospective cohort studies ($n = 462{,}934$ participants) found that participants with the lowest carbohydrate intake had the highest risk of overall (RR 1.22; 95% CI: 1.06, 1.39; $P < 0.001$), CVD (RR 1.13; 95% CI: 1.02, 1.24; $P < 0.001$), and cancer mortality (RR 1.08; 95% CI: 1.01, 1.14; $P = 0.02$) [27].

The Atherosclerosis Risk in Communities (ARIC) study (n = 15,428) [28] as well as a meta-analysis with data from ARIC plus seven multinational prospective studies (n = 432,179) examined the association between carbohydrate intake and all-cause mortality. The analyses demonstrated that both low- (<40% daily energy intake) and high-carbohydrate (>70% daily energy intake) diets were associated with a higher risk of mortality (20% and 23%, respectively) and 50–55% carbohydrate as daily energy intake was associated with the lowest risk of mortality [28]. Results indicated that, when animal-based protein or fat was substituted for carbohydrate, the associated risk of mortality increased by 18% whereas mortality decreased by 18% when carbohydrate was replaced by plant-based protein or fat [28]. Low-carbohydrate dietary patterns favoring animal-derived protein and fat intake from sources such as lamb, beef, pork, and chicken were associated with higher mortality, whereas those that favored plant-derived protein and fat intake, from sources such as vegetables, nuts, peanut butter, and whole-grain breads, were associated with lower mortality, suggesting that the source of food notably modifies the association between carbohydrate intake and mortality [28]. The reasons for the association between carbohydrate restriction and increased mortality include (1) a reduced intake of vegetables, fruits, and grains and an increased intake of animal-based protein, which results in reduced levels of dietary bioactives (i.e., free fatty acids, protein, fiber, minerals, vitamins, and phytochemicals), and (2) higher carbohydrate intakes may be associated with lower economic status and lower-quality (refined) carbohydrate foods [27, 28].

If severe carbohydrate restriction is followed for weight loss, it should be limited to short periods (2–6 months) followed by a transition to a healthy dietary pattern for the long term with adequate intake of fiber-rich carbohydrate foods and inclusion of plant-based proteins and unsaturated fats for nutritional adequacy and to prevent ASCVD [25].

The Dietary Guidelines for Americans (DGA) recommendation for optimal carbohydrate intake is 45–65% of energy intake [15]. However, some very-low-fat/very-high-carbohydrate diets like the Esselstyn [29] and the Ornish diets [30] reduce CVD risk and reverse heart disease [29, 30]. Furthermore, the habitual very-high-carbohydrate/very-low-fat diets consumed by Okinawan Japanese [31] and the Tsimani Indians [32] in South America have shown a reduced rate of ASCVD and an increase in longevity. These diets, although high in carbohydrate, are low in refined carbohydrates [29–32].

However, some ultra-low-fat-very-high-carbohydrate diets such as the Esselstyn diet [29] and the Ornish diet [30] have been shown to reduce CVD risk and reverse heart disease [29, 30]. Furthermore, the habitual very-high-carbohydrate/very-low-fat diets consumed by Okinawans in Japan [31] and the Tsimani Indians [32] in South America have shown a reduced rate of ASCVD and an increase in longevity. These diets are high in carbohydrate but low in refined carbohydrates [29–32].

10 Nutrition and Lifestyle Recommendations for Triglyceride Reduction

- Weight loss has the most profound TG lowering effect. Weight loss of approximately 5–10% of body weight can lower TG 20% as well as reduce the risk of developing metabolic syndrome (MetS) and T2DM [1–3]. One rapid weight loss study examined 125 patients with MetS over 17 weeks and reported a 45% reduction in TG with a 15% weight loss on a very-low-calorie diet [33].
- Avoid excessive intake of carbohydrate especially refined carbohydrates, e.g., sugar and sweets. When 60–65% of energy is consumed as carbohydrate, it leads to upregulation of very-low-density lipoprotein (VLDL) secretion.
- Choose vegetable oils and lower the intake of fat to <35% of caloric intake.
- Include fiber-rich whole grains, vegetables, fruits, low-fat or nonfat dairy products, fatty fish, poultry, tofu, soybeans, lentils, and legumes.
- Abstain or limit alcohol intake as alcohol can raise triglyceride levels.
- Have a regular physical activity such as walking for a minimum of 30 min on most days of the week.
- If TGs are ≥500 mg/dL, a very-low-fat diet (≤15% of calories from fat) is recommended to prevent pancreatitis.

Addition of an omega-3 supplement that provides 2–4 gm/d (EPA + DHA) may confer an additional TG reduction. The REDUCE IT multicenter randomized double-blind placebo-controlled trial in 8179 subjects followed for 4.9 years, prescription dose of 4 g/day of n-3 FA (icosapent ethyl), reported a TG reduction of ≥30% in statin-treated subjects with TG ≥ 500 mg/dL and a 20–30% reduction in subjects with TG 200–499 mg/dL [34]. A total of 8179 patients were enrolled (70.7% for secondary prevention of cardiovascular events) and were followed for a median of 4.9 years. A primary endpoint event occurred in 17.2% of the patients in the icosapent ethyl group, as compared with 22.0% of the patients in the placebo group (hazard ratio, 0.75; 95% confidence interval [CI], 0.68–0.83; $P < 0.001$); the corresponding rates of the key secondary endpoint were 11.2% and 14.8% (hazard ratio, 0.74; 95% CI, 0.65–0.83; $P < 0.001$). The rates of additional ischemic endpoints, as assessed according to a prespecified hierarchical schema, were significantly lower in the icosapent ethyl group than in the placebo group, including the rate of cardiovascular death (4.3% vs. 5.2%; hazard ratio, 0.80; 95% CI, 0.66–0.98; $P = 0.03$). A larger percentage of patients in the icosapent ethyl group than in the placebo group were hospitalized for atrial fibrillation or flutter (3.1% vs. 2.1%, $P = 0.004$) [34].

11 Saturated Fats, Trans Fats, Omega-3, Omega-6, and Monounsaturated Fats

Saturated fats and trans fats exhibit the greatest adverse effect on atherogenic cholesterol levels and should be replaced with unsaturated fats, both polyunsaturated fatty acids (PUFA) and monounsaturated fatty acids (MUFA) from plant sources

[1, 2, 35]. An isocaloric substitution of saturated fat with monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA) led to a 15% and 25% reduction, respectively, in CVD risk [35].

Foods high in saturated fats and dietary cholesterol (e.g., meat, organ meats, full-fat dairy products, eggs, and tropical oils (coconut and palm oil)) should be limited to <7% of energy intake. In a 2000 kcal dietary pattern, this would translate to 120 kcal per day and 12 gm of saturated fat. In a 1600 kcal diet pattern, this would translate to 7 or 8 gm per day [3, 16, 17].

The ACC/AHA prevention guidelines recommend intake of *trans* fats should be avoided to reduce ASCVD risk [1]. In a large cohort study, Wang et al. [36] investigated 83,349 women from the Nurses' Health Study (July 1, 1980, to June 30, 2012) and 42,884 men from the Health Professionals Follow-up Study (February 1, 1986, to January 31, 2012) who were free of CVD, cancer, and DM at baseline. Dietary fat intake was assessed at baseline and updated every 2–4 years. Information on mortality was obtained from systematic searches of the vital records of states and the National Death Index, supplemented by reports from family members or postal authorities. Data were analyzed from September 18, 2014, to March 27, 2016 [36].

During 3,439,954 person-years of follow-up, 33,304 deaths were documented. After adjustment for known and suspected risk factors, dietary total fat compared with total carbohydrates was inversely associated with total mortality (hazard ratio [HR] comparing extreme quintiles, 0.84; 95% CI, 0.81–0.88; $P < 0.001$ for trend). The HRs of total mortality comparing extreme quintiles of specific dietary fats were 1.08 (95% CI, 1.03–1.14) for saturated fat, 0.81 (95% CI, 0.78–0.84) for PUFA, 0.89 (95% CI, 0.84–0.94) for MUFA, and 1.13 (95% CI, 1.07–1.18) for trans fat ($P < 0.001$ for trend for all). Replacing 5% of energy from saturated fats with equivalent energy from PUFA and MUFA was associated with estimated reductions in total mortality of 27% (HR, 0.73; 95% CI, 0.70–0.77) and 13% (HR, 0.87; 95% CI, 0.82–0.93), respectively. The HR for total mortality comparing extreme quintiles of n-6 PUFA intake was 0.85 (95% CI, 0.81–0.89; $P < 0.001$ for trend). Intake of ω-6 PUFA, especially linoleic acid, was inversely associated with mortality owing to most major causes, whereas marine n-3 (omega-3) PUFA intake was associated with a modestly lower total mortality (HR comparing extreme quintiles, 0.96; 95% CI, 0.93–1.00; $P = 0.002$ for trend) [36].

In summary, current evidence [37] supports that different types of dietary fatty acids have divergent effects on CVD risk, and the effects also depend strongly on the replacement macronutrient. A significant reduction in CVD risk can be achieved if SFAs are replaced by unsaturated fats, especially PUFA. Intake of trans fat is consistently associated with higher CVD risk. Both n-6 and n-3 PUFA are associated with lower CVD risk [37]. The ACC/AH [1, 2], NLA [3], and the 2015–2020 DGA [15] recommend a greater emphasis on types of dietary fats than total amount of dietary fat and recommend replacing foods high in saturated fats with foods high in unsaturated fats, especially PUFA for CVD prevention [1–3, 15, 37].

A recent meta-analysis of 13 trials reported that marine omega-3 (n-3) supplementation lowers risk for myocardial infarction, CHD death, total CHD, CVD death, and total CVD. Risk reductions appeared to be linearly related to marine omega-3 dose [38]. Higher intakes of n-3 and n-6 fatty acids were associated with

the lowest levels of inflammatory biomarkers [39]. Increased intake of n-6 fatty acids did not lead to increased pro-inflammatory cytokines, e.g., CRP, IL-6, and soluble TNF receptors 1 and 2 [39]. Both n-3 and n-6 fatty acids were inversely associated with pro-inflammatory interleukin-1Ra and positively associated with anti-inflammatory transforming growth factor-β [39]. Red and processed meat are associated with increased inflammatory biomarkers [40]. Spices such as turmeric (curcumin), cinnamon, and fenugreek seeds exhibit anti-inflammatory effects [18]. Types and sources of fats and their effects on serum lipids are listed in Appendix B.

12 Fish Intake

Compared to little or no intake, two servings (6–8 oz) per week of fatty fish or seafood providing 250–500 mg/day of marine n-3 PUFA, i.e., eicosapentenoic acid (EPA) and docosahexanoic acid (DHA), were associated with a 36% decreased risk of CHD mortality. A 10% reduction in CVD risk was reported in plant n-3 alpha linolenic acid (ALA) intake studies between the highest and lowest tertile of intake. Only 0.2–8% of ALA is converted to EPA [36]. An ALA intake of 0.6–1.2% of energy is recommended [1–3, 15].

13 Dietary Cholesterol

The ACC/AHA [1–2] and NLA [3] recommend that a diet containing reduced amounts of cholesterol can be beneficial to decrease ASCVD risk [1–3]. Due to the relatively higher content of cholesterol in egg yolks, it remains advisable to limit intake to <200 mg/day to reduce LDL-C especially for persons at high risk for CVD including diabetes [1–3]. Heart-healthy dietary patterns are low in dietary cholesterol as they have a relatively high ratio of polyunsaturated fats to saturated fats [16]. This is achieved by minimizing the intake of major sources of saturated fat (animal fats) and including liquid nontropical vegetable oils [16]. Consumption of each 100 mg dietary cholesterol/day increased LDL-C by 1.93 mg/dL, although there are hyper- and hypo-responders. Higher consumption of dietary cholesterol or eggs was significantly associated with higher risk of incident CVD and all-cause mortality in a dose-response manner [41]. Choosing plant-based protein sources limits cholesterol intake [1–3, 16]. A 3 oz serving of shrimp is equivalent to about a whole egg. Shrimp and other shellfish which are otherwise quite low in saturated fat and have minimal effects on raising blood cholesterol can be part of a heart-healthy dietary pattern when paired with other lean animal-based or plant-based protein sources.

In summary, the AHA recommends that healthy individuals may include up to a whole egg or equivalent daily with the following exceptions [16, 42].

- Vegetarians (lacto-ovo) who do not consume meat-based cholesterol-containing foods may include more dairy and eggs in their diets in moderation [16, 42].
- Patients with dyslipidemia, particularly those with diabetes mellitus or at risk for heart failure, should be cautious in regularly consuming foods rich in cholesterol [1–3, 16].
- For older normocholesterolemic patients, given the nutritional benefits and convenience of eggs, consumption of up to two eggs per day is acceptable within the context of a heart-healthy dietary pattern [16, 42].

14 Dietary Adjuncts: Viscous Fiber, Phytosterols, Dietary Supplements, and Probiotics

14.1 Viscous Fiber

Viscous fibers such as beta-glucans, pectin, gums, and mucilage reduce LDL-C. The NLA recommends that 5–10 g/day of viscous fiber will reduce LDL-C by 4–10% and can be increased up to 25 gm as tolerated [2, 3]. Food sources of viscous fiber include oats, barley, legumes, lentils, apples, pears, plums, oranges, broccoli, Brussels sprouts, carrots, and peas. Supplements are available as fiber laxatives and contain psyllium and methyl cellulose [2, 3].

14.2 Phytosterols

The ACC/AHA/NLA recommends that 2 g/day dose of phytosterols/phytostanols (PS) will reduce LDL-C by 5–10% [2, 3]. A typical western diet provides 200–400 mg/day and a vegan diet provides 400–800 mg/day. PS lowers LDL-C by competing with dietary cholesterol for absorption. Furthermore, an increase in the intracellular PS level upregulates the adenosine triphosphate-binding cassette transporter (ABC) G5/G8 to move all sterols including cholesterol out of the enterocytes and into the lumen. PS is available in fortified beverages, supplements, or chews [2, 3]. The lipid-lowering impact of PS-fortified products (both free plant sterols and stanols and their esterified forms) for lowering atherogenic cholesterol was similar in response to fat versus nonfat foods and dairy vs. nondairy foods at intakes of $\leq$2 g/day [2, 3, 43, 44]. To achieve maximal efficacy, foods or supplements containing phytosterols should be taken during main meals, when cholesterol presence in the gut lumen is higher than in the fasting state due to the stimulation of biliary secretions containing cholesterol and to the dietary cholesterol derived from food [2, 3, 43, 44]. An increased intake of carotenoid-rich fresh fruit and vegetables is recommended due to a reduced absorption of fat-soluble vitamins (carotenoids) following intake of plant sterol-/stanol-enriched food such as margarines made from

stanol esters [2, 3, 43, 44]. Persons with sitosterolemia should avoid foods fortified with PS. PS can be safely consumed in combination with statin medications to aid LDL cholesterol lowering [2, 3, 43, 44].

14.3 Nutraceuticals/Dietary Supplements

Nutraceuticals may be an additional option for patients who cannot tolerate statins because of severe muscle pain. Emerging evidence shows that bergamot, berberine, artichoke leaf extract, red yeast rice (RYR), soluble fiber, and plant stanols and sterols as monotherapy or adjunctive therapy may offer an alternative to prevent CV events by lowering LDL-C [43, 44]. As determined by an International Expert Panel, evidence for selected nutraceuticals and dietary supplements with Class I (means recommended or indicated) or Class IIa (means should be considered) is summarized in Appendix C by dose, % LDL-C reduction, level strength of evidence, and their safety profiles [44]. Class 1 evidence was defined by the panel as evidence and/or a general agreement that a given treatment is beneficial, useful, and effective. Class II was defined as conflicting evidence and/or divergence of opinion about the usefulness/efficacy of the treatment [44]. However, Class IIa was defined as weight of evidence/opinion was in favor of usefulness/efficacy and should be considered [44].

In a RCT conducted in China, RYR extracts (xuezhikang) with an average content of 2.5–3.2 mg of monacolin, administered to a population of about 5000 subjects with previous coronary events such as a myocardial infarction (China Coronary Secondary Prevention Study), led to a 20% reduction in LDL cholesterol levels, compared to placebo. The cholesterol-lowering effect was associated with a significant decrease of fatal and nonfatal coronary events, stroke, and all-cause mortality (−31%, −44%, and −32%, respectively) over the 4-year duration of the trial [45]. Combining statins with RYR-based supplements is discouraged for pharmacodynamic reasons (both have the same mechanism of action) and comparable side effects [43, 44]. In many of the RYR supplements, the amount of monacolin is now 10 mg, likely due to the European Food Safety Authority's (EFSA) approval of the claim of "maintenance of normal cholesterol values" at this dose exclusively [43]. Considering the widespread availability of RYR supplements, the absolute incidence of the related adverse side effects is rather low [43]. However, medical supervision is important for the use of supplements, especially with regard to possible interactions between RYR and other drugs, and for the selection of appropriate patients for this treatment [43].

14.4 Probiotics

Nonfat or low-fat yogurt without added sugar can be an important nutritional component of a heart-healthy diet. A review of 26 clinical studies and 2 meta-analyses of multiple probiotic strains reported both *L. reuteri* and *E. faecium* significantly lowered LDL-C by 8.9–11.6% and 5%, respectively [18, 44, 46]. *L. reuteri* was

provided in yogurt or capsule form and significantly lowered LDL-C and inflammatory markers versus placebo [18, 44, 46]. More research is needed to recommend probiotics as a supplement to improve lipid profile [18, 44].

15 Referral to a Registered Dietitian-Nutritionist (RDN) in a Team-Based Collaborative Care Approach for the Prevention and Treatment of ASCVD Risk Factors

The ACC/AHA/NLA recommend including an RDN in a team-based collaborative approach as an effective strategy for the prevention and treatment of ASCVD risk factors [1–3].

15.1 Role of the Registered Dietitian-Nutritionist (RDN)

Patients with dyslipidemia and cardiometabolic risk factors such as elevated blood pressure, prediabetes, diabetes, overweight, obesity, and metabolic syndrome (MetS) should be referred to an RDN for multiple visits for medical nutrition therapy [1–3, 12]. Sikand et al. [12] conducted a systematic review and meta-analysis of 34 primary studies (n = 5704) and reported that multiple visits with a RDN for medical nutrition therapy led to significant improvements in lipids, BMI, blood pressure, and A1c along with cost savings from a reduction in medications for dyslipidemia, blood pressure, and diabetes. Successful outcomes of medical nutrition therapy are also attributed to personalization of patients' cardioprotective dietary patterns by the RDN while providing support and accountability for long-term success [1–3, 12, 25].

Medical nutrition therapy by the RDN includes four components: (1) nutrition assessment, (2) nutrition diagnosis, (3) nutrition intervention and monitoring, and (4) evaluation and communication with the referring healthcare provider [12]. Personalization by the RDN includes tailoring the cardioprotective dietary pattern to the patients' personal and work lifestyle, food preferences, culture/religion/ethnicity, and economic and psychosocial needs [12].

15.2 Referral to a Multidisciplinary Lipid Clinic or a Preventive Cardiology Clinic/Program

Referral to a multidisciplinary lipid clinic or a preventive cardiology clinic/program could be beneficial for both primary and secondary prevention of ASCVD [1–3, 12]. These programs include a multidisciplinary team such as a preventive cardiologist or a lipidologist, an RDN, and an exercise physiologist [1–3, 47].

15.3 Referral to a Comprehensive Lifestyle Weight Management Program

Patients with obesity (BMI ≥ 30) should be referred to an intensive, multidisciplinary behavioral intervention program [1–3]. An RDN is an important member of the comprehensive lifestyle intervention team and helps patients achieve a healthy body weight by personalizing their cardioprotective dietary pattern and increased physical activity to promote overall health and decrease ASCVD risk. Comprehensive multidisciplinary lifestyle intervention programs for weight reduction increase the likelihood of successful long-term weight management outcomes [1–3, 12, 25, 48, 49].

16 Alcohol

High alcohol intake is associated with elevated TG especially when obesity is present. Patients with hypertriglyceridemia should be advised to reduce or eliminate alcohol. Complete abstinence is recommended in patients with TG ≥500 mg/dL. Drinking in excess can lead to alcoholism, high blood pressure, obesity, stroke, breast cancer, suicide, and accidents. While no society endorses the initiation or use of alcohol for cardiovascular risk reduction purposes, any current use should be limited to ≤7 drinks per week for women and ≤14 drinks per week for men consumed in a non-binge pattern. A drink is one 12 ounce beer, 5 ounces of wine, 1.5 ounces of 80-proof spirits, or 1 ounce of 100-proof spirits [1–3, 15, 50].

17 Conclusion

Adults should eat a heart-healthy diet which emphasizes plant-based foods such as vegetables, fruits, legumes, nuts, whole grains, and also lean protein foods and fish. Limit foods high in saturated fats and dietary cholesterol. Minimize trans fat, sodium (salt), processed meats, refined carbohydrates, and sugar-sweetened beverages and foods. Include dietary adjuncts such as viscous fiber, plant sterols/stanols, soy, and long-chain omega-3 fatty acids. Weight loss of 5–10% of initial weight, achieved through comprehensive lifestyle intervention, has been shown to improve BP, delay the onset of T2DM, improve glycemic control in T2DM, and improve lipid profile. Research has shown that personalized nutrition counseling by an RDN over multiple visits led to improved lipids, weight, HbA1c, and high blood pressure along with cost savings. A collaborative team-based approach includes referral to an RDN for personalized nutrition counseling (medical nutrition therapy) to help patients achieve their nutrition goals and to provide support and accountability.

Appendix A: American Heart Association-Recommended Dietary Pattern Based on Dietary Approaches to Stop Hypertension Feeding Trials (DASH)[a] [17]

Food group	Amount/day	Amount/week
Fruits: fresh/frozen/canned (unsweetened preferred (cups)	2	14
Vegetables: fresh/frozen/canned (cups)	2½	10½
Dark green vegetables (cups)[b]		1½
Red/orange vegetables (cups)[b]		5½
Beans and peas (cups)[b]		1½
Starchy vegetables (cups)[b]		5
Other vegetables (cups)[b]		4
Grains; emphasize whole grains/high in dietary fiber (oz eq/day)	6	42
Whole grains (oz eq/day)	3	21
Other grains (oz eq/day)	3	21
Protein foods (oz eq)	5½	39
Lean meat, poultry, eggs, oz eq		26
Fish, preferably oily fish, oz eq		8
Nuts, seeds, legumes, oz eq[a]	1	5–7
Dairy: fat-free or low fat, cups	3	21
Oils: unsaturated sources (g/day [Tbsp])	45 (3)	415 (21)
Fiber (g)	31	217
Solid fats (g [% of total kcal])	13 (6)	91 (6)
Added sugars (g [kcal])	25 (100)	175 (700)
Sodium (mg)[c]	<2300 mg	<16,100

Note: The American Heart Association's basic dietary pattern is similar to the Dietary Approaches to Stop Hypertension (DASH) and MyPlate, with the following caveats:

DASH restricts sweets to five per week rather than an added sugar limit in teaspoons

DASH allows a lower range of total fat, with a slight increase in meat (rather than 45 g of oil, DASH allows 30 g–45 g)

On a 2000 kcal diet, DASH includes 6 oz of meat/fish/poultry. Vegetable protein sources are encouraged

[a]Based on 2000 kcal; adjustments should be made to meet energy needs

[b]Indicates no daily requirement, rather weekly intake as noted

[c]Overall goal for sodium is 1500 mg/day, but gradual reduction to achieve 2300 mg/day may be more realistic; average US intake for adults is 3500 mg/day

Appendix B: Types and Sources of Fats and Their Effect on Serum Lipids [1–3]

1. *Monounsaturated fat (omega-9)* may lower LDL-C and ASCVD risk.
    - Extra-virgin olive oil, canola oil, peanut oil
    - Avocados, olives (very high in sodium)
    - Unsalted nuts: almonds, peanuts, pecans, pistachios, hazelnuts
2. *Polyunsaturated fat (omega-6 and plant omega-3)* helps lower LDL-C when they replace saturated fat.
    - Omega-6 linoleic acid: corn oil, safflower oil, sunflower oil, soybean oil, sunflower seeds
    - Omega-3 alpha-linolenic acid: flax seed oil, canola oil, soybean oil, English walnuts, edamame, hemp seeds, chia seeds, flax seeds, and fenugreek seeds
3. *Saturated fats* raise LDL-C. Saturated fats should be avoided or eaten in small amounts. Saturated fats are solid at room temperature.
    - Fatty cuts of lamb, pork, beef, poultry with skin, beef fat, lard, bacon, sausage, hotdogs
    - Whole milk and whole milk products: butter, ghee, cheese, cream, ice cream, yogurt made from whole milk
    - Palm oil, palm kernel oil, and coconut oil and coconut cream
4. *Trans fats* raise LDL-C and CVD risk and should be avoided if they are labeled as partially hydrogenated fats.
    - Baked goods: pastries, cakes, donuts, cookies
    - Fried foods: French fries, fried chicken, onion rings, and deep-fried snacks cooked in reused oil
    - Stick margarine, shortening
    - Butter, meat, cheese, and dairy products

Appendix C: Summary of Selected Nutraceuticals/Dietary Supplements for LDL-C Reduction Along with Class and Level of Evidence by an International Expert Panel [44]

Nutraceutical	Daily dose	% LDL-C reduction	Evidence recommendation by class	Level of evidence	Improvement in other CV parameters
Plant sterols and stanols	400–3000 mg	8–12%	IIa	A	↓ hs-CRP
Viscous fiber	5–15 g	5–15%	IIa	A	↓ TG, BG, wt, CVD risk
Red yeast rice	600–1200 mg	15–25%	I	A	↓ ApoB, hsCRP, CV events in 2° prevention
Berberine	500–1500 mg	10–15%	I	A	↓ TG, BG, BP, ApoB, hs-CRP
Bergamot	500–1000 mg	15–40%	IIa	A	↓ sdLDL, hs-CRP
Garlic extract	5–6 g	5–10%	IIa	A	↓ BP, platelet aggregation
Green tea extracts	1000 g	5%	IIa	A	↓ BP
Artichoke leaf extract	1–3 g	5–15%	IIa	B	↓ TG, AST, ALT, BG
Curcumin	1–3 g	5%	IIa	B	↓ TG, Lp(a), glucose, A1c, hs-CRP, TNF-alpha, IL-6, ↑HDL-C, adiponectin

Abbreviations
Class of recommendation
Class 1 is recommended or indicated because of evidence or general agreement that a given treatment is beneficial, useful, and effective
Class IIa should be considered because weight of evidence/opinion is in favor of usefulness/efficacy
Level of evidence
Level A: data derived from multiple randomized controlled trials or their meta-analysis
Level B: data derived from a single randomized controlled clinical trial or large nonrandomized studies

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Diet Resources

American College of Cardiology

https://www.cardiosmart.org/nutrition/
https://www.cardiosmart.org/News-and-Events/2018/08/Strategies-for-Improving-Diet-and-Improving-Heart-Health
https://www.cardiosmart.org/~/media/Documents/Infographics/Heart-Healthy%20Diets.ashx/

American Heart Association

https://www.heart.org/en/healthy-living/healthy-eating/eat-smart/nutrition-basics
https://www.cardiosmart.org/nutrition

Academy of Nutrition and Dietetics

https://www.eatright.org/-/media/eatright-files/nationalnutritionmonth/handoutsandtipsheets/nutritiontipsheets/2020/20healthtipsfor2020_nnm20_final.pdf

National Lipid Association

National Lipid Association Clinical Lifestyle Modification Tool (CLMT) Kit www.lipid.org/CLMT
Follow links to
- DASH Dietary Pattern
- Mediterranean style Dietary Pattern
- Vegetarian/Vegan Dietary Pattern
- And many more

Let's Eat for the Health of it. Choose MyPlate.gov. www.cnpp.usda.gov/Publications/Myplate/DG2010Brochure.pdf
Heart and Vascular Diseases, Detailed Information on Cholesterol, Heart Attack, High Blood pressure, Obesity, Other Heart and Vascular Diseases. www.nhlbi.nih.gov.health/prof/heart/index.htm
Calorie Results and Food Tracking Worksheets. www.choosemyplate.gov/professionals/food_tracking_wksht.html
Your Guide to Lowering Blood Pressure with DASH. www.nhlbi.nih.gov/helath/public/heart/hbp/dash/new_dash.pdf
FDA Consumer Updates. http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm372915.htm

Physical Activity Strategies

Barry A. Franklin

Key Points

- The benefits of regular moderate-to-vigorous PA, and the associated improvements in CRF, far outweigh the risks for most individuals. Nevertheless, ostensibly healthy, inactive individuals starting to exercise should begin slowly, generally with a walking program, gradually increasing the intensity of exercise, provided they remain asymptomatic. Moderate- to high-risk individuals may particularly benefit from supervised exercise therapy.
- The US Preventive Services Task Force 2018 advised against routine screening with exercise testing to prevent cardiovascular events. On the other hand, asymptomatic patients who might benefit from exercise testing before beginning an exercise program include habitually sedentary individuals with multiple risk factors, an elevated coronary artery calcium score, or a family history of premature CHD who plan to start a vigorous exercise program or those whom the clinician suspects may be ignoring symptoms or not giving an accurate history.
- Vigorous exercise appears to be more effective than moderate-intensity exercise in reducing cardiovascular risk. Similarly, when comparing increased levels of PA versus CRF, the reductions in risk are more than twice as great for CRF.
- The optimal cardiovascular benefits of exercise are most likely to be achieved by the gradual progression of exercise training intensity, expressed

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as METs. Among patients with and without CHD, each 1-MET increase in exercise capacity confers an ~15% decrease in mortality up to about 10 METs, beyond which the additional survival benefits largely plateau.
- Unaccustomed vigorous PA, particularly when performed by inactive, unfit individuals with known or occult CVD, can acutely increase the risk of cardiac events, including sudden cardiac death and acute myocardial infarction.
- For deconditioned or inactive individuals, the minimum or threshold intensity for improving CRF approximates 30–45% VO_2R, which corresponds to ~60–70% of the highest heart rate achieved during peak- or symptom-limited exercise testing.
- As exertion-related acute cardiovascular events are often preceded by warning symptoms, patients should be strongly advised that symptoms require immediate cessation of endurance training/competition and medical review.
- Extreme endurance exercise training regimens are associated with potential cardiac maladaptations in some individuals, including accelerated coronary artery calcification, elevated cardiac biomarker release, myocardial fibrosis, and atrial fibrillation, as well as cardiovascular events, which may be described by a reverse J-shaped dose-response curve.
- The recent ACC/AHA Primary Prevention guidelines suggest at least 150 min of moderate-intensity exercise or 75 min of vigorous-intensity PA per week, or combinations thereof. Structured exercise should be complemented by upper body training, resistance training, and increased lifestyle PA. Using a pedometer can be helpful in tracking daily step totals.

1 Introduction

There is abundant evidence that the amount of habitual physical activity (PA) and the level of cardiorespiratory fitness (CRF) are inversely related to the risk of coronary heart disease (CHD). Nevertheless, regular exercise does not confer "immunity" to acute cardiac events. Moreover, high-volume, high-intensity exercise training regimens appear to induce maladaptive cardiac remodeling in some individuals. This chapter reviews PA strategies in individuals with and without CHD, with specific reference to the cardiovascular benefits of regular moderate-to-vigorous PA and improved CRF, the concept of oxygen consumption reserve, contemporary PA recommendations, value of progressing exercise training intensities, evolution of personalized activity intelligence, and complementary exercise interventions, including upper body training, resistance training, lifestyle PA, and high-intensity interval training. Additional topics include extreme exercise and

cardiovascular health, using technology to promote PA, and strategies to enhance exercise adherence.

2 Epidemiologic Studies

In an early meta-analysis of 43 studies of the relation between physical activity (PA) and coronary heart disease (CHD) incidence, the relative risk of CHD in relation to physical inactivity ranged from 1.5 to 2.4, with a median value of 1.9 [1]. Moreover, the relative risk of a sedentary lifestyle appeared to be similar in magnitude to that associated with other major CHD risk factors. Another systematic review and meta-analysis of 33 PA studies, including 883,372 participants, reported risk reductions of 30–50% for cardiovascular mortality and 20–50% for all-cause mortality among the most physically active cohorts [2]. More recently, researchers analyzed data from two major ongoing cohort studies to evaluate the influence of five low-risk lifestyle factors on premature mortality and life expectancy in the US population [3]. The five low-risk lifestyle factors included not smoking; body mass index 18.5–24.9 kg/m^2; ≥30 min per day of moderate-to-vigorous PA; moderate alcohol intake; and a healthy diet score. During up to 34 years of follow-up, adherence to all five lifestyle-related factors significantly increased life expectancy at age 50 years for both men and women, 12.2 and 14 years, respectively, as compared with those who adopted "zero" low-risk factors. The most physically active cohorts of men and women demonstrated 7–8-year gains in life expectancy!

3 Cardiovascular Impact of Regular Physical Activity: Potential Underlying Mechanisms

Regular moderate-to-vigorous PA, structured exercise, or both can decrease the risk of initial and recurrent cardiovascular events, presumably from multiple mechanisms, including anti-atherosclerotic, anti-ischemic, anti-arrhythmic, anti-thrombotic, and psychologic effects (Fig. 1). In addition, ischemic and biochemical cardiac preconditioning offers a unique and undervalued nonpharmacological approach to prevent and attenuate acute coronary syndromes. Specifically, acute bouts of aerobic exercise impose an isolated stress on the myocardium such that cellular biochemistry is favorably altered and an ischemic resistant phenotype is conferred, at least temporarily [4]. Accordingly, it appears that regular increases in the rate-pressure product and somatic and cardiac metabolism evoked by moderate-to-vigorous PA can reduce subsequent infarct size and/or the potential for malignant ventricular arrhythmias triggered by acute myocardial ischemia [5].

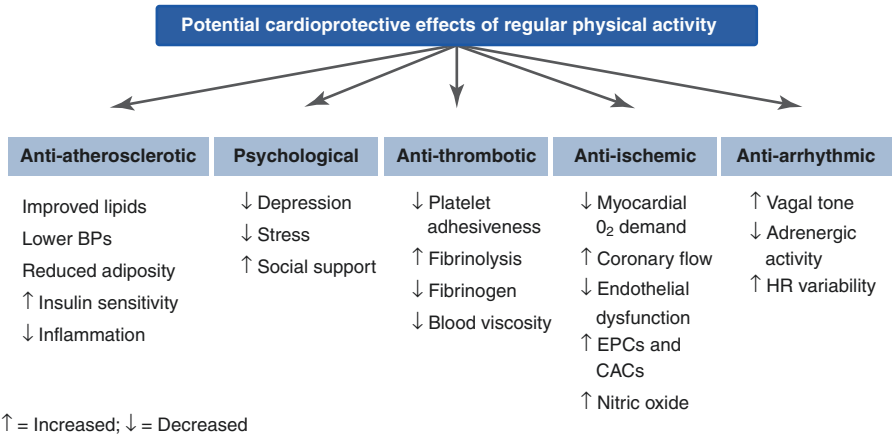

Fig. 1 A moderate- to vigorous-intensity endurance exercise program sufficient to maintain and enhance cardiorespiratory fitness may provide multiple mechanisms to reduce nonfatal and fatal cardiovascular events. BP blood pressure, CACs cultured angiogenic cells, EPCs endothelial progenitor cells, HR heart rate, ↑ increased, ↓ decreased, O_2 oxygen

3.1 Benefits of Vigorous Versus Moderate-Intensity Physical Activity

Emerging research strongly suggests that the gradual progression of exercise intensities, from moderate-to-vigorous to high-intensity training regimens (in selected individuals), may result in even greater cardioprotective benefits. Accordingly, vigorous PA (usually defined as ≥60% functional capacity or 70–89% of the measured maximal heart rate) appears to be superior to moderate-intensity exercise (40–59% of functional capacity or 55–69% of the maximal heart rate). Although some have defined vigorous- and moderate-intensity PA as ≥6 metabolic equivalents (METs; 1 MET = 3.5 mLO_2/kg/min) and 3.0–5.9 METs, respectively, these absolute values do not account for the fact that the cardiac demand of any PA is determined not by the specific metabolic level but by the metabolic demand relative to the individual's functional capacity [6].

Relative to the all-cause mortality reduction associated with exercise, intensity and duration appear to be inversely related. For example, the mortality reduction associated with a regular 5-min run approximates a 15-min walk, and a 25-min run is comparable with a 105-min walk [7]. In addition, at comparable levels of total energy expenditure, vigorous exercise seems to be more effective than moderate-intensity exercise in reducing cardiovascular risk [8]. Vigorous exercise intensities are also more effective than moderate intensities at increasing cardiorespiratory fitness (CRF), expressed as METs, especially for individuals with higher baseline CRF [9]. This has additional prognostic significance, since higher levels of CRF have been repeatedly shown to confer a lower risk of cardiovascular and all-cause mortality [10]. Other possible mechanisms associated with the incremental and

Table 1 Multiple mechanisms by which vigorous-intensity exercise training may be more effective than moderate-intensity exercise at reducing cardiovascular risk

↑	Parasympathetic tone
↑	Period of diastole and NO vasodilator function
↓	Shear stress on endothelial walls
↑	Artery compliance
↓	Plaque rupture
↓	Adverse ventricular remodeling
↓	Incident AF and/or HF
↓	Endothelial dysfunction and myocardial ischemia
↓	Arrhythmias
↑	Heart rate variability
↓	Sympathetic outflow
↓	Inflammation

Based on data from Ref. [11]
NO nitric oxide, *AF* atrial fibrillation, *HF* heart failure, ↑ increased, ↓ decreased

additive cardioprotective benefits of vigorous-intensity exercise training are shown in Table 1 [11].

4 Cardiorespiratory Fitness and Physical Activity as Separate Coronary Heart Disease Risk Factors: Comparative Benefits

Numerous studies now suggest that CRF is one of the strongest prognostic markers in persons with and without chronic disease, including CHD [10]. In fact, higher levels of CRF are associated with a reduced risk of developing hypertension, type II diabetes, atrial fibrillation, chronic kidney disease, and major cardiovascular events, including heart failure, myocardial infarction, stroke, and coronary artery bypass grafting [12]. Williams [13] reported that the risks of CHD and cardiovascular disease (CVD) decreased linearly in association with increasing percentiles of PA (Fig. 2). In contrast, there was a precipitous decrease in risk when the lowest is compared with the next-lowest percentile of CRF. Beyond this demarcation, the reductions in risk parallel those observed with increasing PA but was more than twice as great for CRF. Three important findings emerged from this report. First, being unfit warrants consideration as an independent risk factor. Second, a low level of CRF or aerobic capacity (VO_2 max) increases the risk of CVD to a greater extent than merely being physically inactive. Third, the primary beneficiaries of regular exercise appear to be those comprising the bottom 20% of the CRF/PA continuum. Although the cut points vary depending on age and gender, an exercise capacity <5–6 METs generally indicates a higher mortality group, whereas CRF levels of 9–12 METs or higher are associated with a marked survival advantage, including men and women with and without known CHD [14–18].

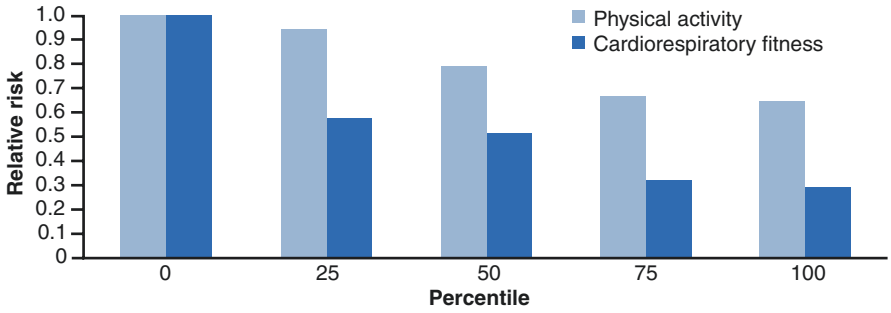

Fig. 2 The risks of coronary heart disease and cardiovascular disease decrease in association with increasing percentiles of physical activity and cardiorespiratory fitness, corresponding to 30% and 64% in the most active and fit individuals, respectively. Interestingly, little or no additional benefit occurs when moving from the 75th to the 100th percentile, that is, "good" to "excellent," suggesting a plateau in relative risk. (Based on data from Ref. [13])

4.1 Impact of CRF on Mortality and Other Health Outcomes

For the primary and secondary prevention of CHD, each 1-MET increase in CRF confers an ~15% decrease in mortality up to about 10 METs, beyond which the additional survival benefits largely plateau [19, 20]. This reduction in mortality compares favorably with the survival benefit conferred by commonly prescribed cardioprotective medications (i.e., low-dose aspirin, statins, ß-blockers, angiotensin-converting enzyme inhibitors) after acute myocardial infarction. In addition, individuals with low PA and/or CRF levels have higher annual healthcare costs [21], higher rates of incident heart failure [22], and increased cardiovascular events at any given coronary artery calcium score [23] and are 2–3 times more likely to die prematurely than their fitter counterparts when matched for coronary risk factor profiles [16, 24]. Increased levels of PA and/or CRF before hospitalization for acute coronary syndromes and elective or emergent surgical procedures also appear to confer more favorable short-term outcomes. A widely cited investigation of 2172 patients hospitalized for acute coronary syndromes (mean +/− SD age = 65.5 +/− 13 years; 76% men) evaluated the effect of prehospital and 1-month post-hospital discharge CVD health outcomes [25]. After adjusting for potential confounders, patients who were physically active demonstrated 0.56 lower odds of in-hospital mortality and 0.80 lower odds of recurrent cardiovascular events within the first 30 days of hospital discharge. Short-term complications after bariatric surgery [26] and coronary artery bypass grafting [27] have also been linked to reduced preoperative levels of PA or CRF (Fig. 3) [28].

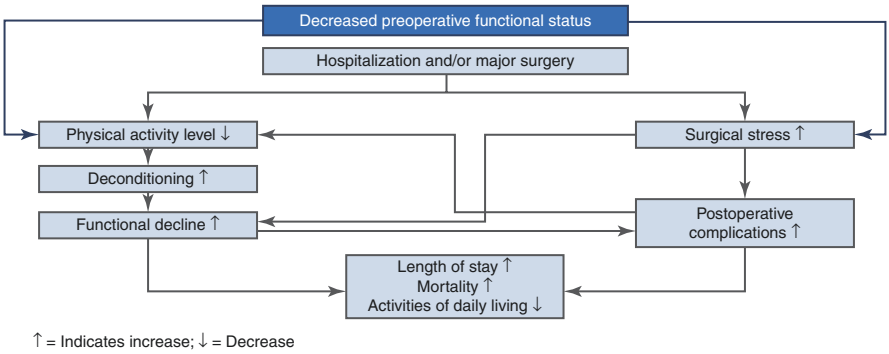

Fig. 3 Possible impact of decreased preoperative physical activity or cardiorespiratory fitness on hospitalized patients undergoing emergent or elective surgery with specific reference to short-term outcomes. (Adapted from Hoogeboom et al. [28], with permission from Wolters Kluwer Health)

5 Exercise Prescription/Programming

Selected health professionals, including exercise physiologists, physical therapists, and nurse clinicians, are generally responsible for writing exercise prescriptions, under the supervision of a physician (in clinical settings). Several professional associations, such as the American College of Sports Medicine and the American Council on Exercise, offer instruction and proficiency standards and competency certification. Structured exercise training sessions should include a preliminary aerobic warm-up (~10 min), a continuous or accumulated conditioning phase (≥30 min), and a cooldown (5–10 min) followed by stretching activities. These pre- and post-exercise components may not be necessary for conventional walking programs. The warm-up facilitates the transition from rest to the aerobic conditioning phase, reducing the potential for ischemic electrocardiographic responses, which can occur with sudden strenuous exertion [29]. The ideal warm-up for any endurance activity is the same activity but at a lower intensity. Hence, individuals who use brisk walking during the endurance phase should conclude the warm-up with a moderate walking pace. Similarly, cycle ergometry at 150–300 kilogram-meters per minute (kg-m/min) serves as an ideal warm-up for individuals who train at 450–600 kg-m/min. The cool-down provides a gradual recovery from the intensity of the endurance phase. A walking cool-down enhances venous return during recovery, decreasing the likelihood of hypotension and related sequelae (e.g., post-exercise light-headedness). It also facilitates the dissipation of body heat, promotes more rapid removal of lactic acid than stationary recovery, and ameliorates the potential deleterious effects of the post-exercise rise in plasma catecholamines [30].

5.1 The Concept of Oxygen Consumption Reserve (VO_2R)

One of the most commonly employed methods of establishing the target heart rate (THR) for training is the maximum heart rate (MHR) reserve method [31]:

$$\text{THR} = \left(\text{MHR} - \text{resting heart rate}\left[\text{RHR}\right]\right) \times \left(\text{exercise intensity}\right) + \text{RHR}$$

Although it was traditionally believed that a given percentage of the heart rate reserve corresponded to the same percentage of the VO_2 max [32], more recent studies have shown that it more closely approximates the same percentage of the oxygen uptake "reserve" (% VO_2R) [33]. This concept relates heart rate reserve to a level of metabolism that starts at a resting level (i.e., 1 MET) rather than from zero. An additional advantage is increased accuracy in establishing training workloads for low-fit patients. To calculate the target VO_2 (TVO_2) based on VO_2R, the following equation is used:

$$\text{TVO}_2 = \left(\text{VO}_2\ \text{max} - \text{VO}_2\ \text{rest}\right)\left(\text{exercise intensity}\right) + \text{VO}_2\ \text{rest}$$

This equation has the same form as the Karvonen et al. [31] or heart rate reserve calculation of the THR. In the TVO_2 equation, VO_2 rest is 3.5 mL O_2/kg/min (1 MET), and the exercise intensity is as low as 30% (for extremely unfit or deconditioned individuals) to 80%. Intensity is expressed as a fraction in the equation. For example, what is the TVO_2 at 40% of VO_2R for a patient with a 4-MET exercise capacity (i.e., a VO_2 max of 14.0 mL/kg/min)?

$$\text{TVO}_2 = \left(14.0 - 3.5\right)\left(0.40\right) + 3.5 = \left(10.5\right)\left(0.40\right) + 3.5 = 4.2 + 3.5 = 7.7\,\text{mL / kg / min or}\,2.2\,\text{METs}$$

Once an appropriate TVO_2 (MET) level is identified, the training METs may be estimated from the resting and exercise heart rate response, the rule of 2 and 3 miles per hour (mph; graded treadmill walking), or by selecting an activity with an appropriate MET requirement from published tables (Table 2) [34].

Table 2 Energy cost (METs) of common occupational and leisure-time physical activities

Light (<3.0 METs)	Moderate (3–<6 METs)	Vigorous (≥6 METs)
Cycling (stationary, light intensity)	Cycling (as transportation)	Cycling (race)
Fishing	Mowing lawn	Heavy farming (bailing hay)
Golf	Swimming (moderate)	Swimming (fast)
Sweeping	Table tennis	Tennis
Walking slowly or strolling	Walking briskly	Walking briskly uphill or jogging

METs metabolic equivalents. (Based on data from Ref. [34])

5.2 Exercise Modalities/Training Intensities

The most effective exercises for the endurance or conditioning phase include walking, graded walking, jogging, running, stationary cycle ergometry, outdoor cycling, swimming, skipping, rowing, arm ergometry, and combined arm-leg ergometry. To improve CRF, the "minimum" or threshold intensity for training approximates 30–45% of the VO_2R, which corresponds to ~60–70% of the highest heart rate achieved during peak- or symptom-limited exercise testing [9, 35, 36]. Over time, the exercise intensity should be increased to 50–80% of the VO_2R (or maximal heart rate reserve) to further increase CRF, provided one remains asymptomatic. The widely used Borg Rating of Perceived Exertion (RPE) scale [37] provides an adjunctive methodology to regulate the exercise intensity (Table 3). Exercise rated as 12–15 (6–20 scale), between "somewhat hard" and "hard," or 4–6 (0–10 scale), between "somewhat strong" and "very strong," is generally considered appropriate. However, during the first 4–6 weeks of training, ratings of 11–13 (category scale) and 3–4 (category-ratio scale) are strongly recommended.

5.3 Contemporary PA Recommendations

Moderate- to vigorous-intensity PA (MVPA), which corresponds to any activity ≥3 METs, has been consistently shown to reduce the health risks associated with numerous chronic diseases and the risk of developing them [38]. Because unaccustomed vigorous PA is associated with acute cardiac events [39], advocating

Table 3 Ratings of perceived exertion

Category scale		Category-ratio scale	
6		0	Nothing at all
7	Very, very light	0.5	Very, very weak (just noticeable)
8		1	Very weak
9	Very light	2	Weak (light)
10		3	Moderate
11	Fairly light	4	Somewhat strong
12		5	Strong (heavy)
13	Somewhat hard	6	
14		7	Very strong
15	Hard	8	
16		9	
17	Very hard	10	Very, very strong (almost max) maximal
18			
19	Very, very hard		
20			

Adapted from Borg [37], with permission from Wolters Kluwer Health

regular brisk walking, before gradually advising the progression to graded walking or jogging, is strongly recommended for previously inactive middle-aged and older adults [40]. To promote and maintain health, moderate-intensity aerobic (endurance) PA for a minimum of 30 min for 5 days each week, or vigorous-intensity PA for a minimum of 20 min for 3 days each week, or combinations thereof, is recommended [38]. However, even lesser amounts of exercise appear to be beneficial. Wen et al. [7] found that subjects who walked just 15 min a day or 90 min a week had a 14% reduction in death rates over an average follow-up of 8.1 years compared to their inactive counterparts. Although traditional recommendations suggest that accumulated MVPA bouts should last 10 or more minutes to achieve the 30-min daily minimum, recent studies suggest that even shorter periods of MVPA, accrued over time, can evoke cardiovascular and metabolic health benefits [41, 42].

6 Progression of Exercise Training Intensities for Optimal Cardiovascular Benefits

Most middle-aged and older individuals, with and without CHD, initiate exercise programs at ~2–3 METs, corresponding to walking at ~2–3 mph, but fail to increase the intensity of their exercise over time as their CRF improves [43]. This failure prevents them from achieving the maximal reduction in their risk of CVD.

CRF levels are influenced by age and gender, and little additional survivor benefit occurs when levels increase from "good" to "excellent," suggesting there is a plateau in the reduced relative risk for CVD that can be achieved through exercise [13, 15, 16]. The following table (Table 4) provides "good" fitness levels and recommended aerobic training requirements (METs) to achieve them for men and women [11]. To delineate reference standards for CRF, we employed the Fitness Registry and the Importance of Exercise: A National Database (FRIEND) [44]. Age- and gender-adjusted "good" fitness levels were calculated at the 60th percentile.

In our experience, if patients can progress to training intensities that are 60–80% of the VO_2R, without adverse signs/symptoms or excessive RPEs (i.e.,

Table 4 "Good" fitness levels for middle-aged and older men and women and the training aerobic requirements associated with these cardiorespiratory fitness levels

		Age groups (y)				
		30–39	**40–49**	**50–59**	**60–69**	**70–79**
Men	Good fitness	≥12.9	≥11.5	≥10.0	≥8.7	≥7.7
	Training METs	8.1–10.5	7.3–9.4	6.4–8.2	5.6–7.2	5.0–6.4
Women	Good fitness	≥9.2	≥8.2	≥7.2	≥6.1	≥5.5
	Training METs	5.9–7.6	5.3–6.8	4.7–6.0	4.1–5.1	3.7–4.6

Adapted from Franklin et al. [11], with permission from Elsevier

≥15 [hard work] on the 6–20 scale), it is likely that they can attain the corresponding age- and gender-adjusted cardioprotective fitness levels that are compatible with decreased mortality and increased survival. For example, "good" fitness for a 65-year-old man is ≥8.7 METs; accordingly, a training intensity of 5.6–7.2 METs, achieved after 6–12 months of slow progressive increases in exercise intensity, provided the patient remains asymptomatic, would serve as a worthwhile goal. This training intensity approximates single tennis or brisk walking (4.5–5.0-mph pace) (Table 2) [34] or graded treadmill walking (3.0 mph, 7.5% grade). Although not all patients will achieve "good" CRF levels for their age group, most will be able to increase CRF levels beyond the "bottom 20%," thus significantly improving survival and health outcomes. Those who attain the age-/gender-recommended training MET levels are likely to achieve "good" fitness and optimal cardiovascular benefits.

6.1 *Energy Expenditure of Graded Treadmill Walking: Rule of 2 and 3 mph*

As stated above, walking at 2 and 3 mph approximates 2 and 3 METs, respectively [45]. At a 2-mph speed, each 3.5% grade increment adds an additional MET to the energy expenditure. For individuals who can walk at the faster speed, that is, 3 mph, each 2.5% increase in treadmill grade adds an additional MET. Thus, walking at a 3 mph, 7.5% grade, would approximate 6 METs.

6.2 *Using the Heart Rate Index Equation to Estimate METs During Exercise*

A simple method for estimating oxygen uptake during PA, expressed as METs, in persons with and without heart disease, including those taking ß-blockers, employs the resting and exercise heart rates using the heart rate index equation [46]:

$$\text{METs} = \left(6 \times \text{Heart Rate Index}\right) - 5$$

where the heart rate index equals the activity heart rate divided by the resting heart rate.

Example: A tennis player's resting heart rate of 60 beats per minute (bpm) is increased to 120 bpm during a tennis match. His MET level is estimated as follows: 120 bpm/60 bpm = 2.0 heart rate index which is multiplied by 6, yielding 12, from which we subtract 5, yielding an estimated 7 METs (120/60 × 6) − 5 = (2 × 6) − 5 = 7 METs.

6.3 Evolution of Personalized Activity Intelligence

Recently, researchers developed a new fitness metric termed the personalized activity intelligence or PAI score, which is derived from the cumulative fluctuations in heart rate over the most recent 7 days, to provide an approximation of the relative intensity of PA and associated energy expenditure. It was based on changes in heart rate obtained from the HUNT Fitness Study database involving >60,000 participants over 2 decades, which monitors the intensity of PA as it relates to the development of CVD [47]. PAI is calculated based on the individual user's age, gender, resting heart rate, and maximum heart rate and gives more credit for vigorous as opposed to mild- to moderate-intensity PA. For example, a 30-min intense bike ride earns eight times the PAI score that an hour-long 3-mile walk earns for the same individual, 56 versus 7 PAI points, respectively [48]. According to the above-referenced HUNT study analysis, including >1 million person-years of observations during an average follow-up of 26.2 years, men and women achieving a weekly PAI level $\geq$ 100 had a 20 +/− 3% reduced risk of CVD mortality compared with an inactive control cohort [47]. Collectively, these data, and another relevant report [49], suggest that large daily fluctuations in heart rate and associated energy expenditure, expressed as METs, appear to confer not only increased survival benefits but decreased healthcare costs as well.

7 Complementary Training Modalities/Techniques

7.1 Upper Body Training

Lower extremity training does not necessarily confer training benefit to the upper extremities and vice versa. Moreover, many activities of daily living require arm work to a greater extent than leg work. Consequently, patients who rely on their upper extremities for occupational or recreational activities should be advised to train the arms as well as the legs, with the expectation of improved cardiorespiratory and hemodynamic responses to both forms of effort. Recommendations for dynamic arm exercise are shown in Table 5 and include three variables: the appropriate exercise heart rate, the workload or power output that will elicit a safe and effective load for training, and the proper training equipment or modalities [50].

Table 5 Recommendations for dynamic arm exercise training

Variable	Comment
Target heart rate	~10–15 bpm lower than for leg training
Work rate	~50 ± 10% of the power output (kg-m/min) used for leg training
Equipment	Arm ergometer, combined arm-leg ergometer, rowing machine, wall pulleys, simulated cross-country skiing devices

Based on data from Ref. [50]

7.2 Resistance Training

Resistance training can provide an effective method for increasing muscle strength and endurance, preventing and managing a variety of chronic medical conditions, favorably modifying selected coronary risk factors, and enhancing psychosocial well-being. In fact, studies suggest it is superior to aerobic or endurance exercise training in enhancing bone mineral density, muscle mass and strength, insulin sensitivity, and basal metabolism [51]. Resistance training has been shown to attenuate the rate-pressure product when any given load is lifted, which may reduce cardiac demands during daily activities such as carrying packages or lifting moderate-to-heavy objects [52, 53]. There are also intriguing data to suggest that strength training can increase muscular endurance capacity without an accompanying increase in CRF [54]. Other studies have shown that muscular strength is inversely associated with all-cause mortality [55] and the presence of metabolic syndrome [56] independent of CRF.

Although the traditional weight-training prescription has involved performing each exercise three times (e.g., 3 sets of 10–15 repetitions per set), it appears that 1 set provides similar improvements in muscular strength and endurance, at least for the novice exerciser. Consequently, single-set programs performed at least two times a week are recommended rather than multiset programs, because they are highly effective, less time-consuming, and less likely to cause musculoskeletal injury or soreness. Such regimens should include 8–10 different exercises at a load that permits 8–15 repetitions per set [51].

7.3 Lifestyle or Incidental Physical Activity

Randomized clinical trials have shown that an alternative approach to structured exercise, that is, increased lifestyle PA, has similar effects on CRF, body composition, and coronary risk factors as a conventional exercise program [57, 58]. These findings have important implications for public health, suggesting a viable alternative to habitually sedentary individuals who are not ready to comply with a formal exercise regimen. Accordingly, preventive medicine specialists should counsel patients to integrate increased PA into their daily lives. A 30-min documentary on the health benefits of walking, called Walking Revolution (http://vimeo.com/65986201), which is accessible on line, is highly motivational. A dog is a terrific walking partner, as are friends, neighbors, and family members. A phone app (http://everybodywalk.org/appl) to track walking, as well as programs that use pedometers (e.g., America on the Move) [59], to enhance awareness of PA by progressively increasing daily step totals, can be helpful in this regard. According to one systematic review, pedometer users in varied exercise interventions significantly increased their PA by an average of 2491 steps per day more than their control counterparts [60].

7.4 High-Intensity Interval Training (HIIT)

HIIT involves intermittent, usually regularly timed, 1–3-min bouts of high-intensity activity alternating with brief periods of MVPA. Numerous studies have compared the effectiveness of moderate-intensity continuous training (MICT) with HIIT for improving CRF and other measures of cardiovascular function in patients with and without CHD. In studies of healthy adults, HIIT regimens have been shown to induce greater increases than CRF than MICT, especially when the total work performed during training is comparable [61]. Among patients with CVD, including heart failure, HIIT was superior to MICT in improving CRF, physical work capacity, left ventricular remodeling (i.e., ejection fraction), and brachial artery flow-mediated dilation (endothelial function) [62]. On the other hand, a meta-analysis of 10 studies (n = 472 CHD patients) revealed that MICT was associated with a more marked decline in patients' average resting heart rate and body weight when compared with HIIT [63]. Moreover, a small study in CHD patients found a nearly six-fold higher risk for exercise-related acute cardiovascular events during HITT versus MICT [64]. In summary, although most studies suggest that HIIT elicits slightly greater increases in CRF (by ~0.5 MET) than MICT, while simultaneously providing a more time-efficient training alternative, concerns regarding the safety of repeated near-maximal exercise bouts in patients with known or suspected CHD suggest that it should not be recommended or prescribed, especially in unsupervised, nonmedical settings [65].

8 High-Volume, High-Intensity Endurance Training and Potential Adverse Cardiovascular Outcomes: Too Much of a Good Thing?

The favorable risk factor profiles and superb cardiac performance of long-distance runners, coupled with the finding that regular endurance exercise prevents cellular senescence in animals and humans, have led an increasing number of middle-aged and older adults to the conclusion that "more exercise is better." However, an increasing number of reports now suggest that potentially adverse cardiovascular manifestations may occur following high-volume and/or high-intensity long-term exercise training/competition. Accelerated coronary artery calcification, exercise-induced cardiac biomarker release, myocardial fibrosis, atrial fibrillation, and even sudden cardiac death have been reported in endurance athletes [6]. Other studies, in men and women with and without CHD, have reported a heightened mortality risk or poorer cardiovascular outcomes in those cohorts performing excessive exercises [66–68]. This relationship had been increasingly described by a U- or reverse J-shaped dose-response curve, with a plateau in benefit or even adverse health effects in some individuals at more extreme levels [69]. Because of the therapeutic effects of exercise, as well as the increased aerobic requirements and cardiac

demands, underdosing and overdoing are possible. Accordingly, these reports should be considered when recommending extreme exercise regimens. Despite these concerns, the benefits associated with regular MVPA far outweigh the risks for the majority of the population [6].

9 Using Technology to Promote Physical Activity

Digital tools such as social media, mobile games on smart phones and tablets, varied apps that promote PA, and activity trackers may assist in reducing barriers to regular PA by helping patients with planning, increasing access to fitness programs, and providing daily goal reminders [70]. Self-monitoring techniques or devices (e.g., pedometers, accelerometers, personalized activity intelligence, heart rate monitors) can be helpful in this regard. Active-play video gaming can also be used to promote healthy weight and PA in children and adolescents, middle-aged and older adults, and patients with chronic disease [71]. One study in healthy adults, using an open-circuit indirect metabolic chamber, reported a wide range of aerobic requirements (1.3–5.6 METs) during Wii Sports and Wii Fit Plus game activities [72]. These levels of energy expenditure correspond to very slow (<1 mph) to extremely fast (~4.5 mph) walking speeds. Accordingly, using active-play video gaming to meet daily or weekly PA requirements may serve as a gateway to structured exercise regimens. In aggregate, these data suggest that using technology, a contributor to the physical inactivity epidemic, can also be part of the solution.

10 Strategies to Enhance Adherence to Physical Activity

Although many patients can be motivated to initiate an exercise program, maintaining the commitment can be challenging. Unfortunately, negative variables often outweigh the positive variables contributing to sustained interest and enthusiasm, leading to a decline in exercise adherence and program effectiveness. Common impediments to regular exercise include inadequate supervision/coaching, time inconvenience, musculoskeletal problems, exercise boredom, cost issues, lack of program awareness, intercurrent illness or injury, work- or family-related conflicts, and neutral or negative spousal support. Physicians and allied health professionals have an ethical obligation to inform patients of the dangers of physical inactivity, to assess our patient's barriers to being more active, and to counsel them regarding safe and effective exercise practices. Additionally, we can improve exercise compliance by referring our patients to quality physical conditioning programs that offer professional supervision and have proven efficacy. Several research-based counseling and motivational strategies may enhance patient interest and facilitate initiation of and compliance with a structured exercise program, increased lifestyle PA, or both (Table 6). Clearly, the built environment, including community parks and

Table 6 Strategies to enhance exercise compliance

Assess exercise habits and counsel patients to be physically active
Evaluate the patient's "readiness to change," and target interventions accordingly
Establish short-term, attainable goals; evaluate progress at subsequent office visits
Minimize injury with a moderate exercise prescription; emphasize gradual progression
Advocate exercising with others (i.e., social support)
Avoid overemphasis of regimented calisthenics
Consider gender differences in activity programming
Provide positive reinforcement through periodic testing and feedback of results
Recruit spouse support of the exercise program
Use progress charts or a computerized data system to record individual exercise achievements
Encourage patients to use certified, enthusiastic exercise professionals
Stress participation in activities that are enjoyable
Include an optional recreational game to the conditioning program format

walking and bike paths, should be supported by local governments to increase the accessibility to lifestyle PA.

11 Conclusions

We must conclude as William C. Roberts MD, Editor-in-Chief, *The American Journal of Cardiology*, summarized in 1984: "Exercise training? An agent with lipid-lowering, anti-hypertensive, positive inotropic, negative chronotropic, vasodilating, diuretic, anorexigenic, weight-reducing, cathartic, hypoglycemic, tranquilizing, hypnotic and anti-depressive qualities" [73]. The challenge for physicians and other healthcare providers is to refer increasing numbers of patients to home, club, or medically supervised exercise programs so that many more individuals may realize the cardioprotective and general health benefits that regular PA can provide. Exercise is medicine, and for the vast majority of patients who are not regularly active, the prescription remains unfilled.

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Obesity Management and Prevention of Cardiovascular Disease

Chellse Gazda and Jaime P. Almandoz

Summary

- The obesity epidemic continues to grow and contributes significantly to morbidity, mortality, and healthcare costs.
- Body fat distribution and physical fitness can be more important than BMI for determining cardiovascular and other health risks.
- Lifestyle modification results in modest weight loss that is proportional to calorie deficit and adherence.
- A consistent decrease in calorie intake of 500–750 kcal/day or 30% of energy intake is more important than diet type for weight loss.
- People with obesity should aim for ≥150 min per week of physical activity in general and 300 min per week for weight loss maintenance.
- Anti-obesity medications and bariatric surgeries are effective tools for achieving weight loss when conservative measures are unsuccessful but are used in less than 2% of eligible people.
- Bariatric surgery and weight loss decrease overall mortality, major adverse cardiovascular events, type 2 diabetes, and other metabolic complications.

1 Introduction

The USA remains in the grip of a growing obesity epidemic. Excess body weight contributes to at least 18% of deaths in the USA, which makes it the second leading preventable cause of death. This is due to increases in insulin resistance, metabolic

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syndrome, type 2 diabetes, cardiovascular disease, and obesity-related cancers [1]. In 1962, 13% of the population was overweight; but according to the 2015–2016 National Health and Nutrition Examination Survey (NHANES), 31.8% is overweight and a further 39.8% of US adults have obesity [2]. It is predicted that by 2030, approximately 49% of the US population will be obese with one in four falling into the severe obesity category [3].

Childhood obesity is also on the rise. Between 1971 and 1974, 10.2% of children were overweight and 5.2% were obese [2]. Current data show that 16.6% of US children are overweight, 18.5% have obesity, and 5.6% are classified as having severe obesity [2]. Evidence shows that children with obesity are more likely to become adults with obesity than children with a healthy body weight. Once uncommon, increasing numbers of children and adolescents are being diagnosed with type 2 diabetes and metabolic complications of excess body weight [4]. Between 2002 and 2015 in the USA for youth aged 10–19 years, the incidence of type 2 diabetes increased across all groups of race and ethnicity, except for whites. For the periods 2002–2010 to 2011–2015, there was an adjusted overall annual percent change increase of 4.8% in type 2 diabetes incidence, with the greatest increases among Asian and Pacific Islander (7.7% per year), Hispanics (6.5% per year), and African Americans (6% per year) [5].

The prevalence of obesity has increased for many reasons. Dietary factors include larger portions sizes, increased consumption of calorie-dense processed foods, affordability and availability of fast-casual dining options, and greater intake of sugar-sweetened beverages [6]. On a daily basis in the USA, 63% of youth and 49% of adults consume at least one sugar-sweetened beverage, and 36.6% of adults consume high-calorie fast food [7, 8]. In addition, we have become more sedentary as jobs, leisure activity, and transportation require far less physical activity [6].

Professional societies, including the American Heart Association (AHA), the American College of Cardiology (ACC), and the Obesity Society, have partnered to create guidelines on how to manage obesity to decrease cardiovascular risk (Fig. 1) [9]. These recommendations provide a systematic approach for assessing patients with obesity according to body mass index (BMI) and cardiovascular disease (CVD) risk factors to facilitate clinically meaningful weight loss.

1.1 An Increase in Obesity

In the USA, all states have obesity rates that exceed 20% with the greatest prevalence in the southern and midwestern states (Fig. 2 CDC obesity rates in the USA) [10]. National health surveys show that minority populations, especially Blacks and Hispanics, and the socially disadvantaged are disproportionally affected by obesity when compared with whites, Asians, and more affluent groups [11]. In less developed countries, especially in rural areas, the undernutrition of poverty has been replaced by excessive consumption of low-quality calories. The increase in BMI

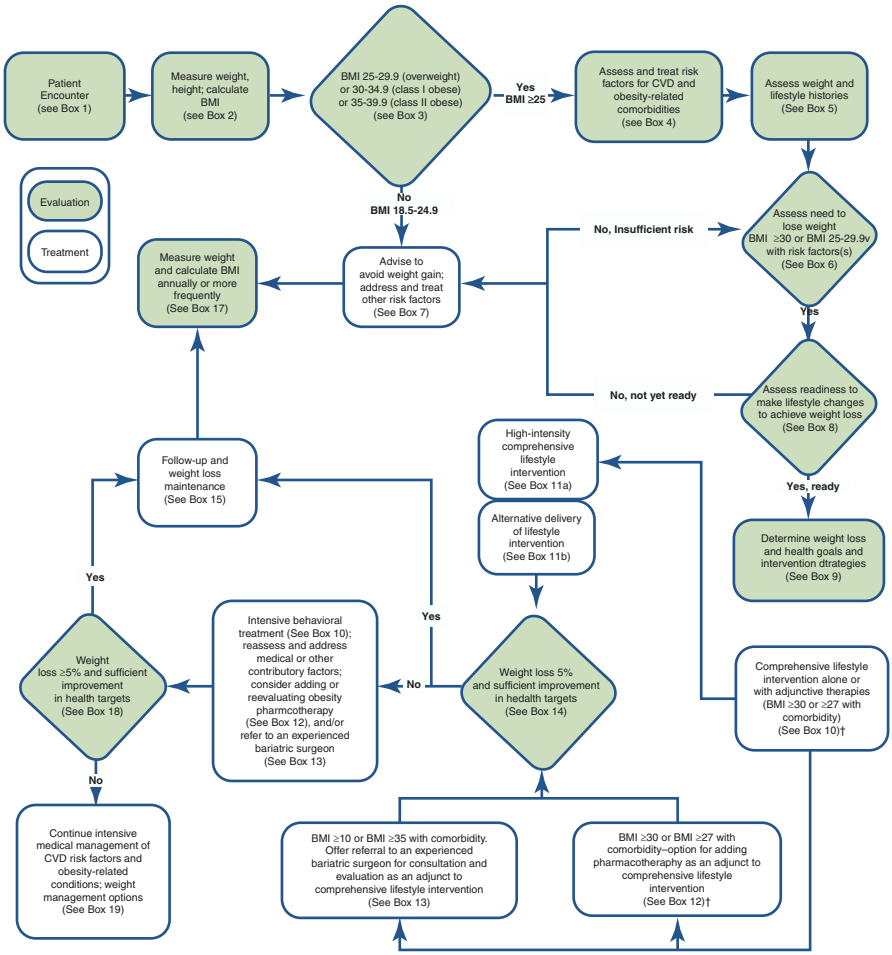

Fig. 1 Treatment algorithm—chronic disease management model for primary care of patients with overweight and obesity. This algorithm applies to the assessment of overweight and obesity and subsequent decisions based on that assessment. BMI cutpoint determined by the FDA and listed on the package inserts of FDA-approved obesity medications. BMI body mass index, CVD cardiovascular disease, FDA US Food and Drug Administration. (Reprinted from Jensen et al. [9], with permission from Elsevier)

seen in these settings is contributing to a global escalation in obesity and its complications [12].

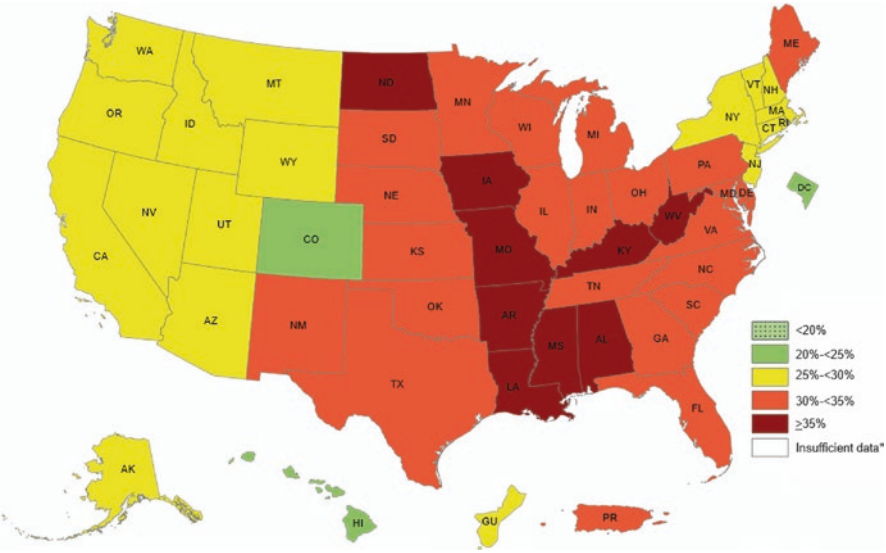

Fig. 2 Prevalence† of self-reported obesity among US adults by state and territory, BRFSS, 2018. (Reprinted from CDC [10])

1.2 The Cost of Obesity

Individuals with overweight and obesity are more likely to develop chronic medical conditions including hypertension, dyslipidemia, metabolic syndrome, type 2 diabetes, cardiovascular disease, and certain cancers [13]. In 2008 dollars, the estimated medical cost of obesity in the USA was $147 billion [14]. Obesity also increases costs indirectly to employers and society through absenteeism, decreased productivity, and disability [15]. It is estimated that obesity-related absenteeism costs $4.3 billion per year in the USA [16]. A retrospective Kaiser Permanente study published in 2001 showed that patients with a BMI ≥30 kg/m^2 had 36% higher annual healthcare costs [17].

1.3 Measures of Obesity: Body Mass Index

Body mass index (BMI) is a numerical expression of body weight relative to height in kg/m^2. BMI is widely used to evaluate populations, screen patients for obesity, and classify degrees of body weight. The classifications of body weight based on BMI are shown in Table 1 [18].

Although BMI correlates with body fat percentage, it is a crude tool for estimating body composition and cardiometabolic risk, especially in patients with cardiovascular disease [19]. Notably, a meta-analysis showed that BMI cutoffs have a low

sensitivity for identifying excess adiposity and miss approximately half of individuals with excess body fat [20]. The sensitivity of BMI for excess adiposity varies by race. For instance, Asian and Hispanic populations typically have higher body fat and visceral fat at a lower BMI when compared with Caucasians [21, 22]. In addition, African American men and women tend to have less visceral adipose tissue relative to total body fat compared with Caucasians [23]. Therefore, more physiologic measurements of obesity, which focus on body composition and quantifying visceral or ectopic fat, may be more clinically meaningful to identify at-risk patients.

1.4 Measures of Obesity: Waist Circumference

Obesity is a risk factor for insulin resistance, type 2 diabetes, and CVD; however, not every person with obesity develops type 2 diabetes or CVD [24]. Individuals with excess visceral adipose tissue, relative to other adipose depots, are at substantially greater risk for insulin resistance and features of the metabolic syndrome [25, 26]. Waist circumference (WC) and waist-to-hip circumference ratios are simple measures of abdominal obesity that correlate with incident CVD events and can therefore be used for CVD risk stratification [27, 28]. A healthy WC for women is <89 cm (<35 inches) and <102 cm (<40 inches) for men [28]. People of Asian heritage are at increased risk for developing metabolic complications at a smaller WC; therefore in this population a healthy WC is <79 cm (<31 inches) for women and <89 cm (<35 inches) for men [29]. According to the International Diabetes Federation (IDF), waist circumference cutoffs for the European population are ≤94 cm for men and ≤80 cm for women [30]. The IDF recommends that ethnic South and Central Americans use the same cutoffs as South Asians (≤90 cm for men and ≤80 cm for women) and that sub-Saharan Africans and Eastern Mediterranean and Middle East (Arab) populations use the European cutoffs until more data is available [30]. The Dallas Heart Study showed that a ratio of WC relative to hip circumference, commonly referred to as the waist-to-hip ratio (WHR), was a better predictor of prevalent atherosclerosis than BMI or WC [31]. Waist circumference and WHR are relatively simple risk assessment tools that correlate with CVD, which do not require costly equipment, extensive training, phlebotomy, or radiation exposure.

Table 1 BMI classifications of body weight

Classification	BMI
Underweight	<18.5
Healthy weight	18.5–24.9
Overweight	≥25
Obese	≥30
Class I	30–34.9
Class II	35–39.9
Class III	≥40

1.5 *Measures of Obesity: Additional Tools*

Body composition analysis allows for quantification of the metabolically significant components of the body, such as skeletal muscle and fat depots. While population studies demonstrate a clear link between BMI and CVD morbidity and mortality, there is significant heterogeneity in CVD risk profiles for individuals at a given BMI. Some of these differences can be explained by differences in body fat distribution, especially visceral and ectopic fat depots [32].

Assessment of body composition can be done by hydrostatic weighing, air displacement plethysmography, bioelectrical impedance analysis, dual-energy X-ray absorptiometry (DXA), computed tomography (CT), magnetic resonance imaging (MRI), and magnetic resonance spectroscopy (MRS) [33]. Studies using MRI and DXA show that CVD risk is lower in those with relatively greater lower body (gluteo-femoral) subcutaneous adipose tissue (SAT), whereas there was increased risk for CVD in those with greater amounts of visceral adipose tissue (VAT) [34]. Figure 3 shows the results of a study published in the *Journal of the American College of Cardiology* demonstrating the relationship between SAT and VAT on cardiovascular risk factors [35].

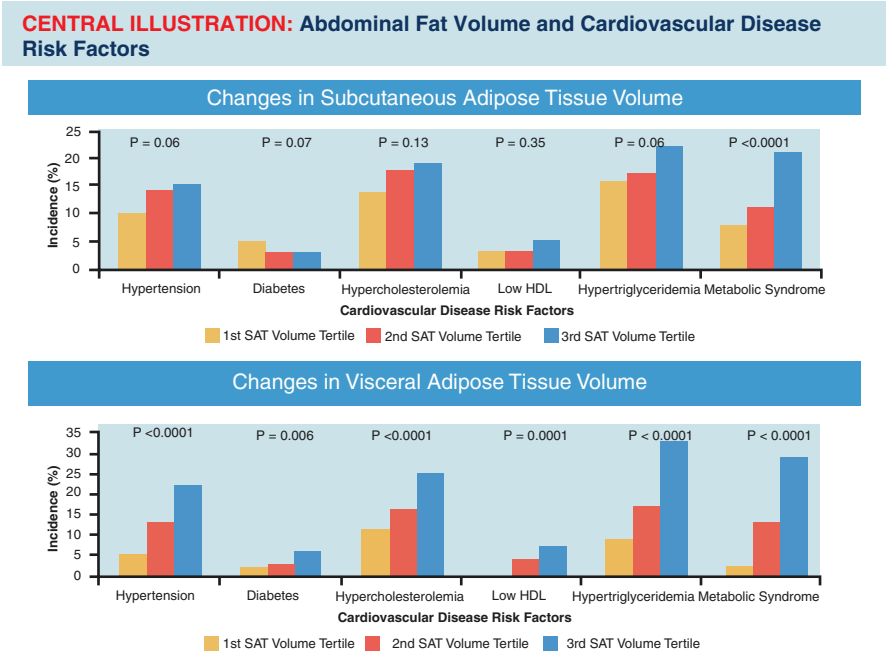

Fig. 3 Abdominal fat volume and cardiovascular disease risk factors. (Reprinted from Lee et al. [35], with permission from Elsevier)

2 Obesity and Heart Disease

2.1 Background

Excess body weight and high BMI are associated with increased rates of atherosclerotic CVD, heart failure, dysrhythmias, and sudden cardiac death [36]. A gain of 10 kg in body weight can increase the rate of coronary artery disease (CAD) by 12% [36]. An increase in BMI by 1 kg/m^2 unit is associated with a 4% rise in ischemic stroke, 6% rise in hemorrhagic stroke, 5% increase in heart failure in men, 7% increase in heart failure in women, and 4% increase in newly diagnosed atrial fibrillation [36]. Obesity, as measured by BMI, is also a strong predictor for overall mortality, which is thought due to the causal relationship between obesity and CVD. At a BMI of 30–35 kg/m^2, median lifespan is decreased by 2–4 years, and at a BMI of 40–45 kg/m^2, it is reduced by 8–10 years, which is similar to tobacco use [37]. For these reasons, working toward a healthier body weight is paramount for preventing and reducing morbidity and mortality in patients with obesity.

2.2 Mechanisms for Obesity and CVD

Adipocytes release significant numbers of biological mediators that impact body weight regulation, insulin resistance, circulating lipids, inflammation, and coagulation, which contribute to endothelial dysfunction and atherosclerotic disease [36]. Excess body weight, especially when associated with weight gain in adulthood, facilitates the clustering of cardiovascular and metabolic risk factors known as metabolic syndrome. This is important as the metabolic syndrome is associated with an increased risk in CHD of 30% in men and 56% in women [38]. When we consume excess calories, healthy SAT expands by hypertrophy and hyperplasia to buffer the positive energy balance (Fig. 4) [24]. Visceral adiposity, characterized by increases in VAT and ectopic fat deposition, develops pathologically when SAT does not sufficiently expand. This process, characterized by dysfunctional adipocytes, adipokine dysregulation, inflammation, and insulin resistance, is influenced by sex, age, genetics, and a multitude of other factors [39, 40].

Visceral adipose tissue has distinct metabolic properties. The circulation from VAT is drained primarily by the portal vein toward the liver. When there is increased visceral adiposity, the liver is exposed to higher levels of free fatty acids, glycerol, and other factors that induce dysfunctional hepatic metabolism of glucose, insulin resistance, and increased production of triglyceride-rich lipoproteins. Excess lipids subsequently accumulate in "ectopic" tissue systems that are typically lean, such as the liver, pancreas, heart, and skeletal muscle.

Ectopic fat deposition is pathognomonic for dysfunctional SAT [41]. Several studies have shown a connection between nonalcoholic fatty liver disease (NAFLD), which is a form of ectopic fat, type 2 diabetes, and CVD [42, 43]. Additionally,

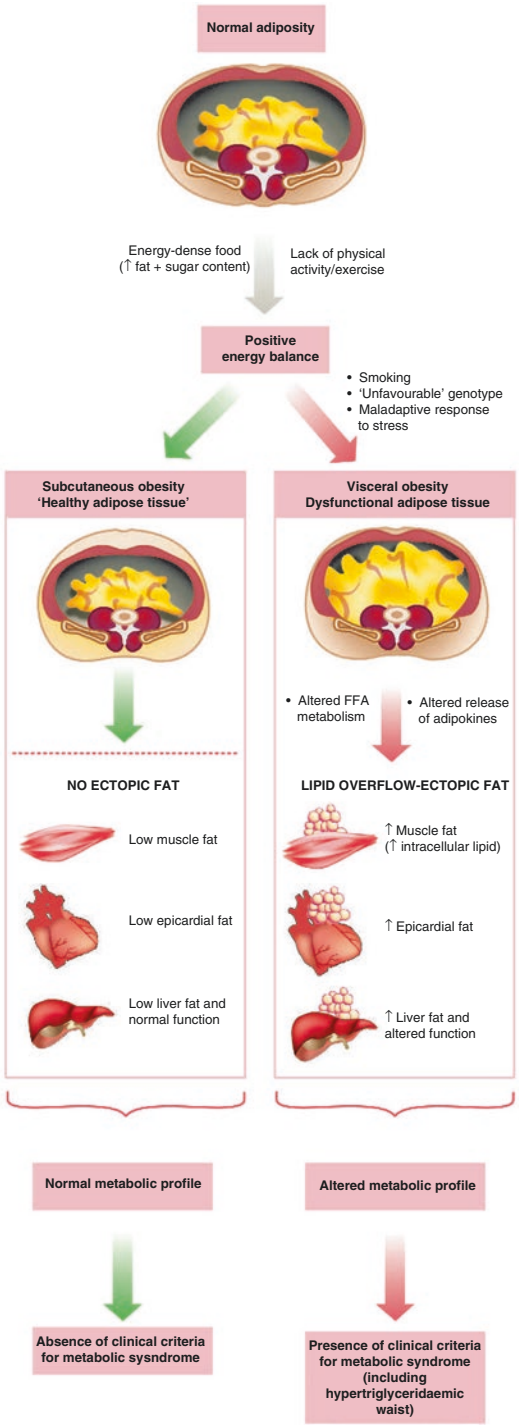

Fig. 4 The lipid overflow-ectopic fat model. (Reprinted from Després and Lemieux [145], with permission from Springer Nature)

there is an association between epicardial and pericardial fat deposition with CVD, independent of BMI and traditional cardiovascular risk factors [44, 45]. This relationship between visceral and ectopic fat with cardiovascular disease, independent of BMI, highlights the clinical importance of looking beyond BMI to regional fat distribution as a clinically more important measure of cardiovascular risk.

Obesity is also associated with elevated cardiac output and blood pressure, both of which affect the structural integrity of the heart [36]. Elevated blood pressure, secondary to activation of the renin-angiotensin-aldosterone system and increased sympathetic tone, causes greater left ventricular afterload, remodeling, left ventricular hypertrophy, and dysfunction [36]. The mechanism for atrial fibrillation in patients with obesity is secondary to chamber dilation, paracrine fibrosing effects of epicardial fat, inflammation, sympathetic activation, and hypoxia related to obstructive sleep apnea [36]. Obesity has also been associated with risk of sudden cardiac death, which is likely due to ventricular tachyarrhythmias that result from remodeling and prolonged ventricular repolarization and QT interval [36].

2.3 Benefits of Weight Loss

Weight loss occurs when there is a consistent negative energy balance; however, this is a gross oversimplification of a complex neurohormonal and behavioral homeostatic process [46]. SAT and VAT decrease in a dose-response relationship to calorie restriction and activity-related energy expenditure. Notably, decreases in VAT in response to lifestyle modification can be seen independent of changes in body weight [47]. This implies that physiological improvements can occur for patients with excess VAT who change their body composition but do not lose weight.

The intensive lifestyle intervention arm of the Diabetes Prevention Program (DPP) included recommendations to follow a healthy low-calorie, low-fat diet, to engage in moderate physical activity for ≥150 min per week, and a comprehensive curriculum of 16 educational sessions reinforcing these themes. Structured interventions like the DPP indicate that a non-sustained weight loss of 5–7% can improve cardiovascular risk factors, including metabolic syndrome, hyperglycemia, blood pressure, and atherogenic dyslipidemia [48]. Notably, there was a 58% reduction in the incidence of type 2 diabetes compared to standard care [49]. However, participants in the DPP and Finish Diabetes Prevention Study did not have lower cardiovascular morbidity or mortality in spite of a structured lifestyle modification that resulted in modest weight loss and cardiovascular risk-factor reduction [50, 51].

Recently, the Da Qing Diabetes Prevention Study published 30-year outcome data of a 6-year lifestyle intervention that resulted in a 1.9 kg weight loss [52, 53]. The combined intervention and modest associated weight loss resulted in a decrease in CVD events and mortality and a 1.4-year increase in life expectancy [53]. The average BMI of the study participants was 25.7 kg/m^2, and although body weight decreased in the intervention group, weight loss was only advised for participants with a BMI >25 kg/m^2. It has therefore been suggested that given the relatively

small decrease in BMI, the improvements in diabetes risk and mortality occurred as a result of lifestyle changes, independent of weight loss [53].

In the Look AHEAD study, over 5000 people ages 45–76 years, with reasonably controlled type 2 diabetes and average BMI of 36 kg/m^2, were randomized to either an intensive lifestyle modification or diabetes support and education groups. The primary outcome was occurrence of a composite cardiovascular outcome (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalized angina) [54]. The intensive lifestyle group participated in multiple individual and group counseling sessions with a goal of losing >7% body weight through diet, which consisted of 1200–1800 kcal/day and use of meal replacement products, along with increasing participants' physical activity to >175 min per week. The diabetes support group participated in three group educational sessions focused on diet, physical activity, and behavioral changes during the first 4 years and annually thereafter [54]. The study did not show any difference in CV death or a composite of major adverse cardiovascular events (MACE) after 8.6% weight loss over 10-year follow-up [54]. However, a post hoc analysis demonstrated that in subjects who lost >10% body weight, there were a 20% decrease in CV mortality and 21% decrease in a composite of major adverse cardiovascular events (MACE) [55].

From these studies, we can extrapolate that there is probably a cardiovascular risk reduction dose-response relationship to weight loss. Although there is significant heterogeneity in the populations studied, these studies support that there are improvements in CV risk factors at >5% weight loss and decreases in MACE and mortality seen at >10% weight loss.

3 Obesity Management

Obesity prevention and treatment are important public health and clinical objectives. In 1977, the Healthcare Financing Administration, which was the predecessor to Center for Medicare and Medicaid Services (CMS), specifically stated that "Obesity is not a disease," which contributed to a lack of coverage for obesity care [56]. It was not until 2013 that obesity was formally recognized as a disease by the American Medical Association (AMA) in the hope that it would increase patient awareness, advocacy, and access to evidence-based obesity treatments [56]. However, this decision went against recommendations of the AMA's own Council on Science and Public Health and separately caused significant controversy among healthcare providers and policymakers [57]. It is important to note that still only 65% of people with obesity recognize it as a disease and less than 55% are concerned that their excess weight may impact their future health [58].

In spite of rising rates in obesity and associated costs, US medical schools are not sufficiently preparing students to prevent and treat this epidemic [59]. The inadequate physician training contributes to the lack of dialogue between patients and healthcare providers around excess body weight. A recent study of patient and provider attitudes and experiences of obesity management found that only 71% of people with obesity had spoken with a healthcare provider about their weight in the prior 5 years and fewer than 40% in the prior 6 months [58].

There is also significant discordance in reasons why providers and patients do not discuss weight during medical visits. For example, 65% of providers thought that patients were too embarrassed to bring it up, whereas only 15% of patients with obesity felt that way. Additionally, 82% of people with obesity felt "completely" responsible for their weight loss, and 44% did not broach the topic with their provider for that reason [58]. It is therefore important to prepare clinicians who manage patients with obesity to initiate conversations about body weight and to discuss the implications for long-term health.

4 Dietary Approach

4.1 Dietary Strategies for Weight Loss

The 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults provides calorie intake guidance for patients to achieve a net negative energy balance [9]. The guidelines recommend that women consume 1200–1500 kcal/day and men consume 1500–1800 kcal/day to lose weight [9]. This can be adjusted for body weight, comorbidities, and activity level to achieve a calorie deficit of 500–750 kcal or 30% per day [9]. Changes in body weight will depend on the magnitude and consistency of the calorie deficit achieved. These recommendations should be reinforced by trained interventionists such as a dietician, psychologist, or health counselor throughout 14 visits over a 6-month period of time [9]. While it is important to keep the patient's weight loss goals in mind, it should be emphasized that even modest reductions in weight loss of 5–10% can improve cardiometabolic factors such as glycemic control, blood pressure, and cholesterol [60].

Energy needs vary between individuals and can be estimated or measured by a variety of methods. Predictive equations like Harris-Benedict or Mifflin St. Jeor use age, sex, height, and weight to estimate basal metabolic rate [61]. These equations can be inaccurate as they do not account for differences in lean body mass, history of calorie restriction, prior weight loss, and other factors that influence metabolic rate. Indirect calorimetry can be used clinically to estimate resting metabolic rate when patients have a history of significant weight loss or calorie restriction, for example, due to a history of bariatric surgery or anorexia nervosa [62].

4.2 Studies Assessing Various Diets

Patients and practitioners struggle to navigate the numerous diet programs and fads proposed for weight loss. A randomized controlled trial that compared the Atkins, Ornish, Weight Watchers, and Zone diets showed that weight loss depended more on adherence to the diet than the type of diet [63]. These findings were supported by a subsequent randomized study that compared diets of various macronutrient

compositions, which found that calorie restriction was more important than dietary composition for weight loss [64].

A meta-analysis that incorporated 48 randomized controlled trials compared many well-known programs such as the Atkins, Jenny Craig, Nutrisystem, Weight Watchers, and Zone diets [65]. The authors concluded that low-carbohydrate and low-fat diets were associated with more weight loss than no intervention, and adherence to caloric restriction rather than diet type was most important for weight loss [65]. As seen in other studies, their data showed a tendency toward weight loss plateau at 6 months, further supporting the recommendation that choosing a diet patients can adhere to rather than a particular diet type is more important for maintaining weight loss [65].

In recent years, there has been more interest in very-low-carbohydrate or ketogenic diets for weight loss, whereby participants consume less than 50 grams of carbohydrate per day. Attention has been driven by data that include a meta-analysis of 13 studies, which suggest that people on ketogenic diets lose more weight and keep more of it off relative to those on low-fat diets [66]. Aside from carbohydrate restriction, the ketogenic diet focuses on participants consuming around 80% of their calories from fat, which is thought to have a satiating effect that makes calorie restriction easier [67]. The ketogenic diet does not follow decades of prior dietary guidelines to limit fat intake and instead focuses on limiting carbohydrates not calories. This novel approach may be appealing for people who feel that traditional diets do not work for them. Studies have also shown that ketogenic diets are associated with decreases in visceral adipose tissue and improvements in insulin sensitivity; however these benefits may be offset by increases in LDL cholesterol and decreases in consumption of dietary fiber and whole grains [68].

In the POUNDS Lost study, fiber intake was shown to be associated with greater adherence to calorie restriction and superior weight loss. Therefore, fiber may be an additional tool to promote satiety and help with dietary adherence [69]. The Institute of Medicine recommends 21–26 grams of fiber per day for women and 30–38 grams of fiber for men, but the typical American diet falls short of these goals [70]. In clinical practice, it is common to recommend fiber supplements, such as psyllium husk, to help with hunger and changes in bowel habit experienced with calorie restriction and dietary modification.

Programs that modify the timing of food consumption to simplify calorie restriction have received significant media coverage and attention in the past several years. Time-restricted feeding encourages participants to consume food ad libitum for a continuous 8-h period, typically 10 a.m. until 6 p.m., which results in an energy restriction of around 350 kcal per day [71]. Intermittent fasting, where participants consume 25% of energy needs on fast days and 125% of energy needs on alternating “feast” days, did not show superior weight loss, adherence, or cardio-protection when compared to daily calorie restriction [72]. Although these are currently very popular dieting strategies, significant benefits have not been demonstrated over traditional calorie restriction in randomized controlled studies.

4.3 Dietary Recommendations

Consistent calorie restriction is needed to achieve and maintain weight loss. Recent dietary strategies have focused on novel approaches such as dramatically limiting carbohydrate intake or the timing of food consumption. While there is some evidence that low-carbohydrate diets may be superior for weight loss and metabolic outcomes, high-quality, long-term studies are lacking [73]. Dietary interventions should be individualized for the patient to achieve an appropriate calorie deficit by acceptable means in order to promote consistency.

The 2019 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline on the Primary Prevention of Cardiovascular Disease maintains that individuals with overweight and obesity should focus on calorie restriction and also emphasizes increasing intake of vegetables, fruits, nuts, whole grains, vegetable or lean animal protein, and fish. The guidelines also recommend minimizing the intake of trans fat, red and processed meats, refined carbohydrates, and sugar-sweetened beverages to prevent cardiovascular disease [74].

5 Physical Activity

5.1 Physical Activity Gaps

Only one in four US adults meets the recommended levels of physical activity [75]. Physical inactivity adds around $117 billion per year to healthcare costs and contributes to the development of obesity, type 2 diabetes, hypertension, hyperlipidemia, CVD, and cancers of the bladder, breast, colon, uterus, esophagus, kidney, lung, and stomach [75]. Aside from insufficient levels of planned vigorous-intensity physical activity, studies and systematic reviews have demonstrated a clear relationship between sedentary behavior, elevated BMI, metabolic syndrome, type 2 diabetes, CVD, and mortality [76, 77]. In recent years, wearable technology devices have become popular tools to increase casual activity and estimate calorie expenditure. However, a well-designed randomized clinical trial showed that the addition of wearable technology to a structured lifestyle intervention actually resulted in less weight loss over 24 months [78]. Although these devices can help to decrease sedentary behaviors, they may provide feedback that is not helpful for weight loss.

5.2 Aerobic Training Guidelines and Benefits

The American College of Sports Medicine directs patients and providers to the US Department of Health and Human Services guidelines for physical activity [79]. These guidelines recommend 150–300 min of moderate physical activity per week,

75–150 min of vigorous-intensity aerobic physical activity, or an equivalent combination of the two [80]. This is in line with the 2013 AHA/ACC/TOS Obesity Treatment Guidelines, which recommend that patients increase aerobic exercise to approximately 30 min per day or ≥150 min per week as part of a comprehensive weight management program [9]. For those who are able to achieve >300 min/week, the reduction of the above conditions is even greater [80].

5.3 Strength Training Guidelines and Benefits

Activity guidelines recommend muscle strengthening exercises of major muscle groups at least 2 days per week [80]. The benefits of resistance training include improvements in muscle strength and bone density and maintenance of weight loss [80]. When appropriate for the individual, weight training should be done to the extent that completing an additional repetition would be difficult [80].

5.4 Weight Loss and Maintenance

Physical activity can contribute to the negative energy balance needed for weight loss or to counterbalance calorie intake for weight maintenance. Contrary to popular belief, individuals who focus solely on physical activity will only lose around 3% of their body weight [81]. However, a regimen that combines moderate calorie restriction with physical activity yields more weight loss than either of these in isolation [82].

A study of sedentary women that compared exercise regimens of different intensity and duration (vigorous intensity/high duration, moderate intensity/high duration, moderate intensity/moderate duration, or vigorous intensity/moderate duration) found no significant difference in weight loss between groups at 12 months. These findings suggest that total energy expenditure is more important for weight loss than exercise intensity or duration [83]. A combination of aerobic exercise and resistance training should be recommended, as this leads to greater reductions in subcutaneous and visceral fat and an increase in lean body mass, which contributes to resting metabolic rate [84, 85].

Aside from weight loss, there are additional health benefits to exercise. Cardiorespiratory fitness has been shown to be inversely related to the risks of metabolic syndrome in people with obesity and may be more important than BMI for assessing cardiovascular risk [86]. Physical activity promotes cardiovascular health in a multitude of ways (Fig. 5) [87]. After accounting for moderate to vigorous physical activity, one study found that increased breaks in sedentary time were associated with improved waist circumference, BMI, triglycerides, and 2-h plasma glucose levels [88]. This suggests that even small changes in physical activity can be metabolically beneficial.

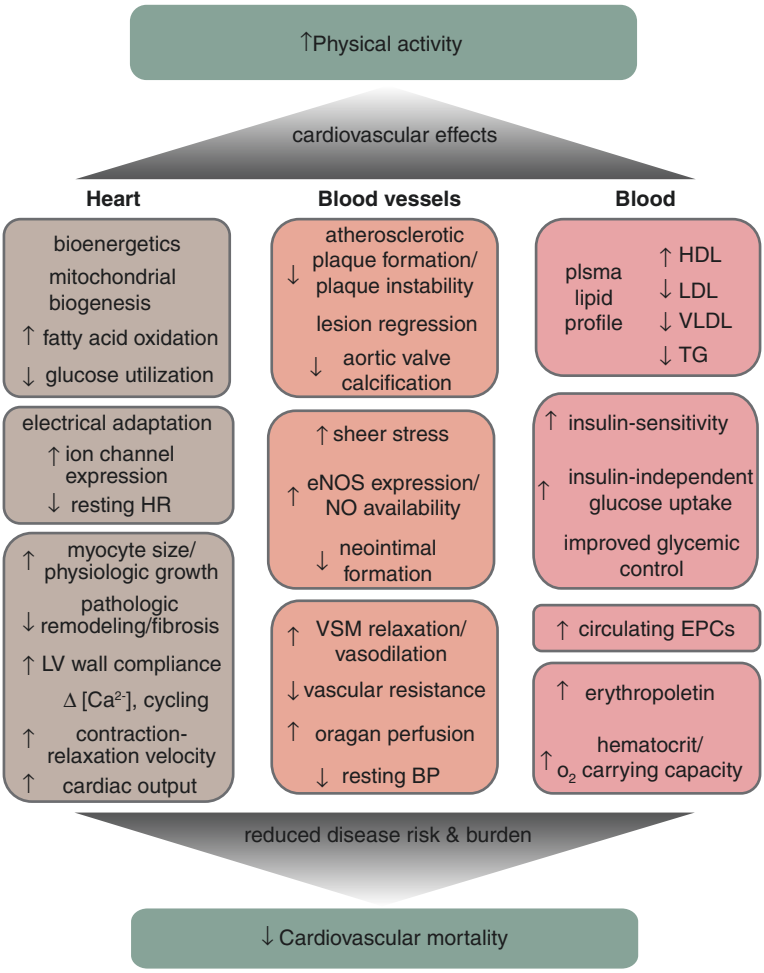

Fig. 5 Overview of major cardiovascular effects of exercise. (Reprinted from Nystoriak and Bhatnagar [87], with permission from Creative Commons License 4.0: https://creativecommons.org/licenses/by/4.0/)

For cardiovascular health and disease prevention, the US Department of Health and Human Services Guidelines for adults are a good place to start. Although physical activity is most often emphasized for weight loss, it is also a powerful tool to prevent weight gain and decrease comorbidities independent of weight loss. People with obesity and physical deconditioning should gradually increase intensity and duration of physical activity with a goal of ≥150 min/week. Activity programs should be combined with calorie restriction to achieve clinically meaningful weight loss. Recommendations should include decreasing sedentary time, walking more, vigorous aerobic activity, and resistance training. Once patients achieve their goal weight, higher levels of physical activity (200–300 min/week) are often needed to

prevent weight regain [9]. These recommendations are also consistent with the 2019 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline on the Primary Prevention of Cardiovascular Disease [74].

6 Medications

6.1 Indications for Medications

For weight loss, anti-obesity medications (AOMs) are intermediate choices between lifestyle modification and bariatric surgery in terms of efficacy, cost, and risk. Data suggest that patient satisfaction and weight loss are greater when AOMs are used for weight loss compared with lifestyle modification alone [89, 90]. Professional societies and the NIH recommend considering AOM for patients who would benefit from weight loss with a BMI > 30 or with a BMI 27–29 with at least one weight-related comorbidity, such as hypertension, dyslipidemia, type 2 diabetes, or obstructive sleep apnea [91–94].

Studies of large health systems show that in spite of interest from patients and guidelines from professional societies, less than 2% of eligible patients receive prescriptions for AOM [95]. The low utilization of medication for weight loss is due to several factors, which include lack of provider experience with AOM, misinformation or bias that obesity is a behavioral disease that should be treated with lifestyle change alone, patient and provider safety concerns, and lack of insurance coverage [96, 97].

6.2 Medication Effects and Options

FDA-approved AOMs facilitate weight loss by decreasing calorie intake, except for orlistat, which causes malabsorption of dietary fat-calories [91]. Therefore, AOMs are most effective when used as part of a plan to create a calorie deficit that involves calorie restriction, physical activity, and behavioral modification. Contrary to the belief of many patients, approved AOMs do not increase "metabolism" or thermogenesis, and none of them are approved for use during pregnancy [91].

The FDA-approved AOMs are listed in Table 2 [94, 98–111]. Providers should select AOM based on mechanism of action, the presence of comorbidities, and contraindications. For example, stimulant AOMs like phentermine should not be used in patients with significant anxiety, hypertension, or other cardiovascular contraindications. The glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide should be considered for patients with diabetes or hyperglycemia as this class has beneficial effects on glycemic control and diabetes prevention [112, 113].

Providers should start AOM and titrate the dose, as directed, according to side effects and weight loss results. Patient should be seen regularly to reinforce lifestyle modification, monitor for adverse effects, adjust doses of weight-sensitive medications (e.g., insulin or antihypertensives), and stop AOMs that are not effective [91].

Table 2 Medical treatment options for obesity

Drug (generic)	Dosage	Mechanism of action	Weight loss in kg/% body weight loss; duration of clinical studies	Common side effects	Contraindications	Cost
Phentermine	15–37.5 mg/day in one to two divided doses 8 mg 3 times daily	Norepinephrine-releasing agent	6.3 kg; 2–24 wk	Headache, elevated BP, elevated HR, insomnia, dry mouth, constipation, anxiety Cardiovascular: palpitation, tachycardia, elevated BP, ischemic events Central nervous system: overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache, psychosis Gastrointestinal: dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbance Allergic: urticaria Endocrine: impotence, changes in libido	Anxiety disorders (agitated states), history of heart disease, uncontrolled hypertension, seizure, MAO inhibition, pregnancy and breastfeeding, hyperthyroidism, glaucoma, history of drug abuse, sympathomimetic amines	$
Diethylpropion	75 mg/d	Norepinephrine-releasing agents	6.5 kg; 6–52 wk	Same as phentermine	Same as phentermine	$

(continued)

Table 2 (continued)

Drug (generic)	Dosage	Mechanism of action	Weight loss in kg/% body weight loss; duration of clinical studies	Common side effects	Contraindications	Cost
Orlistat	120 mg TID 60 mg TID	Pancreatic and gastric lipase inhibitor	7.9 kg/7.9% for 120 mg dose 7.1 kg/7.1% for 60 mg dose; 1 year	Decreased absorption of fat-soluble vitamins, steatorrhea, oily spotting, flatulence with discharge, fecal urgency, oily evacuation, increased defecation, fecal incontinence	Cyclosporine (taken 2 h before or after orlistat dose), chronic malabsorption syndrome, pregnancy and breastfeeding, cholestasis, levothyroxine, warfarin, anti-epileptic drugs	(OTC) $-->$$$ (prescription)
Phentermine (P) and topiramate (T)	3.75 mg P/23 mg T ER QD (starting dose) 7.5 mg P/46 mg T ER daily (recommended dose) 15 mg P/92 mg T ER daily (high dose)	GABA receptor modulation (T) plus norepinephrine-releasing agent (P)	8.1 kg/7.8%(recommended dose), 10.2 kg/9.8% (high dose), 1 year	Insomnia, dry mouth, constipation, paresthesia, dizziness, dysgeusia	Pregnancy and breastfeeding, hyperthyroidism, glaucoma, MAO inhibitor, sympathomimetic amines	$$
Naltrexone/ bupropion	32 mg/360 mg two tablets QID (high dose)	Reuptake inhibitor of dopamine and norepinephrine (bupropion) and opioid antagonist (naltrexone)	6.2 kg/6.4%; 1 year	Nausea, constipation, headache, vomiting, dizziness	Uncontrolled hypertension, seizure disorders, anorexia nervosa or bulimia, drug or alcohol withdrawal, MAO inhibitors	$$

Drug (generic)	Dosage	Mechanism of action	Weight loss in kg/% body weight loss; duration of clinical studies	Common side effects	Contraindications	Cost
Liraglutide	3 mg QD	GLP-1 receptor agonist	8.4 kg/8.0%; 1 year	Nausea, vomiting, pancreatitis	Medullary thyroid cancer history, multiple endocrine neoplasia type 2 history	$$$
Cellulose and citric acid hydrogel	Three capsules (2.25 grams) with 500 mL of water before lunch and dinner	Cellulose and citric acid form a three-dimensional matrix that occupies volume in the stomach and small intestine to create a sensation of fullness and increase satiety	6.4%; 24 weeks	Gastrointestinal side effects: diarrhea, abdominal distension, change in bowel habits, flatulence, abdominal pain, may alter the absorption of medications	Patients who are pregnant or are allergic to cellulose, citric acid, sodium stearyl fumarate, gelatin, or titanium oxide Avoid use in patients with the following conditions: esophageal anatomic anomalies, including webs, diverticuli, and rings; suspected strictures (such as patients with Crohn's disease); or complications from prior gastrointestinal (GI) surgery that could affect GI transit and motility	TBD

Based on data from Refs. [94, 98–111]

QD daily, *BID* twice daily, *TID* three times a day, *QID* four times a day, *wk* week, *h* hour, *mg* milligrams, *kg* kilograms, *mL* milliliters, *MAO* monoamine oxidase, *GABA* gamma aminobutyric acid, *GLP1* glucagon-like peptide-1 receptor, *BP* blood pressure, *HR* heart rate, *OTC* over-the-counter rate, *$* price <$100 for 30-day supply, *$$* price between $101 and 350 for 30-day supply, *$$$* price >$500 for 30-day supply

6.3 Medication Considerations in CVD and Type 2 Diabetes

People who have existing cardiovascular disease, increased CVD risk, or uncontrolled hypertension should not take simulant AOM like phentermine or diethylpropion [91]. For these high-risk individuals, prescribers should consider a GLP-1 receptor agonist (liraglutide) [91]. Lorcaserin was studied in patients with established CVD or with multiple risk factors for CVD and was found to be effective for weight loss and non-inferior to placebo for MACE defined as cardiovascular death, myocardial infarction, or stroke [114]. However, in February of 2020, the FDA removed lorcaserin from the market due to concerns about cancer risk [115].

Liraglutide is the only GLP-1 receptor agonist that is FDA approved for weight loss. However, there are several GLP-1 receptor agonists that are approved for the management of type 2 diabetes and cardiovascular risk reduction, which also facilitate weight loss. These include liraglutide (at a lower dose than prescribed for obesity management), dulaglutide, and semaglutide [116–118].

Sodium-glucose uptake transporter-2 (SGLT-2) inhibitors are used for blood glucose management in patients with type 2 diabetes. SGLT-2 inhibitors are not approved specifically for weight management, but they are associated with a 2–3 kg weight loss and have cardio-protective properties [118, 119].

7 Surgical Management of Obesity

7.1 Surgical Options

Bariatric procedures are effective tools for weight loss and weight maintenance but are used in only 1% of those who meet criteria for surgery [120]. Bariatric surgery should be considered for patients with a BMI $\geq$ 40 kg/m^2 or with BMI $\geq$ 35–39 kg/m^2 and at least one weight-related comorbidity. The American Society for Metabolic and Bariatric Surgery estimates that over 250,000 bariatric procedures are performed in the USA every year [121]. The majority of weight loss surgeries are performed in the Northeast even though the highest prevalence of obesity is in the South [122]. In recent years, there has been increasing interest in endoscopic and endoluminal procedures for weight loss. However, these procedures are typically not covered by insurance, and they lack the robust data available for more traditional bariatric surgeries.

Similar to lifestyle and medication management for obesity, primary care providers do not discuss bariatric surgery with the majority of patients who meet criteria. However, when the discussion is initiated by the patient, over 80% of primary care providers are supportive of the concept, with around 18% subsequently placing a referral for bariatric surgery [123]. Lack of knowledge about insurance coverage and out-of-pocket expenses also limit referrals and patients' access to bariatric surgery.

There are four types of bariatric surgery that are primarily performed in the USA. The surgeries and expected weight loss are shown in Fig. 6 [124–127]. The majority of bariatric surgeries are performed laparoscopically, and the most common surgeries are sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) [120, 121, 128]. The SG represents over 60% of surgeries and causes gastric restriction by removing the greater curvature of the stomach [128]. Roux-en-Y gastric bypass constitutes around 17% of procedures and is a combination of gastric restriction and intestinal bypass, which limits food intake and facilitates calorie malabsorption [128]. Laparoscopic adjustable gastric banding (LAGB) and biliopancreatic diversion with duodenal switch (BPDS) each represent around 1% of procedures. The popularity of the adjustable gastric band has decreased due to high rates of weight loss failure, device malfunction, and subsequent revision [129]. Biliopancreatic diversion with duodenal switch is usually reserved for patients with very elevated BMI. BPDS can be performed in a staged fashion with an initial sleeve gastrectomy, which is followed by an intestinal bypass at a later time point. Although this procedure is associated with superior weight loss and metabolic outcomes relative to the other surgeries, its efficacy is offset by higher rates of complications and nutritional deficiencies [130, 131].

7.2 Surgical Weight Loss Outcomes

In randomized controlled trials, the average weight loss achieved at 3 years was 24.5% for RYGB and 21.1% for SG [125]. In this study, the difference in weight loss between RYGB and SG remained significantly greater for RYGB out to 5 years (23% vs 19%, $p = 0.01$) [132]. However, a subsequent multicenter study of Swiss

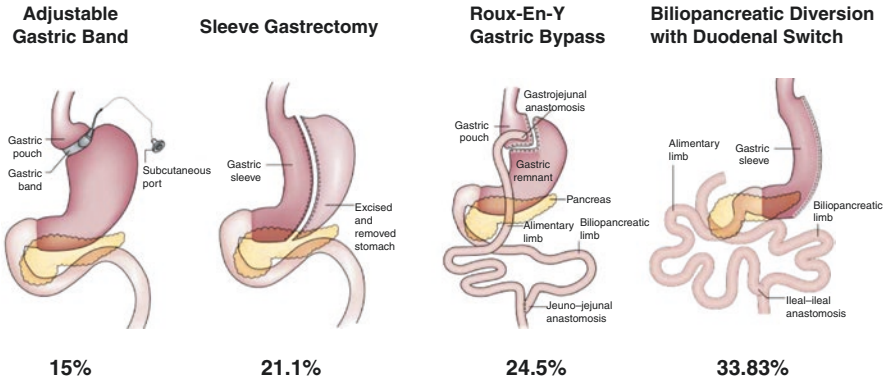

Fig. 6 Bariatric surgeries and average weight loss. Average weight loss with adjustable gastric band is 15% [126], sleeve gastrectomy is 21.1% [125], Roux-en-Y gastric bypass is 24.5% [2], and biliopancreatic diversion with duodenal switch is 33.82% [124]. (Illustration of surgeries image reprinted from Nguyen and Varela [127], with permission from Springer Nature)

bariatric surgery facilities reported no difference in weight loss between RYGB and SG at 5 years of follow-up [133].

7.3 Surgical Benefits

Bariatric surgery has beneficial effects on cardiovascular risk factors, morbidity, and mortality (Table 3) [134] . Studies have shown improvements in cardiac structure and function as well as reductions in markers of inflammation, thrombosis, subclinical atherosclerosis, and endothelial dysfunction [135]. The Swedish Obesity Study prospectively evaluated patients who underwent gastric bypass, banding, or vertical banded gastroplasty. It demonstrated that the patients who underwent bariatric surgery had significantly lower rates of cardiovascular death as well as lower rates of cardiovascular events [136]. A large retrospective, observational, matched cohort study compared patients with obesity and type 2 diabetes who underwent bariatric surgery with matched nonsurgical controls [137]. The primary endpoint was a 6-point composite MACE that consisted of all-cause mortality, coronary artery events, cerebrovascular events, heart failure, nephropathy, and atrial fibrillation [137]. Secondary endpoints included the individual components of the primary endpoint and a 3-point MACE of all-cause mortality, myocardial infarction, and ischemic stroke [137]. The incidence of the primary endpoint at 8 years was significantly lower in the bariatric surgery group compared to the control group (30.8% vs

Table 3 Cardiovascular benefits of weight loss surgery

Hypertension	Lowering of systolic and diastolic blood pressure Resolution of hypertension
Type 2 diabetes	Reduction in blood glucose and HbA_{1C} Reduction in insulin resistance Prevention of progression of impaired glucose tolerance to type 2 diabetes mellitus Resolution of type 2 diabetes mellitus Reduction in mortality because of type 2 diabetes
Dyslipidemia	Lowering of serum low-density cholesterol and triglycerides levels Increase in serum high-density lipoprotein cholesterol levels Resolution of dyslipidemia
Hyperuricemia	Resolution of hyperuricemia
Metabolic syndrome	Resolution of metabolic syndrome
Nonalcoholic fatty liver disease	Improvement in liver steatosis, inflammation, and fibrosis Resolution of nonalcoholic fatty liver disease
Chronic kidney disease	Decrease in albuminuria and glomerular hyperfiltration
Left ventricular hypertrophy	Reduction in left ventricular mass index
Obstructive sleep apnea	Resolution of obstructive sleep apnea
Coronary heart disease	Reduction in mortality because of coronary heart disease

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47.7%) [137]. All-cause mortality was significantly lower in the surgery group compared to control (10% vs 17.8%) with an absolute 8-year risk difference (ARD) of 7.8% [137]. Weight loss surgery was also associated with lower rates of the secondary outcomes in the surgical group compared to control including 3-point MACE (17.0% vs 27.6%, respectively; absolute risk difference, 10.6%), coronary artery events (7.9% vs 11.6% with ARD of 4.2%), cerebrovascular events (4.1% vs 5.6% with ARD of 1.8%), heart failure (6.8% vs 18.9% with ARD 12.9%), nephropathy (6.1% vs 16.3% with ARD 11.1%), and atrial fibrillation (7.9% vs 13.6% with ARD 6.5%) [137]. These data suggest that bariatric surgery should be considered in at-risk groups, especially those with type 2 diabetes, as it improves cardiovascular risk factors and significantly decreases cardiovascular morbidity and mortality.

Bariatric surgeries are also important tools for managing obesity in people with type 2 diabetes. In the STAMPEDE trial, subjects with type 2 diabetes were randomized to medical therapy, SG, or RYGB and experienced 4.5%, 21.1%, and 24.5% weight loss, respectively. The surgeries and weight loss were associated with diabetes remission at 2 years in 27% of SG and 42% of RYGB participants [138]. The rates of diabetes remission decreased to 15% in SG and 22% in RYGB groups at 5 years [132]. In spite of body weight regain and diabetes recidivism, long-term improvements in health, cardiovascular risk, and mortality are persistent in people with diabetes when compared with medically managed controls. Bariatric surgery should be considered for disease management and risk reduction for suitable candidates in this at-risk group [137].

7.4 Surgical Complications

Bariatric complications vary by procedure type and patient population. These include bleeding, anastomotic leaks, strictures, bowel obstruction, hernias, ulceration, nutritional deficiencies, diarrhea, dumping syndromes, and gallstones [128]. A retrospective database review has shown that the mortality rate for laparoscopic RYGB is similar to that of knee arthroplasty (0.3%) and composite complication rates were similar to those for cholecystectomy and hysterectomy [139]. Patients and providers should be made aware that these procedures are beneficial and relatively safe.

7.5 Endoscopic Bariatric Procedures

Endoscopic procedures for weight loss are increasing in popularity and availability. Intragastric balloons decrease food intake by occupying space within the stomach. These devices are approved for up to 6-month use and then are removed endoscopically. Average weight loss is around 14% and side effects like nausea and vomiting are initially quite common [140]. The TransPyloric Shuttle (TPS) is a removable

gastric balloon that can remain in place for up to 1 year and decreases food intake by affecting gastric outflow. Average weight loss with the TPS is around 10% and is associated with improvements in cardiovascular risk factors [141].

The AspireAssist (AA) is an endoscopically placed percutaneous gastrostomy device that allows for postprandial aspiration of ingested food. The most frequently reported adverse effects for this procedure are abdominal discomfort and peristomal irritation. A randomized controlled trial that compared the AA with lifestyle counseling demonstrated a significant weight loss of 12.1% [142].

Endoscopic sleeve gastroplasty (ESG) is a minimally invasive procedure that decreases the size of the stomach lumen by endoscopic plication. The procedure also reduces food intake by slowing gastric emptying and increasing satiety [143]. Average weight loss with ESG is around 18% and early weight loss appears to predict greater weight loss at 2 years [144].

Endoscopic procedures show promise as alternatives to laparoscopic bariatric surgeries. However, they currently lack the effectiveness and robust data that support the use of more traditional bariatric surgeries for people with obesity.

8 Conclusion

Obesity is a complex disease that results from the interaction of genetics, lifestyle, behavior, environment, policies, and comorbid conditions. Although lifestyle changes that facilitate negative energy balance are the foundation for weight loss, these measures often do not result in enough weight loss to prevent unfavorable cardiovascular and other adverse health outcomes. Medications and surgery are effective but underutilized tools for weight loss, which have varying degrees of efficacy and adverse effects. Aside from public health initiatives to prevent and manage obesity on a population level, patients need individualized education and solutions to overcome barriers for managing obesity. Better education for healthcare providers is needed to overcome stigma and bridge gaps in providing evidence-based obesity care that will decrease cardiovascular risk factors and mortality.

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Smoking and Vaping

Russell V. Luepker

Summary

- The evidence linking tobacco use to incidence and mortality from CVD is substantial; approximately 480,000 deaths annually in the USA are attributed to cigarette smoking.
- Although tobacco use is declining in the USA, tobacco remains an important problem worldwide.
- Environmental tobacco smoke is responsible for approximately 35,000–40,000 deaths from heart disease annually.
- The advent of the electronic nicotine delivery systems (e-cigarettes) and the habit of vaping adds to nicotine addiction and is a gateway to cigarette smoking for young adults and youth.
- Cigarette smoking has declined significantly through restrictions in smoking sites, increased taxation, and cessation programs.
- Among adults, interventions include behavioral treatment, self-help, and pharmacologic therapy. Healthcare, worksite, and other community programs are invaluable support.
- Physicians and other healthcare providers can have a greater role in initiating tobacco cessation in collaboration with appropriate community and healthcare resources.

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1 Introduction

Cigarette smoking is the leading preventable cause of many chronic diseases. In wealthy countries, smoking contributes more to the number of years of life lost to disability and death than any other factor [1]. In low- and middle-income countries, it is a growing problem as more individuals assume the smoking habit [1]. In the USA, it is estimated that smoking directly contributes to 480,000 deaths/year from a variety of cardiovascular, lung, cancer, and other diseases [2] (Fig. 1). Approximately 14% of American adults currently smoke, and, as they die, their places are taken by new teenage and young adult smokers [3, 4]. Many smokers have quit and cigarette smoking rates are declining (Fig. 2); however, those who continue the practice are frequently the most addicted and resistant to change.

But there is also a new source of nicotine addiction increasingly used. It involves electronic devices designed to deliver the addicting nicotine. These devices are varied but are called electronic nicotine delivery systems (ENDS) or e-cigarettes. The behavior is widely known as "vaping" [5]. Early proponents of vaping argued that the behavior was safe because tobacco leaf wasn't directly burned eliminating many toxic components. And e-cigarettes could be used to help smokers quit [6]. Because ENDS are new, there are few data to assess long-term chronic disease outcomes. There are accumulating data finding short-term health effects of vaping [7–9]. The use of ENDS as a method of quitting tobacco is also debated [10, 11]. But it is clear that many who use ENDS continue to smoke tobacco or they have traded one nicotine delivery system for another. Critically, ENDS have become a gateway for tobacco use among youth and young adults [12, 13].

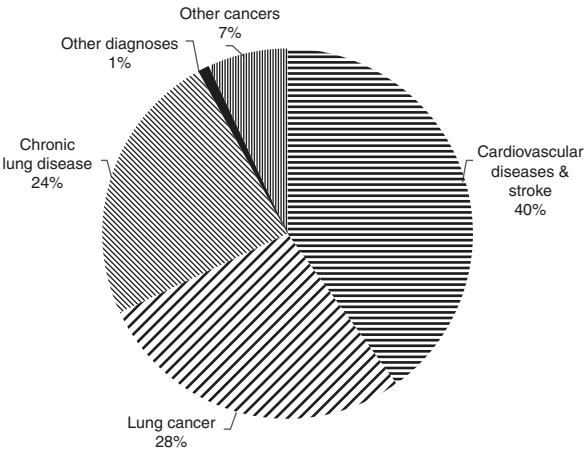

Fig. 1 Annual cigarette smoking – related mortality in the USA, 2005–2009. (Reprinted from U.S. Department of Health and Human Services. The Health Consequences of Smoking—50 Years of Progress. A Report of the Surgeon General. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014. Accessed 1/30/2020)

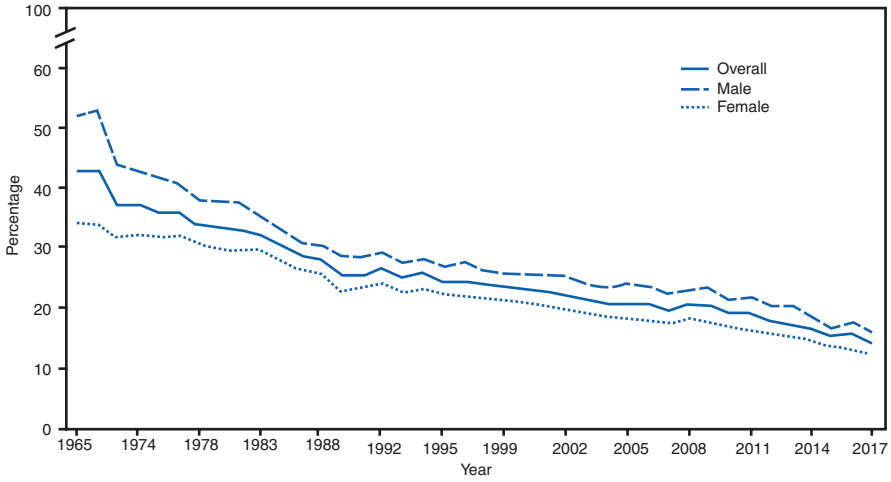

Fig. 2 Percentage of adults aged ≥18 years who were current cigarette smoker,* overall and by sex – National Health Interview Survey (NHIS), USA, 1965–2017*For NHIS years 1965–1991, current smokers included adults who reported that they had smoked ≥100 cigarettes in their lifetime and currently smoked. Since 1992, current smokers included adults who reported smoking ≥100 cigarettes during their lifetime and specified that they currently smoked every day or on some days. Data are not available for 1967–1969, 1971–1973, 1975, 1981, 1982, 1984, 1986, 1989, and 1996 because questions regarding smoking were not included in the NHIS conducted in those years. Related data and documentation can be found at https://www.cdc.gov/nchs/nhis/data-questionnaires-documentation.htm. The figure is a line graph showing the percentage of US adults aged ≥18 years who were current cigarette smokers, overall and by sex during 1965–2017, based on data from the National Health Interview Survey. (Reprinted from Wang et al. [40])

The health impact of smoking is not isolated to the smokers. Nonsmokers exposed to environmental tobacco smoke face increases in chronic disease risk [14]. The association of smoking and increased mortality and morbidity from chronic diseases in smokers and those exposed to secondhand smoke has led to widespread calls for prevention of tobacco uptake by teens, cessation among adult smokers, and a regulation of smoking in public places. This chapter discusses the scientific evidence relating tobacco smoking and ENDS use to cardiovascular risks, trends in use, and strategies for prevention and cessation.

2 Smoking and Cardiovascular Disease

Over the past six decades, extensive research links cigarette smoking to major cardiovascular diseases including myocardial infarction, sudden death, stroke, and peripheral vascular disease [15, 16]. Smoking cessation has been shown to reduce these disease outcomes. These associations are observed in all age, gender, and ethnic groups.

In 1962, epidemiologic studies in Framingham, Massachusetts, and Albany, New York, found an association between coronary heart disease and smoking among men [17]. These same findings were later confirmed among women and those with other cardiovascular diseases [17].

Data from the Multiple Risk Factor Intervention Trial (MRFIT) of 316,099 men found a graded relationship between the number of daily cigarettes and relative risk of coronary heart disease death. The relative risk for 1–25 cigarettes per day was 2.1 and rose to 2.9 for cigarette consumption above 25 cigarettes per day [18]. MRFIT and other studies demonstrated that quitting smoking reduces incident cardiovascular disease morbidity and mortality [17, 19]. The interaction of cigarette smoking with other known risk factors is well-studied. Some suggest that the effect is addictive, whereas others find a multiplicative effect. Regardless, cigarette smoking adds to an individual's cardiovascular risk with hyperlipidemia, obesity, diabetes, hypertension, oral contraceptive use, and electrocardiogram abnormalities [20–22]. Smokers who continue the habit after acute myocardial infarction have significantly higher rates of recurrent events and death compared to those who quit [22].

The mechanisms by which smoking affects cardiovascular disease both acutely and chronically are well characterized through laboratory and human experiments. Nicotine has many pharmacologic effects including sympathetic stimulation and coronary vasoconstriction. Inhaled carbon monoxide from burning tobacco decreases oxygen availability in the blood. Other gases in smoke lead to increases in thrombotic factors including platelet activation. Many of these same effects may be found in ENDS inhalants but there is limited research to date [7–9]. Finally, the wide variety of toxic chemicals found in cigarette smoke lead to enhanced inflammation, endothelial dysfunction, and a prothrombotic state [23, 24].

3 Secondhand Smoke

In recent years there has been an increased focus on the harmful effects of smoke on nonsmoking individuals who are exposed by being around smokers. This growing body of information is summarized in the 2006 Surgeon General's Report, *The Health Consequences of Involuntary Exposure to Tobacco Smoke* [14]. These data find that cardiovascular diseases are increased by environmental tobacco smoke as are cancer and respiratory diseases. A meta-analysis of home-based and worksite studies found an overall increase risk of cardiovascular diseases associated with environmental smoke (RR = 1.49, 95% CI, 1.29–1.72) and suggested relative risk from workplace exposure was similar to that of home-based exposure [25].

The mechanism by which secondhand smoke affects individuals is still debated, but there is a growing body of available information. Mainstream smoke, inhaled by the smoker, differs from sidestream smoke released directly into the environment [14]. Sidestream smoke may be more toxic. Nonsmokers who are exposed regularly to cigarette smoke develop a number of physiologic changes including lower high-density lipoprotein cholesterol, increased fibrinogen, and platelet abnormalities

[14]. Exposed nonsmokers also have acute effects including endothelial dysfunction and lower exercise tolerance. All of these factors are associated with cardiovascular disease. In addition, there are significant pulmonary effects of secondhand smoke.

4 Trends in Cigarette Smoking

Cigarette smoking became widespread in the USA following World War II. During this era, cigarette smoking was explicitly encouraged. As part of food rations (K-rations) used by the army, each soldier received four cigarettes for each meal equaling twelve cigarettes per day [17]. Women gradually attained equivalency with men in smoking rates. By 1965, smoking was a habit of 42.4% of adults [26]. Since 1965, the prevalence of cigarette smoking has decreased, and more individuals never acquire the habit resulting in a substantial decline in national smoking rates to approximately 14% as reported in 2017 (Fig. 2). In a 2010 survey of current smokers, 69% responded that they had an interest in quitting, and 52% attempted to quit over the past year, while only 6% were successful [27].

5 Prevention and Reduction of Tobacco Use Among Youth

Smoking begins with experimentation in middle school and becomes regular in high school where 23% of students report that they have smoked in the last 1–2 days [4]. Smokers become addicted as they grow older and more liberated from the constraints of home and school. In recent years, ENDS use or vaping has dramatically altered nicotine use among youth and young adults. In 2019, e-cigarette use in the prior 30 days was reported in 27% of high school boys and girls. In middle school, 10% of boys and girls reported e-cigarette use in the last 30 days. At the same time, cigarette use in high school was reported by only 4% of girls and 7% of boys. Among junior high students, 2% reported smoking cigarettes [28] (Fig. 3). This represents a dramatic shift in the sources of nicotine addiction in the last few years. The development of ENDS with a strong and consistent nicotine content plus a wide variety of flavors makes initiation of smoking easier for youth and young adults [12, 13, 29].

There is a large and substantial literature on the reduction of cigarette smoking among youth. Initially described in the 1994 Surgeon General's Report on *Preventing Tobacco Use Among Young People*, new research is summarized in the recent 2012 Surgeon General's Report [4]. The most effective strategy is the utilization of mass media messaging targeted to appeal to youth and presented multiple times over media channels and social venues accessed by this age group [4].

Several regulatory approaches have also been effective. The enactment of increased cigarette prices has been particularly effective at reducing smoking among youth as they are more price sensitive than older groups. These have the effect of

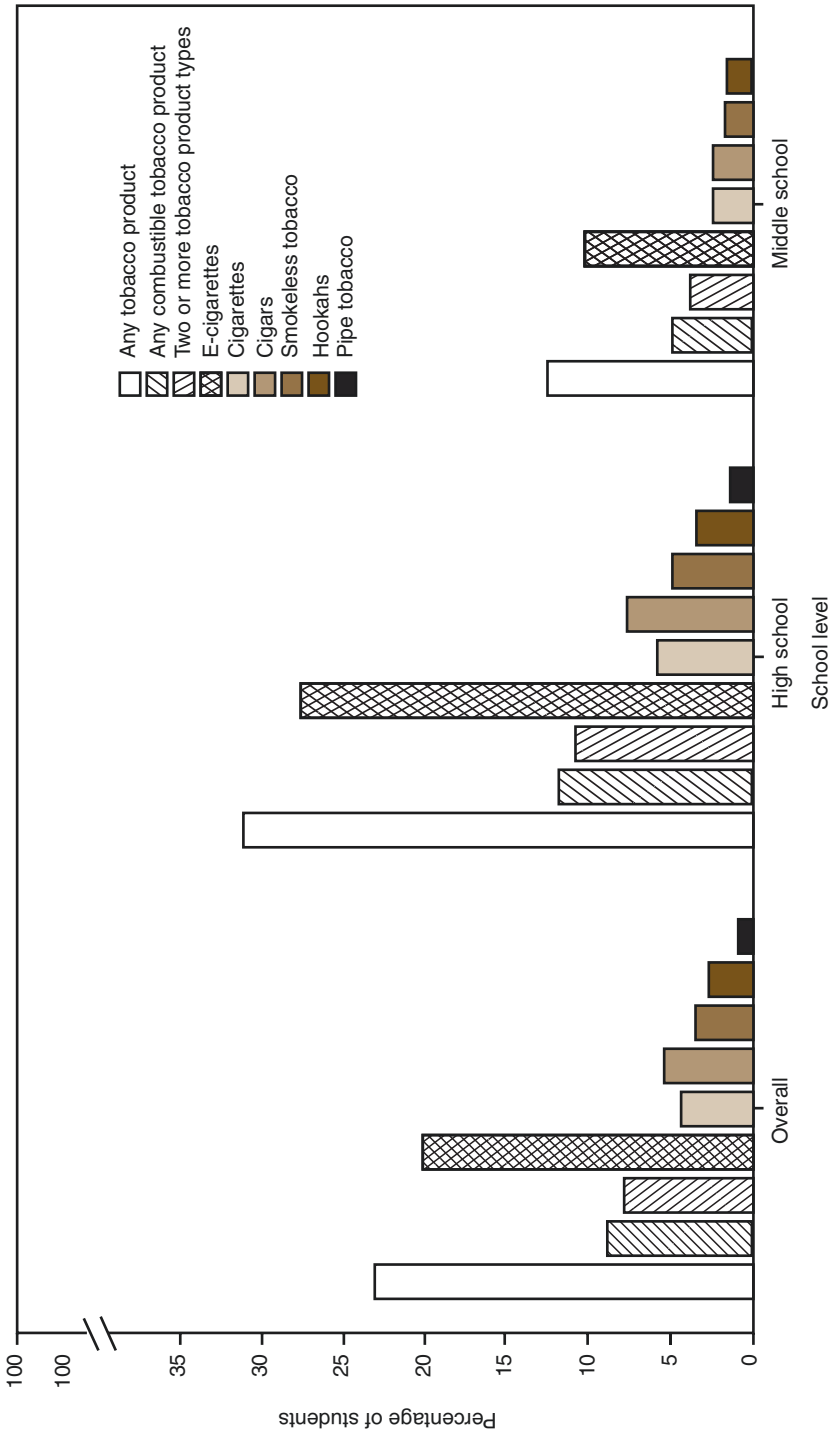
Any tobacco product
Any combustible tobacco product
Two or more tobacco product types
E-cigarettes
Cigarettes
Cigars
Smokeless tobacco
Hookahs
Pipe tobacco
100
100
35
30
25
20
15
10
5
0
Percentage of students
Overall
High school
Middle school
School level

Fig. 3 Percentage of middle and high school students who currently use any tobacco product,[*] any combustible tobacco product,[†] two or more tobacco product types,[§] and selected tobacco products, by school level[¶] and overall – National Youth Tobacco Survey, USA, 2019
Abbreviation: E-cigarettes = electronic cigarettes
*Any tobacco product use was defined as use of e-cigarettes, cigarettes, cigars, hookahs, smokeless tobacco (chewing tobacco, snuff, dip, snus, or dissolvable tobacco products), pipe tobacco, or bidis (small brown cigarettes wrapped in a leaf) on ≥1 day during the past 30 days
[†]Any combustible tobacco product use was defined as use of cigarettes, cigars, hookahs, pipe tobacco, or bidis on ≥1 day during the past 30 days
[§]Defined as use of two or more tobacco products (e-cigarettes, cigarettes, cigars, hookahs, smokeless tobacco, pipe tobacco, or bidis) on ≥1 day during the past 30 days
[¶]On the basis of self-reported grade level among high school students (grades 9–12) and middle school students (grades 6–8), respectively. Current use of pipe tobacco among middle school students is not shown because of unweighted denominator <50 or a relative standard error >30%
Bar chart illustrates the percentage of middle and high school students who currently use any tobacco product, any combustible tobacco product, two or more product types, and selected tobacco products. Percentages are indicated for each school level and overall. Electronic cigarettes (e-cigarettes) were the most common tobacco product type used among middle and high school students and overall. Data were based on the 2019 National Youth Tobacco Survey in the USA. (Reprinted from Wang et al. [28])

both preventing the onset of cigarette smoking and reducing the number of cigarettes smoked. Youth, as well as adults, are also affected by environmental laws restricting the use of tobacco in public places. The limiting of cigarette advertising or outright banning of cigarette advertisement outside of schools has been an important adjunct [4]. Among junior high youth, school-based programs for smoking prevention are also useful as they are found to have short-term effects. Some have resulted in long-term tobacco avoidance [4]. The combination of mass media outreach, regulations restricting public smoking, and prevention programs in schools has been effective at reducing cigarette smoking among youth as shown by the steadily declining patterns of cigarette use in this age group [26]. However, public health officials are now scrambling to deal with the vaping epidemic. Vaping may not respond to these previously successful campaigns against tobacco.

6 Prevention and Cessation Programs for Adults

There has been an overall decline in the prevalence of cigarette smoking in adults; however, this trend has not translated to the young adult demographic. Young adults between the ages of 18 and 25 are among the fastest growing group of smokers and vapers [26, 30]. For this group, many of whom have not yet started smoking, university-based programs are rare, although some have made initial attempts [4]. Health policy and community-based programs are likely to have a more important role in preventing smoking among 18–25-year-old young adults. Sensitivity to tobacco prices, limitations on sites available for public smoking, and other environmental approaches may be very helpful in reducing the prevalence of smoking. For example, over 700 university campuses have banned smoking anywhere on campus. However, many do not yet have vaping policies.

7 Cessation Strategies for Individuals

7.1 Behavioral Treatments

Despite the addictive properties of nicotine, behavioral approaches to smoking cessation are still critical tools. The successful programs, including those utilizing nicotine replacement or other medications, are most successful when they have behavioral treatment components. A number of specific behavioral components include aversive smoking, intra-treatment social support, problem-solving/skills training, setting a quit date, extra treatment social support, weight control, nutrition, exercise, contingency contacts, relaxation techniques, and cigarette fading. Many of these individual treatments are not effective when used alone; however, they serve in combination with other approaches. Help programs include the Centers for Disease Control and Prevention (CDC) “How to quit smoking” (http://www.cdc.

gov/tobacco/campaign/tips/quit-smoking/) and many other programs run by the American Cancer Society (https://www.cancer.org/latest-news/how-to-quit-smoking.html), American Heart Association (https://www.heart.org/en/healthy-living/healthy-lifestyle/quit-smoking-tobacco), and health departments.

7.2 Pharmacologic Interventions

There are social cues and triggers to cigarette smoking for all smokers, which can be confronted by behavioral programs. For the chronic smoker, however, nicotine addiction is the common denominator [31]. A number of pharmacologic products have been recognized as effective for cessation by the Food and Drug Administration (FDA) and approved for use. Most of the aids involve some form of nicotine replacement: nicotine gum, nicotine inhaler, nicotine lozenge, nicotine nasal spray, and the nicotine patch. Each of these products has advantages and disadvantages, but all have the potential to result in a new dependence by some smokers.

The nicotine patch is easy to use and needs to be applied once each day. However, it does not allow flexible dosing once it is placed on the skin and delivery of nicotine is relatively slow. Nicotine gum allows more flexible dosing but can be more difficult to use correctly. Many gum users do not adequately dose with this medication. Nicotine nasal spray has the advantage of flexible dosing in addition to providing faster delivery of nicotine. For many users, eye and nose irritation has been a problem as is the frequent usage needed to build adequate nicotine levels. A nicotine inhaler allows more flexible dosing and mimics the hand to mouth behavior of smoking. The inhaler also has fewer side effects. The nicotine lozenge is convenient and allows flexible dosing. Nicotine replacement therapy has been found to be effective in randomized trials [32].

ENDS, while promoted as a nicotine replacement method to quit cigarettes, is not FDA approved for cessation. There are also a growing number of deaths due to lung injury attributable to vaping [33].

Bupropion hydrochloride (trade name: Zyban) is approved by the FDA for smoking cessation and is available in tablet form. It appears to act on brain chemistry to mimic the effects of nicotine among smokers although its actions are not fully understood. There is evidence to suggest that a combination of a nicotine patch and bupropion may be more effective than either alone [34]. Bupropion has been available for many years as an antidepressant but works well in smokers without symptoms of depression. It has all the potential side effects of antidepressants including suicidal ideation, depression, anxiety, panic attacks, insomnia, and irritability, and seizures are a particular problem with doses above 300 mg/day. Monitoring for these symptoms is recommended along with social support for cessation.

There are several nicotine receptor partial agonists for smoking cessation. These stimulate nicotine receptors more weakly than nicotine itself but help reduce the craving. Only one is approved by the FDA in the USA: varenicline (trade name: Chantix). It is a pill and is available only through prescription. Varenicline should

not be used with other quit smoking products. Common side effects include nausea and insomnia but serious behavioral side effects are also observed. Varenicline received a black box warning in 2009 because of behavioral side effects including agitation, depression, and suicidal ideation [35]. There is also some early evidence of increased cardiovascular disease risk but these observations are not yet confirmed [36].

Cytisine is a plant-based alkaloid with a high binding affinity to the nicotinic acetylcholine receptor. It is widely used in Central and Eastern Europe. Recent clinical trials tested cytisine and found it effective compared to placebo [37]. However, cytisine has not yet been FDA approved for use in the USA as of this writing.

7.3 Clinical Approaches

Clinicians have multiple opportunities to help their patients quit smoking. The first is in the hospital where smoking cessation is obligatory and there is an opportunity to maintain that behavior after discharge. The individual's acute illness, such as cardiovascular disease, may provide a unique opportunity to encourage and maintain cessation. A Cochrane review on interventions for smoking cessation in hospitalized patients made a number of important observations [38]. High-intensity behavioral interventions such as individual counseling, self-help materials, and group therapy beginning during a hospital stay and continuing at least one month after discharge were successful in smoking cessation. They found no effect for interventions of lower intensity or shorter duration (e.g., brief advice). It was also observed that the addition of nicotine replacement therapy significantly increased cessation rates over counseling alone. They found no data to suggest that the addition of bupropion or varenicline to intensive counseling increased cessation rates over what was achieved by counseling alone [38].

Although most quitting smokers are observed to quit "on their own," there are numerous opportunities in the outpatient clinical setting to advance smoking cessation. An overall strategy is outlined in Table 1. Clinicians have a far greater ability to actualize smoking cessation than most believe. Five hints for smoking cessation counseling by physicians are shown in Table 2. The amount of time required to do this is minimal and the potential for change is great [39].

8 Conclusions

Evidence linking tobacco use to cardiovascular disease causation is indisputable. Approximately a half million deaths annually are attributed to cigarette smoking in the USA. The economic burden from medical expenses and indirect costs are enormous, but the human cost in suffering exceeds these. The advent of ENDS or

Table 1 Smoking cessation clinical guideline recommendations for adults

1. Nicotine dependence is a chronic disease that often requires repeated intervention and multiple attempts to quit. Effective treatments exist, however, that can significantly increase rates of long-term abstinence
2. It is essential that clinicians and healthcare delivery systems consistently identify and document tobacco and/or ENDS use status and treat every user seen in a healthcare setting
3. Nicotine dependence treatments are effective across a broad range of populations. Clinicians should encourage every patient willing to make a quit attempt to use the counseling treatments and medication recommended
4. Brief dependence treatment is effective. Clinicians should offer every patient who uses tobacco at least the brief treatments shown to be effective
5. Individual, group, and telephone counseling are effective, and their effectiveness increases with treatment intensity and duration. Two components of counseling are especially effective, and clinicians should use these when counseling patients making a quit attempt: (a) Practical counseling (problem-solving/skills training) (b) Social support delivered as part of treatment
6. Numerous effective medications are available for tobacco dependence, and clinicians should encourage their use by all patients attempting to quit smoking – except when medically contraindicated or with specific population for which there is insufficient evidence of effectiveness (i.e., pregnant women, smokeless tobacco users, light smokers, and adolescents): (a) Seven first-line medications (five nicotine and two non-nicotine) reliably increase long-term smoking abstinence rates: (i) Bupropion SR (ii) Nicotine gum (iii) Nicotine inhaler (iv) Nicotine lozenge (v) Nicotine nasal spray (vi) Nicotine patch (vii) Varenicline (b) Clinicians also should consider the use of certain combinations of medications identified as effective
7. Counseling and medication are effective when used by themselves for treating tobacco dependence. The combination of counseling and medication, however, is more effective than either alone. Thus, clinicians should encourage all individuals making a quit attempt to use both counseling and medication
8. Telephone quitline counseling is effective with diverse populations and has broad reach. Therefore, clinicians and healthcare delivery systems should both ensure patient access to quitlines and promote quitline use
9. If a tobacco user currently is unwilling to make a quit attempt, clinicians should use the motivational treatments shown in the guideline to be effective in increasing future quit attempts
10. Nicotine dependence treatments are both clinically effective and highly cost-effective relative to interventions for other clinical disorders. Providing coverage for these treatments increases quit rates. Insurers and purchasers should ensure that all insurance plans include the counseling and medication identified as effective as covered benefits

Table 2 Counseling: 5A's

Ask: Systematically identify all users at every visit
Advise: Strongly urge all smokers to quit
Attempt: Identify smokers willing to try and quit
Assist: Aid the patient in quitting
Arrange: Schedule follow-up contact

vaping adds to the burden by "hooking" youth and young adults on nicotine and leading to regular tobacco use. Environmental smoke is also an important cause responsible for up to 40,000 innocent deaths from heart disease annually. For adults, behavioral treatments, self-help approaches, and pharmacologic therapy are readily available.

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Alcohol and Cardiovascular Diseases

H. Nicole Tran and Arthur L. Klatsky

Summary

- Due to environmental and genetic factors, there is marked individual variation in susceptibility to health effects of drinking alcohol.
- Heavy drinking is associated with CV and non-CV risks; CV risks include dilated cardiomyopathy, systemic HTN, hemorrhagic stroke, and supraventricular arrhythmias.
- Light-moderate drinking is associated with lower risk of CAD and ischemic stroke.
- Studies of relationships of drinking alcohol to risk of disease endpoints are observational, leaving open the possibility of residual confounding.
- Important potential confounders of alcohol effects include smoking and other lifestyle traits, previous changes in drinking, drinking pattern, and underreporting.
- Underreporting of amount of alcohol intake spuriously makes the threshold for harm appear lower.
- The major factor in drinking and CV relationships is probably ethyl alcohol, while apparent differences between wine, liquor, and beer are mostly due to confounding.
- All heavy alcohol drinkers (>2 drinks per day for men; >1 drink per day for women) should reduce or quit drinking; advice for others needs to be individualized.

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> It is true that many were greatly injured by intoxicating drink, but none seemed to think the injury rose from the use of a bad thing, but from the abuse of a good thing.
>
> Abraham Lincoln: Feb 22, 1842 – (Washington County Temperance Society, Springfield IL)

Because he disliked the diminished mental acuity it produced, Abraham Lincoln drank little alcohol. However, our great poet-President elegantly described in one sentence the basic disparity between effects of lighter and heavier drinking. Multiple medical and social harms from heavy drinking have been evident for millennia. Alcoholic beverages were considered a "good thing" because of the sensory pleasure and social lubrication they provided. While it was widely believed that there was a "safe" or "sensible" limit, scientific evidence for possible medical benefit of lighter drinking did not appear until the twentieth century.

We use an operational definition of "light-moderate" and "heavy" drinking based upon the level of drinking in several epidemiologic studies above which net harm is usually seen. It corresponds to the widely accepted US Agriculture Department definition. The imprecise term "drink" is used, since most persons think in terms of "drinks," not grams of alcohol. For men less than three drinks per day is called "light" or "moderate" drinking, and three or more drinks per day is called "heavy" drinking. For women the definition of heavy drinking is an average of two drinks per day. The lower amount for women is related to lower average size, greater average body fat proportion, and lower metabolism of alcohol in the gastric mucosa. The amount of alcohol is approximately the same in the usual "standard" drink of wine, liquor, or beer. Thus, a 4-ounce glass of table wine at 13% alcohol, 1 ¼ ounces of distilled spirits at 40% alcohol, and 12 ounces of US beer at 5% alcohol all contain about 12.5–15 ml of pure ethyl alcohol.

The disparate relations of alcohol drinking to various cardiovascular (CV) conditions make it wise to consider preventive aspects for several disorders separately [1]. This chapter will briefly discuss alcoholic cardiomyopathy, systemic hypertension (HTN), arrhythmias, stroke, and atherothrombotic disease – with emphasis on coronary artery disease (CAD) (see also Tables 1 and 2). Controversies exist about interpretation of observational epidemiological data showing benefit of light-moderate alcohol intake. Randomized controlled trials (RCT) of such drinking with disease endpoints are absent. For these reasons we discuss epidemiological principles when they are appropriate to the condition under consideration. We try to deal with the need for sound objective advice about drinking alcohol.

1 Alcoholic Cardiomyopathy

"Cardiomyopathy" is variously defined but here means heart muscle disease not due to disorders of the valves, coronary arteries, lungs, or pericardium. Sustained heavy alcohol drinking is among the causes of "dilated cardiomyopathy," characterized by an enlarged heart with lowered ejection fraction. The condition has been recognized for more than 100 years [2], but with understanding clouded by the lack of specific

Table 1 Possible mechanisms for CAD protection by alcohol

Mechanism of alcohol effect	Action and comment	Strength of evidence[a]
Raises high-density lipoprotein (HDL) cholesterol	"Reverse" LDL cholesterol transport from blood vessel wall; a long-term effect; also a possible antioxidant	Very good in observational data for about 50% of alcohol effect; benefit unconfirmed in studies of HDL-raising drugs
Lowers fibrinogen, thromboxane A, and platelet stickiness; increases prostacyclin and endogenous tissue plasminogen activator	Decreased clot formation in atherosclerotic blood vessels (a key factor in CAD events); a short-term action	Good
Lowers risk of type 2 diabetes mellitus	Possibly by reducing insulin resistance Diabetes a major CAD risk trait	Good
Less LDL oxidation in blood vessel walls	Presumably mostly a nonalcohol effect; antioxidants plentiful in red wine, moderate in dark beer	Weak to moderate
Decreased psychosocial stress	Stress a possible CAD risk factor	Weak

CAD coronary artery disease, *LDL* low-density lipoprotein cholesterol, *HDL* high-density lipoprotein cholesterol
[a]Authors' judgment

Table 2 Alcohol in preventive cardiology

Condition	Probable relationship of alcohol*		Comments
	Lighter drinking*	Heavier drinking*	
Dilated cardiomyopathy	Unrelated	One (of several) causes	Unrelated to moderate drinking
Systemic HTN	Little or none	Probably causal in some	Mechanism unknown
CAD	Protective	? Less protective or increased risk	Drinking pattern important; ? Additional benefit from wine phenolics
Supraventricular arrhythmia	? None	Probably a causal factor, especially binges	Mechanism unclear
Hemorrhagic stroke	? Unrelated or slightly increased risk	Increased risk	Via higher BP, antithrombotic actions
Ischemic stroke	Protective	Unclear; varies with subtype	Complex interactions with other conditions

*See text for definitions: *HTN* hypertension, *CAD* coronary artery disease
*Authors' judgment

diagnostic criteria and confusion with cardiovascular beriberi from thiamine deficiency. Solid circumstantial evidence suggests existence of direct toxicity of alcohol upon myocardial cells [2–4]. Most convincing are human and animal data showing nonspecific functional and structural abnormalities in some heavy drinkers. Subclinical abnormalities may precede evident illness for years: The proportion of heavy drinkers with cardiomyopathy is less than the 15–20% that develops liver cirrhosis. Some improve with abstinence or reduced intake [4].

While a molecular mechanism for alcoholic cardiomyopathy remains unclear, one possibility is suggested by a nonoxidative metabolic pathway for alcohol related to fatty acid metabolism in the heart, muscle, pancreas, and brain [5]. Accumulated fatty acid ethyl esters are toxic to myocardial cells, and these compounds are used as markers of chronic alcohol abuse. Recent investigations support evidence that heavy drinking damages mitochondrial function, the power source of muscle cells [6, 7].

An important issue is whether moderate drinking impairs myocardial function. A landmark study [3] in alcoholics showed a clear relation of lifetime alcohol consumption to structural and functional myocardial and skeletal muscle abnormalities. The threshold for heart and skeletal muscle damage was high – equivalent to 120 g alcohol/day for 20 years. It seems clear that this condition is unlikely to result from light-moderate drinking (see related discussion of section "Heart Failure (HF): It Depends on the Cause" below).

2 Hypertension: A Threshold Issue

A link between heavy alcohol intake and systemic HTN is established by cross-sectional and prospective analyses in diverse populations [8, 9]. Support for a causal relationship is evidenced by intervention trials and Mendelian randomization analyses [8, 9]. The evidence is sufficient to state that heavy alcohol drinking is a probable HTN risk factor. However, the threshold for harm is unclear [8–12].

A 1977 Kaiser Permanente (KP) study [10] showed the presence of the alcohol-blood pressure relationship for systolic and diastolic pressure in men and women of three racial groups. Later KP work suggested that ex-drinkers had blood pressures similar to nondrinkers and that elevated pressures regressed within a week upon abstinence [11]. In these observational cross-sectional studies, HTN prevalence was approximately doubled among the heaviest (≥6 drinks daily) drinkers, compared to abstainers or light drinkers. Other investigators reported experiments in hospitalized and nonhospitalized hypertensives and normotensives showed that 3–4 days of taking several drinks and of abstinence raised and lowered BPs [8, 9]. A follow-up KP analysis [12] showed that incidence of adverse sequelae of HTN was similar in alcohol abstainers, light drinkers, and heavy drinkers.

A clear mechanism has not been established. Most likely, the etiology of alcohol-related HTN is multifactorial, possibly including effects on the autonomic nervous system, renin-angiotensin axis, and increased vascular smooth muscle reactivity, as

well as direct endothelial effects, oxidative stress, and inflammatory response [8]. The relationship appears independent from lifestyle or socioeconomic factors such as adiposity, salt intake, education, cigarette smoking, and several other potential indirect explanations [8, 9, 11]. Alcoholic beverage type (wine, liquor, or beer) is not a major factor [8, 9, 11].

Implications for advising patients at risk of CV disease remain an area of contention as light-to-moderate alcohol consumption has been associated with beneficial outcomes for several cardiovascular risk factors and conditions [4, 8]. For example, favorable effects of possible increase in high-density lipoprotein cholesterol (HDL-C) may outweigh adverse consequences of alcohol effects on blood pressure. Studies of all-cause mortality, a global measure of health, show net benefit of alcohol at lower intake levels. Figure 1 shows the all-cause mortality J-curve in all persons with and without full covariate adjustment; full adjustment increases apparent benefit, mostly due to adjusting for smoking. Figure 1 also shows risk of death attributed to CV and to non-CV causes, with benefit concentrated in CV causes.

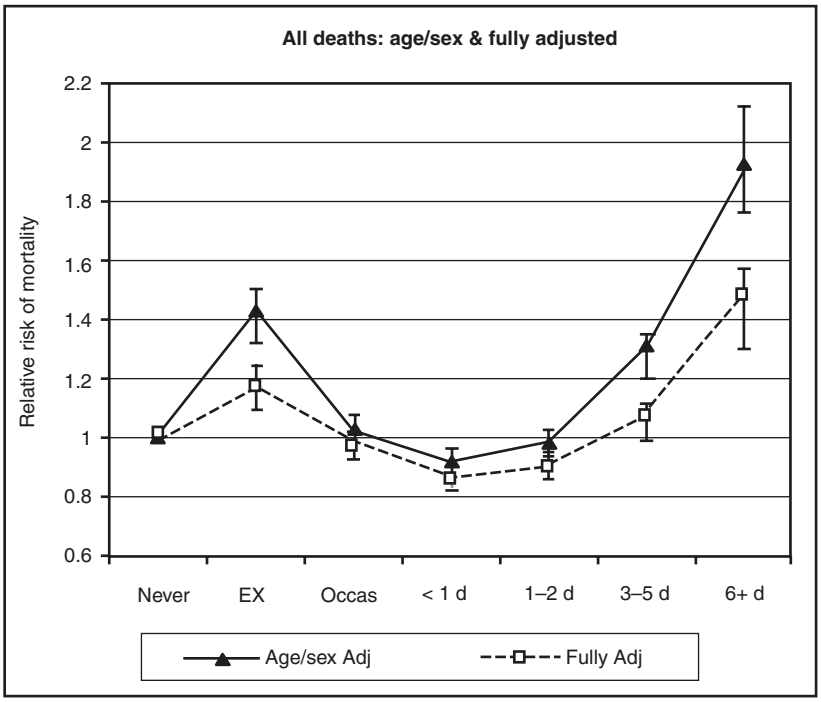
Since both HTN and light-moderate drinking are common, definition of the level of drinking at which increased risk of HTN occurs is very important. Relevant to the threshold issue is a report [13] suggesting that underreporting of heavier alcohol intake is a major factor in the apparent risk of light-moderate drinkers for HTN or all-cause mortality (see Fig. 2). Underreporting of alcohol intake spuriously places some heavier drinkers in light-moderate categories. If there is an underlying threshold relationship, this misclassification spuriously lowers the threshold for apparent harm or produces a spurious continuous relationship. If the true relationship is a J-curve, this misclassification reduces or eliminates the apparent benefit at light-moderate drinkers.

Estimates of the proportion of HTN due to heavy drinking depend substantially upon the drinking habits of the group under study [12]. Even the lowest estimates of attributable risk of 5–7% translate into millions of persons with alcohol-associated HTN in Europe or the USA.

The preponderance of evidence does not favor an adverse effect from light-moderate drinking. While obtaining an alcohol history in the setting of HTN resistant to treatment is standard in most guidelines, low screening and intervention rates have been reported and can have major public health implications for patients with HTN [8, 14, 15]. Heavier alcohol intake can interfere with drug treatment of HTN. Moderation of heavy intake supplements other nonpharmacologic interventions for blood pressure lowering, such as weight reduction, exercise, or sodium restriction [9, 15].

3 Supraventricular Arrhythmias

Alcohol consumption has been associated with supraventricular arrhythmias in several epidemiologic studies. In 1978, Ettinger et al. [16] described an acute disturbance in cardiac rhythm in healthy people after an episode of heavy drinking often


All deaths: age/sex & fully adjusted
Relative risk of mortality
2.2
2
1.8
1.6
1.4
1.2
1
0.8
0.6
Never
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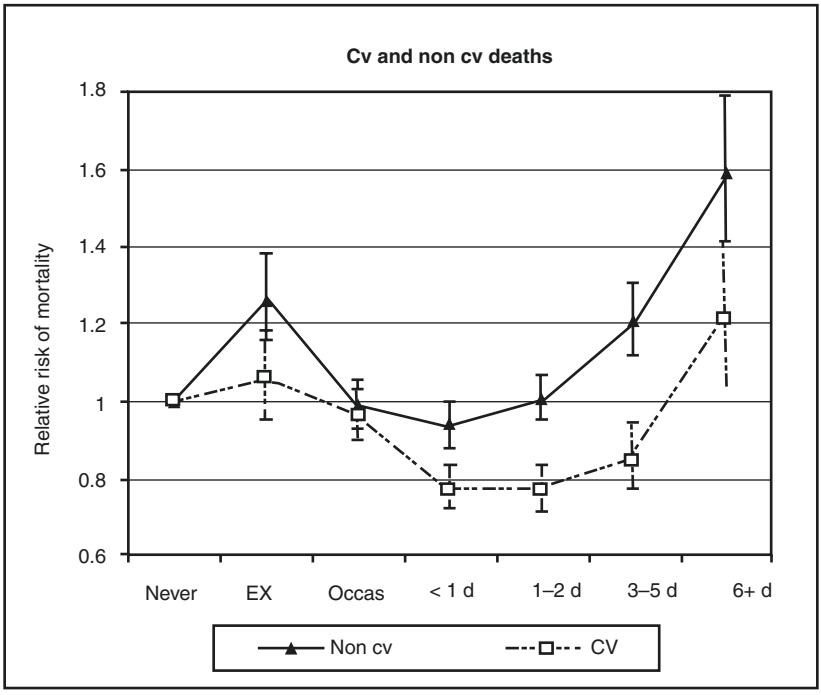
< 1 d
1–2 d
3–5 d
6+ d
Age/sex Adj
Fully Adj


Cv and non cv deaths
Relative risk of mortality
1.8
1.6
1.4
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1
0.8
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Never
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< 1 d
1–2 d
3–5 d
6+ d
Non cv
CV

Fig. 1 All-cause mortality (n = deaths = 21,535 through 2002)* in relation to baseline alcohol intake in 1978–1985 among 128,934 persons. Intake categorized as never, ex-drinkers, occasional (<1 drink/month), or <1, 1–2, 3–5, or ≥6 drinks per day. Fully adjusted Cox proportional hazard models with never drinkers as referent for alcohol categories include age, sex, race, smoking, education, and BMI. Upper panel shows comparison of fully adjusted model in all persons with age-/sex-adjusted model; adjustment does not decrease the apparent protection by light drinking. Lower panel shows models for deaths attributed to cardiovascular (CV) causes and deaths attributed to non-CV causes; apparent benefit of light-moderate drinking is concentrated in CV deaths. (*See Ref. [12] for more detailed description of the baseline cohort)

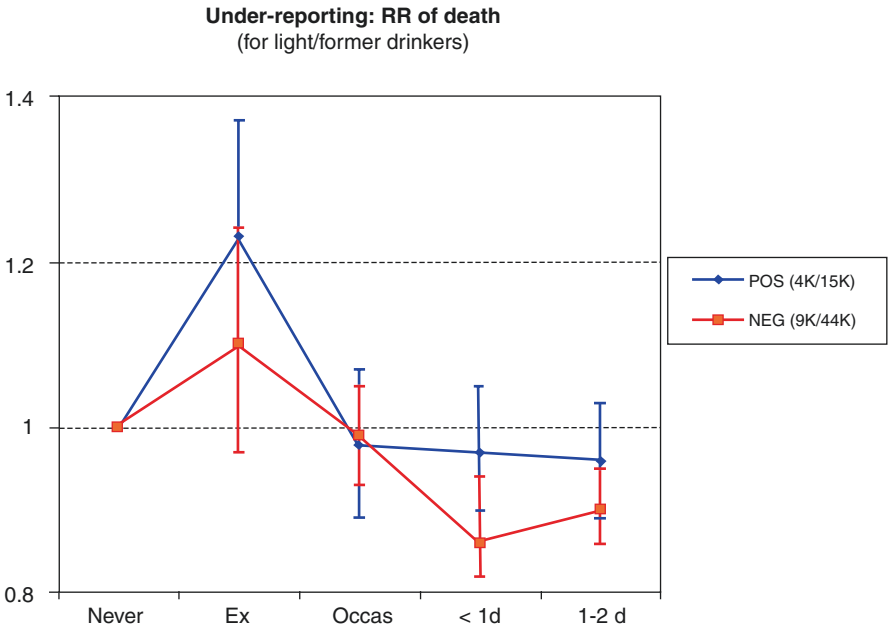

Fig. 2 RR (relative risk) of all-cause mortality (n deaths = 13,478) through 2002 in relation to baseline alcohol intake among 105,378 White or Black men and women with ≥2 examinations that reported light-moderate drinking (<1 or 1–2 drinks per day) in 1978–1985. Inferential risk of underreporting categorized as positive or negative according to all available computerized data. Subjects were positive if they received any alcohol-related diagnosis or ever reported heavy intake. Logistic regression models with never drinkers as referent were controlled for age, sex, race, smoking, education, and BMI. Numbers in parentheses show deaths and subjects in thousands in the models. (For more detail about methodology, see Refs. [13, 55])

during the Christmas or New Year holidays known as "Holiday Heart." This common presentation to the emergency room occurs in persons without evidence of organic heart disease after an episode of binge drinking often with a large meal. Spontaneous conversion is the rule and direct external DC shock or chemical conversions are rarely needed. The rhythm that occurs is commonly atrial fibrillation, though other supraventricular tachycardias like atrial flutter, paroxysmal atrial tachycardia, and isolated ventricular premature beats may occur. Characteristically there is a lack of new episodes with abstinence and recurrence with continued abuse. Suggested mechanisms include cellular damage of gap junctions and myocytes, inflammatory and oxidative stress, sympathetic nervous system activation causing vagal inhibition, and reduced heart rate variability [17]. These could lead to left atrial enlargement and contribute hypertension, obesity, and sleep-disordered breathing [17, 18]. In patients with atrial fibrillation, a dose-dependent relationship with left atrial size and impairment of emptying fraction has been reported for regular alcohol consumption of 15.8 drinks per week compared to nondrinkers [17]. Whether light-to-moderate alcohol consumption may be associated with atrial fibrillation has been controversial [19, 20]. A recent study [20] of moderate alcohol consumption (one to four drinks/day) found a lower risk of heart failure but no association with new-onset atrial fibrillation. The link between heavy alcohol consumption and binge drinking and atrial fibrillation, however, has been well established [21, 22]. Regular high alcohol intake in atrial fibrillation has been found to be a predictor of thromboembolism or death [23], and reduction of such has been shown to lead to less recurrence of atrial fibrillation [24]. Counseling should be individualized to recommend reduction of heavy drinking and avoidance of binge drinking for prevention of supraventricular arrhythmias.

4 Atherosclerotic Coronary Disease: Protection by Alcohol

4.1 Epidemiology: A J-Curve Relationship

Mortality and morbidity statistics that assess all CV conditions are often presented, but it should be kept in mind that CV and CAD are not synonymous. Because CAD is by far the commonest CV condition, it dominates such data. Age, gender, and ethnicity are important with regard to CAD risk. Established environmental risk factors discussed elsewhere in this volume include smoking, HTN, diabetes mellitus, elevated blood levels of low-density lipoprotein cholesterol (LDL-C) and triglycerides, reduced HDL-C, and several pro-thrombotic traits.

The common clinical expressions of CAD are stable and unstable angina, myocardial infarction (MI), and sudden death from cardiac arrest. Relief of angina by alcohol was noted in 1786 in Heberden's classic description [2]. This led to an incorrect assumption that alcohol is a coronary vasodilator. Alcohol's apparent benefit for angina is more likely an anesthetic effect [5]. As the subjective CAD

symptom, angina pectoris, is difficult to quantify and study, MI and death have more often been the endpoints examined.

Observational epidemiologic studies in populations susceptible to CAD have consistently shown less risk of MI and CAD death in moderate drinkers compared to abstainers [4, 25, 26]. With lifelong abstainers as referent, many analyses have shown a U-curve or J-curve association between increasing alcohol intake and CAD. In the absence of long-term randomized controlled trials of CAD event outcomes, observational studies provide the best available data. Other evidence supporting alcohol's CAD benefit includes international comparisons, case-control studies, prospective short-term studies of several CAD risk traits, and analyses of coronary arteriograms. In most studies, the alcohol-CAD relation is nonlinear with heavy drinkers showing higher risk than light drinkers. Possible explanations for the nonlinearity include more binging, more HTN, elevated triglyceride levels, and misdiagnosis of cardiomyopathy as CAD in some heavy drinkers.

Some have questioned the observational data showing an alcohol-CAD association on methodological grounds. One issue often raised is that several early analyses grouped together lifelong abstainers and ex-drinkers. A spurious impression of benefit from light-moderate drinking might ensue if the nondrinking referent group included "sick quitters" with increased CAD risk. Another issue often brought up is that some studies inadequately controlled for baseline CAD. These issues are refuted by the findings from cohort studies with separate categories for ex-drinkers and lifelong abstainers as well as by analyses controlling for baseline CAD [4, 25, 27–29]. See the discussion of causality below with respect to alcohol and CAD.

4.2 Plausible Mechanisms for Lower CAD Risk in Drinkers

Reviews of multiple plausible mechanisms for CAD protection have been published [4, 29–34] (Table 1). A link via HDL-C is well established. Except in individuals with severe liver disease, alcohol ingestion raises HDL-C levels by poorly understood mechanisms. Inverse relationships between HDL-C level and CAD risk probably result from removal of lipid deposits in large arteries plus assisting the prevention of tissue oxidation of LDL cholesterol. Findings suggest that approximately half of the lower CAD risk in drinkers is mediated by higher HDL-C levels [4, 29] and that major HDL subfractions, known as HDL2 and HDL3, are both involved [35]. The failure of HDL-raising medications to have a beneficial effect and more sophisticated characterization of HDL subfractions [36] have raised questions about a simplistic interpretation [37]. Nevertheless, the HDL link remains the best established mechanism to explain the beneficial effect of alcohol on CAD.

Triglycerides are now believed to play an independent role in CAD risk. An alcohol association via triglycerides could be unfavorable because some heavy drinkers have substantially increased blood triglyceride levels. However, light-moderate drinking seldom causes increased triglyceride levels.

Antithrombotic actions of alcohol include inhibition of platelet stickiness and lower fibrinogen levels [29–31]. As thrombosis in atherosclerotic arteries plays a key role in major CAD events, these effects may be important factors in the protective effect of alcohol.

Overeating and physical inactivity are important underlying factors in the current worldwide epidemic of obesity and diabetes mellitus. Heavy alcohol drinking has been linked to higher blood glucose levels and reduced compliance to diabetes management [38, 39]; light-moderate drinking is associated with lower diabetes risk and favorable effects on insulin-glucose metabolism [40]. A meta-analysis of 15 prospective studies [40] demonstrated a U-shaped curve for the association between alcohol intake and type 2 diabetes risk. At one to two drinks per day, there was a 30–40% lower risk compared with abstainers. Since diabetes is a powerful predictor of CAD, this alcohol-diabetes relationship may be an important intermediary.

4.3 Genetic Polymorphism Data

Genetic variants affecting alcohol metabolism theoretically comprise a form of "natural" randomized controlled trial. Evidence suggested that individuals with an alcohol dehydrogenase polymorphism (ADH1C) resulting in "slow metabolism" of alcohol may obtain more CAD benefit [4, 29, 41], thus supporting a causal relationship for the protective effect of light-moderate drinking on CAD. However, subsequent Mendelian randomization analyses have yielded conflicting conclusions [4].

5 Drinking Pattern: A Crucial Factor

Binge drinking is clearly harmful. Other drinking pattern aspects of interest are frequency of drinking (number of days per week), variability over time, and whether the alcohol is taken with food. Reports suggest that drinking at mealtimes is more favorable for CAD and HTN and that frequency of intake may be a strong factor [4].

6 Beverage Choice: Wine, Liquor, or Beer?

The "French paradox" concept refers to the fact that the French, especially in Southern France, have a relatively low incidence of CAD mortality despite an abundance of established CAD risk traits. France is an outlier on graphs of mean dietary fat intake vs. CAD mortality, unless adjusted for wine intake [42], leading to the idea that CAD benefit is largely limited to red wine. The hypothesis that red wine has protective benefit additional to that of alcohol is indirectly supported by the presence of nonalcoholic antioxidant phenolic compounds with antioxidant and

antithrombotic properties in wine, especially red wine [29, 43, 44]. There are several classes of these compounds in grapes and other fruits and vegetables with hypothetical effects that might promote endothelial health, including catechins, quercetin, and resveratrol. These are active in vitro and in animal studies to produce beneficial effects on established biological markers of vascular disease. Effects in humans in vivo are less established, and there are issues related to bioavailability because of limited absorption from the gastrointestinal tract. Resveratrol, in particular, is poorly absorbed, so huge doses would be required for human effects comparable to those reported in other species, quite incompatible with those obtainable from moderate drinking [45]. Epidemiological data in prospective studies suggest that white wine, red wine, and beer may all be effective in reducing CAD risk [1, 29, 44]. The beverage choice issue is complicated by findings that wine drinkers often have a more favorable CAD risk profile [46]. Drinking pattern differences could also play a role, as wine is more often sipped slowly with meals than beer or liquor.

The "French paradox" has caught the public fancy, but the wine/liquor/beer issue is unresolved at this time. It is our opinion that antioxidation is unlikely to be the primary mechanism involved in CAD protection by alcoholic beverages. It seems more likely that ethyl alcohol is the major factor with respect to lower CAD risk.

7 Alcohol and CAD: Is It Causal?

Potential confounding cannot be completely ruled out in the absence of a randomized controlled trial with CAD outcome data. Skeptics about alcohol's benefit have emphasized possible flaws in methodology that might spuriously produce apparent benefit of moderate drinking. As already mentioned, studies that fail to separate lifelong abstainers from ex-drinkers incur risk of contamination of the nondrinker referent group by inclusion of "sick quitters." Possible confounding by healthy lifestyle habits of moderate drinkers has also been postulated. Although less attention has been given to sources of bias that might reduce apparent benefit, confounding probably acts both ways. For example, residual confounding by smoking, a correlate of alcohol drinking in many populations, would reduce apparent benefit by lighter alcohol drinking. Underreporting by heavy drinkers is another likely source of bias against apparent benefit by moderate intake. By placing some heavy drinkers in lighter categories, underreporting distorts many alcohol-health associations. In the case of CAD, underreporting would lessen the apparent benefit of light drinking.

Evidence that persons with an alcohol dehydrogenase polymorphism resulting in "slow metabolizers" of alcohol [41] may have more CAD benefit promised to offer a form of "natural" randomized controlled trial supporting causal relationship for the protective effect of light- moderate drinking on CAD. However, later evidence [47–49] offered conflicting data. Other aspects supporting a causal hypothesis are consistency in studies, plausible biological explanations, relative specificity of benefit for atherothrombotic vascular disease, and the temporal sequence in prospective studies. The lack of a linear relation is not a major issue, since many alcohol-health

associations are nonlinear. While other factors may play a role, a causal, protective effect of moderate alcohol intake is the simplest and probably correct explanation.

8 Cerebrovascular Disease: The Epidemiologic Labyrinth

Analysis of relationships of alcohol drinking and risk of stroke can readily become mired in the labyrinthine interactions of drinking categorizations, nonlinear associations, disparate cardiovascular conditions, and the heterogeneous types of stroke [50, 51]. Systemic HTN is an important risk factor for all types of stroke and a probable intermediary between heavy drinking and increased stroke risk. Antithrombotic effects of alcohol might increase risk of hemorrhagic stroke, both subarachnoid and intracerebral. The same antithrombotic actions might simultaneously lower risk of several types of ischemic stroke. Blood lipid effects of alcohol (see CAD discussion above) might also favorably affect ischemic risk. The preponderance of evidence at present suggests that drinking has these effects, but the relations of alcohol drinking to various types of stroke remain unresolved [1, 32, 50–52].

9 Heart Failure (HF): It Depends on the Cause

Heart failure (HF) is not an etiological diagnosis but a common nonspecific syndrome, usually late in the course of CV disease. Because of improved survival of CV patients and general increase in population longevity, there has been a substantial increase in HF incidence. Multiple risk factors are the rule, with CAD a factor in a majority. Other common underlying factors include HTN, valvular disease, cardiomyopathies (including alcoholic), rhythm disturbances, and systemic problems such as anemia or infection. While alcoholic cardiomyopathy dominated past thinking about alcohol and HF, it is now evident that the alcohol-HF relationship is dependent upon the causes of the syndrome [26]. Heavy, but not light-moderate, drinkers have increased risk of non-CAD-associated HF, but alcohol drinking is inversely related to risk of CAD-associated HF.

Because alcoholic cardiomyopathy was considered to have the most important role in the relationship between alcohol and HF, by the mid-twentieth century, there was widespread belief that alcohol should be avoided by all patients with heart disease. The disparate relationships between alcohol and CV conditions uncovered more recently have invalidated this belief. Several studies of alcohol and HF risk show that light-moderate drinkers are less likely than abstainers to develop HF [26, 53, 54]. In the Framingham Heart Study [53], moderate alcohol intake was associated with reduced HF risk, and even heavier intake was not associated with increased risk.

We performed separate analyses for HF associated with CAD and HF not associated with CAD [54]. For CAD-associated HF, there was an inverse relation with

both moderate and heavy drinking; for non-CAD-associated HF, heavy drinkers had an increased risk. All available data at this time suggest that there is no reason to prohibit light-moderate alcohol drinking in most individuals with heart disease or at HF risk.

10 Conclusions

Table 2 summarizes the disparate alcohol-CV relations, emphasizing the basic differences between favorable relations of light-moderate drinking and unfavorable relations of heavier drinking. We have already presented data showing overall benefits of light drinking for some men and women (see Figs. 1 and 2), a fact that should play a major role in advising about light-moderate drinking. But this is not the complete picture with respect to advice about health effects of alcohol drinking. Such advice needs to be individualized according to the specific medical history and risks of any concerned person. For example, the increased risk of breast cancer outweighs any cardiovascular benefit from moderate drinking in most women <50 years of age, but in postmenopausal women the cardiovascular benefit for total mortality outweighs the breast cancer risk. Generally, men above the age of 40 who are established light-moderate drinkers should not be advised to abstain. Most nondrinkers have good reasons for abstinence, including religious/moral concerns, personal or family history of alcohol problems, or specific medical concerns, and continued abstinence is wise for these persons.

A few commonsense rules are suggested. (1) The overall health risk of a heavy drinker will be reduced by reduction or abstinence. (2) Because of the unknown risk of progression to heavier drinking and alcohol dependence, abstainers should not indiscriminately be advised to drink for CV health benefit. (3) Middle-aged and older established light-moderate drinkers (the majority in the USA and Western Europe) need no change in drinking habits.

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The 2018 AHA/ACC/Multisociety Cholesterol Guidelines: A Personalized Approach to Risk Reduction

Ewa Dembowski, Scott M. Grundy, and Neil J. Stone

Summary

- Summarizes important updates to previous guidelines on reducing atherosclerotic cardiovascular disease (ASCVD) risk through the management of blood cholesterol
- Describes decision algorithms for patients with both elevated absolute short-term and also lifetime risk as well who belong to a treatment benefit group
- Emphasizes the use of shared decision-making, especially to determine statin use in lower-risk primary prevention
- Utilizes a three-step process to inform a treatment decision to reduce ASCVD in primary prevention:

  1. Calculate lifetime and, if 40–75 years, 10-year risk of ASCVD.
  2. Personalize the risk estimation by considering risk-enhancing factors.
  3. Reclassify risk estimation with a coronary artery calcium score if risk decision uncertain.

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- Emphasizes that in a high-risk category, if no contraindications, statins are first line to lower low-density lipoprotein cholesterol (LDL-C) by 50% or more
- Describes the approach to intermediate risk (7.5–19.9%) where moderate-intensity statins to lower LDL-C 30–49.9% are prescribed in the context of a clinician-patient risk discussion
- Highlights an important decision step in secondary prevention to determine the intensity of LDL-C-lowering treatment by determining if patient belongs to a very-high-risk group
- Utilizes a threshold LDL-C value of 70 mg/dL (1.8 mmol/L) to guide determination of prescribing either ezetimibe or PCSK9 inhibitor added to a statin for further absolute risk reduction
- Describes the focus on specific risk factors for women, ethnic/racial considerations, specific considerations for those older than 75 years, and a section on cost-effectiveness, which are new features of these guidelines

1 Introduction

Epidemiologic and clinical evidence have long supported elevated serum cholesterol as a major risk factor for atherosclerotic cardiovascular disease (ASCVD), which remains a leading cause of death and disability in the USA. Individuals with long-term exposure to even moderately elevated levels of low-density lipoprotein cholesterol (LDL-C) are at increased risk of developing ASCVD. Numerous randomized controlled trials (RCTs) have demonstrated that lowering LDL-C levels results in reduced ASCVD events in both secondary and primary prevention.

In 1985, the National Heart, Lung, and Blood Institute sponsored the National Cholesterol Education Program (NCEP) in order to establish elevated serum cholesterol as a risk factor in ASCVD and to initiate a public health program to lower cholesterol levels in the US population. The NCEP published three sets of Adult Treatment Panel (ATP) reports in 1987, 1993, and 2001 that provided recommendations for cholesterol lowering in primary and secondary prevention. The development of national cholesterol guidelines has since been undertaken by the American College of Cardiology (ACC) and the American Heart Association (AHA), who together with ten other collaborating organizations published its first set of guidelines in 2013 [1]. These guidelines represented a major paradigm shift from prior NCEP guidelines, placing the initial emphasis on ASCVD risk reduction noted in randomized controlled trials (RCTs) rather than targeting LDL-C levels. The cholesterol guidelines continue to recommend evidence-based doses of statins as first-line therapy with initiation based on patient evidence-based risk and the use of additional risk-enhancing factors, as opposed to specific "initiation" LDL-C levels as were used in prior guidelines. In addition, to determine risk in primary prevention, the guidelines introduced a 10-year and lifetime ASCVD risk calculator to guide initiation of statin therapy.

Although initially controversial, the risk reduction approach to lipid management presented in the 2013 guidelines has been supported by subsequent analyses [2–4]. Furthermore, from a public health perspective, implementation of the guidelines appears to have improved the lipid and lipoprotein levels among US adults on lipid-lowering medications [5]. Since 2013, further clinical trial data emerged, particularly in support of non-statin therapies as treatment adjuncts in high-risk groups. In addition, new epidemiological data has expanded the knowledge of ASCVD risk assessment. With this new data, an updated AHA/ACC/Multisociety Cholesterol Guideline was published in 2018 [6].

In this chapter, we discuss the 2018 AHA/ACC/Multisociety[1] Cholesterol Guidelines, highlighting its key recommendations and summarizing the reviewed evidence that led to these recommendations. The "top 10" take-home messages are presented in Table 1, providing a concise overview of the guidelines. A more detailed discussion of the guidelines and special considerations in lipid management follows in subsequent pages. Finally, throughout the review, the contribution of relevant new data beyond the 2018 guidelines is discussed when available.

2 Key Concepts

The 2018 AHA/ACC/Multisociety Cholesterol Guidelines is an update of the 2013 ACC/AHA cholesterol guidelines, incorporating the best available evidence to reduce the risk of atherosclerotic cardiovascular disease (ASCVD) through cholesterol management. Recommendations are based on class or strength of recommendation (COR) and level (or quality) of evidence (LOE). Strength of evidence compares benefit of therapy against risk. In Class I recommendation, benefit greatly exceeds risk; therapy is indicated. With Class IIa evidence, benefit still exceeds risk; therapy is reasonable. With Class IIb, the strength of evidence favoring therapy, compared to risk, is not strong enough for a definitive recommendation. The purpose of the IIb recommendation is to comment on an important therapeutic issue for which the evidence remains uncertain.

2.1 Personalization of Risk Assessment and Treatment Plan

A key concept in preventive cardiology is that the expected magnitude of benefit from prevention therapies is influenced by the baseline risk of the patient. For a similar relative risk reduction from a given intervention, such as LDL-C lowering,

[1] American Association of Cardiovascular and Pulmonary Rehabilitation, American Academy of Physician Assistants, Association of Black Cardiologists, American College of Preventive Medicine, American Diabetes Association, American Geriatrics Society, American Pharmacists Association, American Society for Preventive Cardiology, National Lipid Association, and Preventive Cardiovascular Nurses Association

Table 1 Top 10 take-home messages to reduce risk of atherosclerotic cardiovascular disease through cholesterol management

1. In all individuals, emphasize a *heart-healthy lifestyle* across the life course A healthy lifestyle is the foundation of ASCVD risk reduction at all ages and should be emphasized in both primary and secondary prevention plans
2. For secondary prevention of ASCVD, lower LDL-C by using a *high-intensity or maximally tolerated statin* dose The more the LDL-C is reduced during statin therapy, the greater the benefit in terms of risk reduction Use a high-intensity statin or maximally tolerated statin with goal LDL-C reduction of ≥50%
3. For secondary prevention of ASCVD in *very-high-risk patients*, use an LDL-C threshold of ≥70 mg/dl (1.8 mmol/L) to consider addition of non-statins to statins Very high risk is defined as a history of multiple major ASCVD events or one major ASCVD event and multiple other high-risk conditions In very-high-risk patients with ASCVD, it is reasonable to add ezetimibe to maximally tolerated statin therapy when the LDL-C level remains ≥70 mg/dl (≥1.8 mmol/L) In very-high-risk patients with ASCVD, it is reasonable to add PCSK9 inhibitor to maximally tolerated statin and ezetimibe therapy when LDL-C level remains ≥70 mg/dl (≥1.8 mmol/L)
4. In patients with *severe primary hypercholesterolemia* (LDL-C level ≥190 mg/dl) (≥4.9 mmol/L), begin high-intensity statin therapy without calculating a 10-year ASCVD risk If the LDL-C level remains ≥100 mg/dl, adding ezetimibe is reasonable If the LDL-C level on statin plus ezetimibe remains ≥100 mg/dl and the patient has multiple factors that increase subsequent risk of ASCVD events, a PCSK9 inhibitor may be considered
5. In patients with *diabetes mellitus*, 40–75 years of age, and an LDL-C level of ≥70 mg/dl, start moderate-intensity statins without calculating a 10-year ASCVD risk In patients with diabetes mellitus at higher risk, especially those with multiple risk factors, it is reasonable to use a high-intensity statin to reduce the LDL-C level by ≥50%
6. For primary prevention of ASCVD in adults 40–75 years of age, the clinician should employ *shared decision-making* with the patient prior to initiating statin therapy
7. For primary prevention of ASCVD in adults 40–75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dl (≥1.8 mmol/L), at a *10-year ASCVD risk of* ≥*7.5%*, a moderate-intensity statin is recommended If statins are indicated, reduce LDL-C levels by ≥30%, and if 10-year risk is ≥20%, reduce LDL-C levels by ≥50%
8. For primary prevention of ASCVD in adults 40–75 years of age without diabetes mellitus, at a 10-year risk of 5–19.9%, *risk-enhancing factors* (Table 2) favor initiation of statin therapy
9. For primary prevention of ASCVD in adults 40–75 years of age without diabetes mellitus and with LDL-C levels ≥70–189 mg/dl (≥1.8–4.9 mmol/L), at a 10-year ASCVD risk of ≥7.5–19.9%, if a decision about statin therapy is uncertain, consider measuring *coronary artery calcium* (CAC) to improve risk stratification
10. *Assess adherence and response* to LDL-C-lowering medications and lifestyle changes with repeat lipid measurement 4–12 weeks after statin initiation or dose adjustment, repeated every 3–12 months as needed

Adapted from Ref. [6]

Table 2 Risk-enhancing factors

Family history of premature ASCVD
First-degree males, age <55 years; females, age <65 years
Persistently *elevated LDL-C*, optimally three determinants
LDL-C ≥160 mg/dL [4.1 mmol/L); non-HDL-C ≥190 mg/dL [4.9 mmol/L]
Metabolic syndrome
Increased waist circumference, elevated fasting triglycerides [≥150 mg/dL], elevated blood pressure, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 in women mg/dL]; a tally of three makes the diagnosis)
Chronic kidney disease
eGFR 15–59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation
History of *pregnancy-associated conditions*
Preeclampsia
Premature menopause
Age <40 years
Chronic inflammatory disorders
Rheumatoid arthritis, psoriasis, or chronic HIV
High-risk ethnic groups
South Asian ancestry
Persistently *elevated triglycerides*
≥175 mg/dl (≥1.97 mmol/L); optimally three determinations
If measured
Elevated *apolipoprotein B* ≥ 130 mg/dl or ≥2500 nmol/L. A relative indication for its measurement would be triglyceride ≥200 mg/dL (2.3 mmol/L). A level ≥130 mg/dL corresponds to an LDL-C ≥160 mg/dL (≥4.1 mmol/L) and constitutes a risk-enhancing factor
Elevated *high-sensitivity C-reactive protein* ≥2.0 mg/L (≥190 nmol/L)
Elevated *lipoprotein* (*a*) ≥50 mg/dl or 125 nmol/L. A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor especially at higher levels of Lp(a)
Decreased *ankle-brachial index* (*ABI*) <0.9

Adapted from Ref. [6]

patients with a higher absolute risk at baseline will derive a larger absolute risk reduction (ARR) and therefore a lower number needed to treat (NNT) as compared with patients with lower baseline risk. Therefore, risk assessment is critical in deciding intensity of prevention strategies.

Risk assessment is based on a number of patient-specific characteristics. Although risk assessment can be estimated using populations, individual risk requires personalization by the clinician. The 2018 guidelines stress the importance

of this personalization in both assessing risk and developing the treatment plan. The guidelines emphasize shared-decision-making discussions between patients and the healthcare team to ensure that individual risks and preferences are addressed with any treatment. The guideline is intended to serve as the starting point in this personalized approach and shared decision-making.

2.2 Begin with Lifestyle Intervention

Once risk is assessed, all intervention plans begin with lifestyle interventions. The 2018 guidelines continue to emphasize importance of a heart-healthy lifestyle throughout the entire lifespan. Smoking cessation, weight reduction, a health dietary pattern, and participation in regular physical activity are advised for all patients. Discussion of these lifestyle efforts and encouragement of dietary and exercise improvements are essential for all patients, at all visits, even when lipid-lowering pharmacotherapy is also recommended. Dietary patterns should emphasize a plant-based, low-saturated-fat diet. Caloric intake should be adjusted to promote weight loss in overweight/obese patients. Patients should be advised to engage in at least 150 minutes per week of moderate- to vigorous-intensity physical activity. Lifestyle

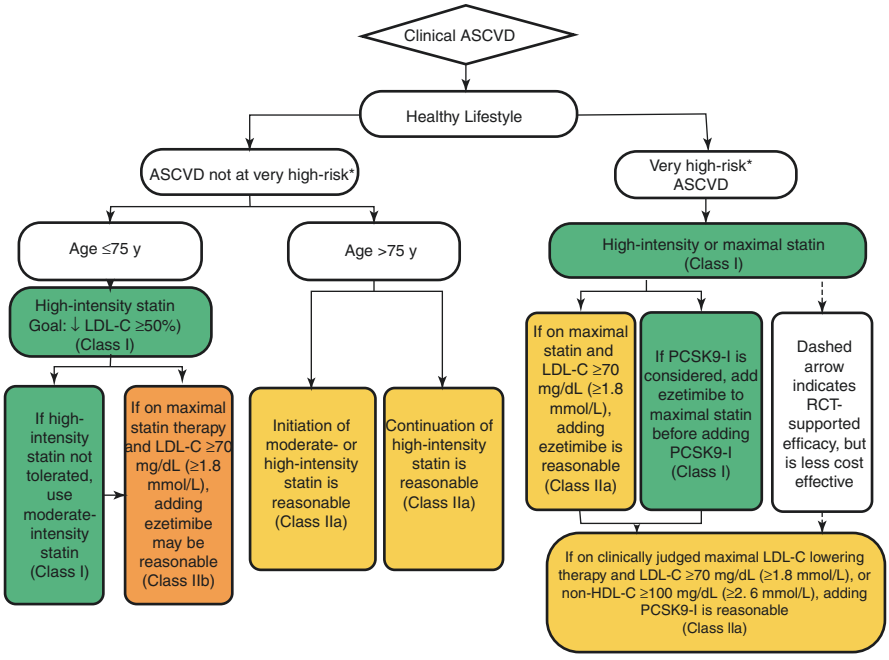

Fig. 1 Secondary prevention flow diagram for the 2018 AHA/ACC/Multisociety Cholesterol Guidelines

intervention is especially important for patients with metabolic syndrome. Promotion of a healthy lifestyle is the foundation of all ASCVD prevention interventions. However, certain patients who are at increased risk for ASCVD may also require pharmacotherapy.

3 Secondary Prevention

3.1 Statins as First-Line Therapy in Secondary Prevention

Patients with a prior diagnosis of ASCVD are at the highest risk for ASCVD events and ASCVD-related death. Therefore, the most aggressive prevention therapies should be allocated to those in secondary prevention. Figure 1 illustrates the recommended approach for cholesterol management in secondary prevention in the 2018 guidelines. The clinical diagnosis of ASCVD is defined as the history of one or more of the following: myocardial infarction and acute coronary syndrome; stable or unstable angina; coronary or other arterial revascularization, stroke, or transient ischemic attack; and peripheral artery disease, including aortic aneurysm, presumed to be of atherosclerotic origin.

Statin therapy remains the cornerstone of ASCVD risk reduction in secondary prevention. Numerous secondary prevention RCTs in patients with established clinical ASCVD demonstrate that lowering low-density lipoprotein cholesterol (LDL-C) with statins results in reduced ASCVD risk [7–10]. The Cholesterol Treatment Trialists' (CTT) meta-analysis [8] of 26 RCTs showed that 38.7 mg/dL (we advise rounding to 40 mg/dL to explain to patients) lowering of LDL-C with statin therapy reduces the risk of major adverse cardiovascular event (MACE) by 21%. Five trials of statin therapy in CTT specifically evaluated the efficacy and safety of high-intensity versus moderate-intensity statin therapy in secondary prevention. In these RCTs, average LDL-C difference between high- and moderate-intensity statin was 19 mg/dL which translated into a 15% further reduction in the risk of MACE. Most importantly, the reduction in MACE was proportional to the absolute reduction in LDL-C. The safety of statin therapy was also assessed in the CTT meta-analysis. In CTT, statin therapy compared to placebo, as well as high-intensity compared to moderate-intensity statin, was not associated with increased significant adverse events such as increased cancer incidence or the risk of hemorrhagic stroke.

Based on this data, the 2018 cholesterol guidelines, similar to 2013, recommend high-intensity statin therapy (atorvastatin 40 or 80 mg, rosuvastatin 20 mg or 40 mg) as the first-line treatment in adults < 75 years with established ASCVD. Once statin therapy is initiated, effective treatment is defined as an equal or greater than 50% reduction in LDL-C from levels prior to treatment. A 50% reduction in LDL-C is a magnitude of reduction that can usually be achieved using high-intensity statins. For those unable to tolerate high-intensity statins due to side effects, moderate-intensity statins (atorvastatin 10–20 mg, rosuvastatin 5–10 mg, simvastatin 40 mg,

lovastatin 40–80 mg, fluvastatin 80 mg, or pitavastatin 1–4 mg) are recommended with expected LDL-C lowering of 30–49%. For those with ASCVD, but >75 years of age, randomized clinical trial data are limited and mostly based upon post hoc analysis of prior trials. The guidelines therefore advise clinicians to engage in shared decision-making concerning initiation or continuation of moderate- or high-intensity statin therapy in this group. While selected patients >75 years may tolerate high-intensity statin therapy, clinicians should consider status of comorbidities, concomitant use of drugs affecting statin metabolism, frailty, excess alcohol intake, history of previous statin intolerance or muscle disorders, unexplained alanine aminotransferase (ALT) elevations ≥3 times the upper limit of normal, or factors of susceptibility such as Asian ancestry in determining intensity of statin dosing [1]. For example, those on protease inhibitors or immunosuppressive agents to avoid transplant rejection should have statin dosing carefully determined to avoid an adverse drug-drug reaction.

The focus of the US guidelines in secondary prevention is on decreasing ASCVD risk by attaining a 50% or more lowering of LDL-C and then using a threshold LDL-C level of 70 mg/dL to determine further intensity of therapy, rather than treating to specific LDL-C number. The current guidelines are consistent with the concept of "lower is better" but emphasize that those at "very high risk" should especially receive the highest-intensity therapy. A simple LDL-C target for secondary prevention does not do this.

Although treatment to a specific LDL target is not recommended, measurement of lipids remains a Class I indication in the 2018 cholesterol management guidelines. Prior data have shown that the lack of explicit LDL-C targets in the 2013 guidelines led to misinterpretation among some providers that routine monitoring of LDL-C while on treatment is not required [11]. This is not the case. Lipid measurement is important to assess response to statin therapy, to gauge statin adherence, to further modify risk assessment, and to determine intensity of therapy. The guidelines continue to recommend repeat lipid measurement 4–12 weeks after statin initiation or dose adjustment, repeated every 3–12 months as needed.

3.2 Non-statin Therapy for Patients with ASCVD at Very High Risk

In line with aggressive treatment of those at greatest risk for ASCVD, the 2018 US guidelines introduce a new risk stratification of patients in secondary prevention. A subset of patients with clinical ASCVD are classified as very high risk (Fig. 1). This group includes patients with a history of multiple major ASCVD events or one major ASCVD event plus additional risk factors: age 65 years or older, heterozygous familial hypercholesterolemia (FH), prior percutaneous coronary intervention/coronary bypass surgery, diabetes (DM), hypertension, chronic kidney disease, current smoking, persistently elevated LDL-C (LDL-C ≥ 100 mg/dL (≥2.6 mmol/L)) despite maximally tolerated statin therapy/ezetimibe, and history of heart failure.

The features associated with very-high-risk status were suggested based on enrollment criteria and ad hoc analyses from the major non-statin RCTs including IMPROVE-IT [12], FOURIER [13], and ODYSSEY-OUTCOMES [14]. Approximately a quarter of patients with ASCVD can be classified into this very-high-risk group [15].

One caveat is worth comment. Some note that a prior major event in someone with heterozygous familial hypercholesterolemia (FH) places these patients in the very-high-risk group [16]. Since most heterozygous FH patients (remembering they are a small percentage of those with LDL-C >190 mg/dL) have LDL-C ≥100 mg/dL despite maximally tolerated statin/ezetimibe therapy, they would fit these criteria.

Very-high-risk adults with clinical ASCVD and LDL-C ≥ 70 mg dL on maximally tolerated statin remain at higher risk for future ASCVD events. In addition, patients in the very-high-risk category benefit most from progressive LDL-C lowering with addition of non-statin therapies.

In IMPROVE-IT [12], 18,144 patients hospitalized for acute coronary syndrome (ACS) within the prior 10 days were randomized to ezetimibe 10 mg plus simvastatin 40 mg daily or simvastatin 40 mg plus placebo. Addition of ezetimibe to moderate-intensity statin therapy resulted in a 2% absolute risk reduction (ARR) of major adverse cardiovascular event (MACE). A more pronounced benefit was found among ACS patients ≥ 75 years of age and those with diabetes, suggesting that these groups may particularly benefit from addition of ezetimibe. In addition, a post hoc analysis of IMPROVE-IT showed that the benefit of ezetimibe plus statin was greatest in patients with high-risk features as defined by the TIMI Risk Score for Secondary Prevention [15]. Nevertheless, caution should be used when extrapolating the findings and implications of IMPROVE-IT beyond that of the population studied (e.g., ACS within the past 10 days).

Similarly, RCTs with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors demonstrate the greatest benefit in those at greatest risk. The FOURIER [13] trial randomized 27,564 patients with clinical ASCVD to evolocumab or placebo in addition to high-intensity statin. During the median follow-up of 2.2 years, addition of evolocumab resulted in lower MACE with an ARR of 1.5%. In a subsequent post hoc analysis of the FOURIER data [17], incidence rates of MACE were higher along with correspondingly lower NNT among all individuals with high-risk features (recent MI, multiple prior MIs, or residual multivessel CAD) compared to those without. In another subgroup analysis from FOURIER [18], patients with PAD remained at higher risk of MACE. The ARR with evolocumab was greater in those with PAD compared to those without: 3.5% versus 1.6% and NNT 29 versus 63. In ODYSSEY OUTCOMES, which randomized post-ACS patients on high-intensity statin to alirocumab or placebo, the greatest ARR of MACE occurred among those with baseline LDL-C ≥ 100 mg/dL with a corresponding NNT of 16.

The significance of the very-high-risk category has been supported by an analysis of ODYSSEY OUTCOMES published after the 2018 guidelines [19]. MACE occurred in 14.4% of placebo-treated patients categorized at very high risk versus in only 5.6% of those not at very high risk. The ARR of MACE was also greatest in patients treated with alirocumab in the very-high-risk category.

Based on the above RCT data, the 2018 guidelines recommend adding a non-statin drug to maximally tolerated statin in patients with ASCVD at very high risk if the LDL-C level remains ≥70 mg/dL. This LDL-C threshold for addition of non-statin therapy is supported by recruitment criteria in the RCTs. The recruitment criteria for ezetimibe in IMPROVE-IT [12] was an LDL-C level of 70 mg/dL or higher. Recruitment criteria for the PCSK9 trials excluded patients with LDL-C levels less than 70 mg/dL [13, 14].

The addition of ezetimibe to high-intensity statin if the LDL-C is still ≥70 mg/dL is recommended first, both in those at and not at very-high-risk status. If the LDL-C remains ≥70 mg/dL on maximal statin and ezetimibe, addition of PCSK9 (evolocumab or alirocumab) is recommended in very-high-risk patients. The stepwise addition of ezetimibe first was based on the generic availability, tolerability, safety, and lower cost of this drug. A simulation analysis from a large population of very-high-risk patients indicates a significant proportion of individuals treated with statin and ezetimibe will achieve an LDL-C level less than 70 mg/dL [12], which therefore may prevent the need for any additional therapy.

For the first time, the new guidelines also include a value statement that emphasizes the need for clinicians and patients to factor in the cost of drugs in determining the most appropriate treatment. The cost-effectiveness of a therapy depends on the cost of therapy as well as the clinical benefit from that therapy as measured by the relative risk reduction associated with the therapy and the baseline event rates in the population of interest [20]. Based on mid-2018 pricing, the guidelines give PCSK9 inhibitors a "low-cost value" for patients at very high risk for ASCVD. However, a subsequent reduction in cost of evolocumab has resulted in a more favorable cost-effectiveness analysis in patients with ASCVD at very high risk as defined by the 2018 ACC/AHA guideline [21].

3.3 Secondary Prevention in Adults >75 Years of Age

In older patients (>75 years) with clinical ASCVD, the guidelines state that it is reasonable to initiate moderate- or high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug-drug interactions, as well as patient frailty and patient preferences. They noted that in this age group, after a risk discussion, it is reasonable to continue high-intensity therapy in those who were tolerating it. The IMPROVE-IT RCT [15] emphasized that more intensive LDL-C lowering is especially beneficial in the older age range presumably because these patients have higher absolute risk than their younger counterparts. In 2019, an updated CTT meta-analysis of patients >75 years of age with history of ASCVD demonstrated that the 21% reduction in MACE per 40 mg/dL reduction in LDL-C with statin therapy was similar in all age groups and decreased insignificantly with age [22]. Older adults usually have a higher absolute risk of recurrent ASCVD, and thus, the ARR in older adults with ASCVD compared to younger patients with ASCVD may be higher.

The present guidelines do not explicitly give recommendations on the use of ezetimibe or PCKS9 inhibitors in older adults >75 years of age. IMPROVE-IT, FOURIER, and ODYSSEY OUTCOMES trials all included patients >75 years; however this group represented a small fraction of the overall study population. Subgroup analysis of IMPROVE-IT showed a stronger effect in patients with age ≥75 years compared to those <75 years (ARR = 8.65% versus ARR = 0.79%) [12]. New post-guideline data has emerged from the EWTOPIA 75 trial on ezetimibe monotherapy in the treatment of older adults ≥ 75 years of age with hypercholesterolemia for primary prevention. This showed significant reduction in cardiovascular events in the treatment group compared with controls [23]. However, the study had several limitations, including an open-label design and loss-to-follow-up issues, and therefore should be interpreted with caution.

4 Primary Prevention

4.1 Risk Assessment Is the Initial Step in Primary Prevention

The 2018 guideline recommendations for cholesterol management in primary prevention are illustrated in Fig. 2. Based on the concept that intensity of prevention should match the absolute risk of the individual patient, risk assessment is the first step in primary prevention of ASCVD. Patients with diabetes mellitus (DM), age 40–75 years, LDL-C 70–189 mg/dL, or severe primary hypercholesterolemia (LDL-C ≥ 190 mg/dL) are shown to be at highest risk and therefore require special consideration for intensive treatment. Further risk assessment is not necessary for these patients and recommendations are discussed separately. It is important to remember that a patient under 40 years with primary elevations of LDL-C ≥ 190 mg/dl should have statin therapy initiated without deferring until age 40 due to increased lifetime risk. In addition, prevention considerations for patients >75 years of age are reviewed separately, as RCT data is limited at this age. Among patients not included in these groups, risk assessment is the foundation to informed decision-making for therapy.

The guidelines support using a validated clinical scoring tool to assess risk. The rationale, evidence, as well as strengths and limitations of risk assessment tools were published in a companion document to the 2018 cholesterol guidelines [24]. Evidence suggests that utilizing risk scores may reduce CV risk factors and increase the use of preventive medications. In particular, the guidelines endorse the US-derived Pooled Cohort Equations (PCEs). The PCEs, derived from four representative US epidemiological cohorts of non-Hispanic whites and African Americans, were introduced in the 2013 guidelines and, since that time, have been validated by a natural history study in a large US cohort [25]. The PCEs estimate a 10-year risk for ASCVD events among adults aged 40–79 years. The calculated 10-year ASCVD risk is classified into four categories: <5% low risk, 5–<7.5% borderline risk, ≥7.5–<20% intermediate risk, and ≥20% high risk.

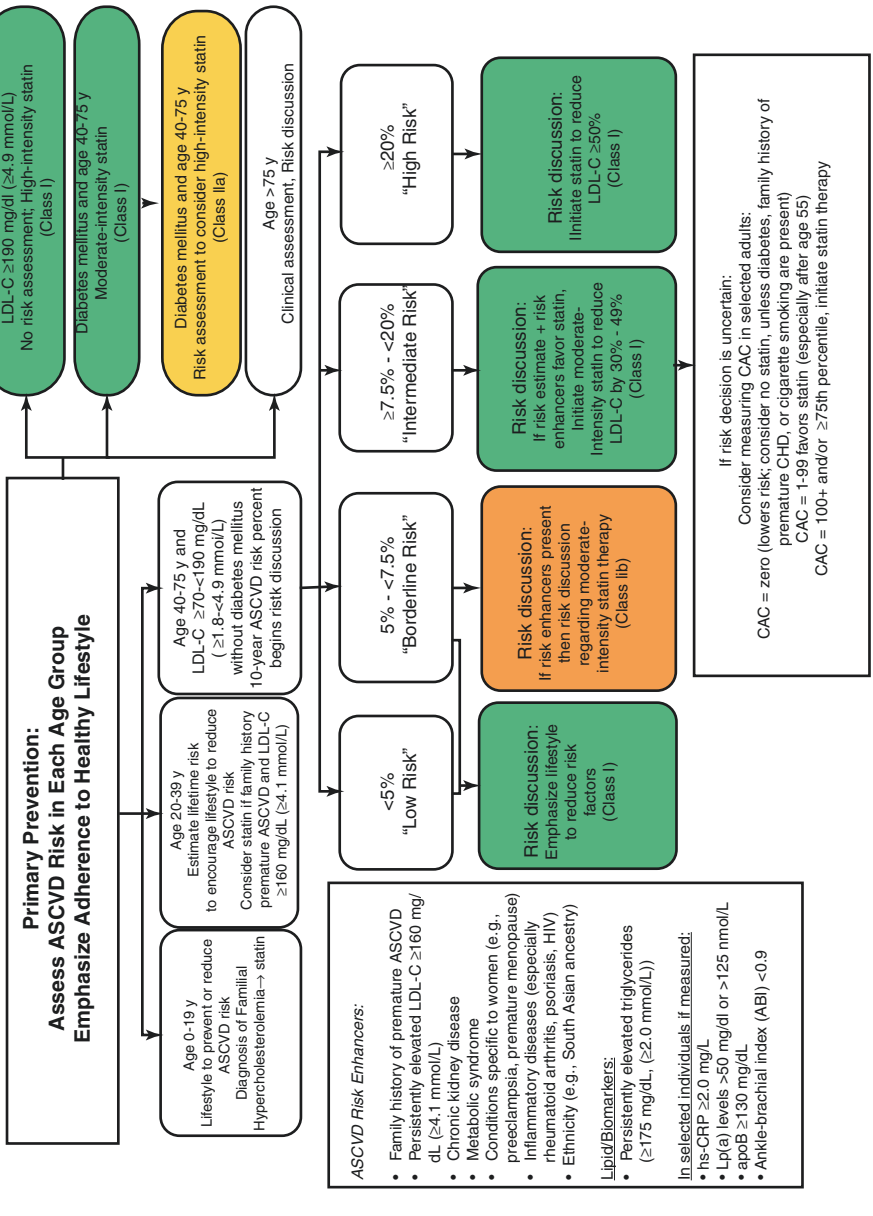

Fig. 2 Primary prevention flow diagram for the 2018 AHA/ACC/Multisociety Cholesterol Guidelines

4.2 Statin Therapy for High-Risk Primary Prevention

Similar to CTT for secondary prevention, a meta-analysis of primary prevention trials demonstrates that lowering low-density lipoprotein cholesterol (LDL-C) with statins reduces ASCVD risk [26]. The 2018 guidelines recommend statin therapy for high-risk patients, defined as having a 10-year ASCVD risk ≥20%. The goal of this therapy is to reduce LDL-C by 50%. In general, either a fasting or nonfasting plasma lipid profile is effective for estimating initial ASCVD risk and documenting baseline LDL-C [27]. Fasting LDL-C measurements are recommended to monitor response to therapy. In general, maintaining a heart-healthy dietary pattern can reduce LDL-C levels by 10 to >15%. Moderate-intensity statin therapy can be expected to reduce LDL-C by another 30–49% and high-intensity statins by ≥50%. The maximum percentage change will usually occur 4–12 weeks after implementing an intervention.

As mentioned above, two groups in primary prevention require special consideration for therapy without calculating a risk score: patients with DM and those with severe primary hypercholesterolemia. These groups should be considered at "highest risk" for ASCVD in primary prevention. Further assessment with risk calculators, regardless of score, should not reclassify these patients into a lower-risk category.

Moderate-intensity statin therapy is recommended in all adult patients with DM based on multiple primary prevention trials demonstrating substantial benefit in this population [28]. However, CTT demonstrated that there is a wide spectrum of risk among patients with DM. Therefore a high-intensity statin to target a > 50% reduction in LDL-C is reasonable among those with DM and multiple risk factors or DM-specific risk enhancers that are independent of other risk factors in DM. These include long duration of DM (≥10 years for Type 2 and ≥20 years for Type 1), albuminuria ≥30 mcg of albumin/mg creatinine, eGFR <60 mL/min/1.73 m, retinopathy, neuropathy, and ankle brachial index <0.9. These criteria may also help clinicians decide in the context of a risk discussion if moderate statin therapy may be considered for those adults with DM aged 20–39 years.

Another highest-risk group includes those patients with severe primary hypercholesterolemia (LDL-C ≥ 190). A small proportion of these patients will have low-density lipoprotein receptor (LDLR), APOB, or PCSK9 gene mutations for familial hypercholesterolemia (FH). ASCVD risk is sixfold higher in patients with LDL-C ≥ 190 mg/dL and no FH mutation and 22-fold higher in those with LDL-C ≥ 190 mg/dL and an FH mutation [29]. Patients with FH are exposed to elevated LDL-C levels since birth, and this explains the high cardiovascular burden, mainly of coronary heart disease. FH is one of the most common genetic lipid disorders and its prevalence is around 1/250 in general population [30]. Unfortunately, FH is often underdiagnosed and undertreated; data from the USA estimate only 52% are treated even when diagnosed [31].

The 2018 guidelines recommend use of a high-intensity statin to reduce the high lifetime risk in patients with primary elevation of LDL-C ≥ 190. Secondary causes

of dyslipidemia such as obstructive liver disease, nephrotic syndrome, hypothyroidism, or poor or extreme diets should be ruled out before starting statin therapy. If LDL-C remains ≥100 mg/dL, additional therapy with ezetimibe should be considered. PCSK9 inhibitors may also be considered in select patients with persistently elevated lipids. The new guidelines also recommend "reverse cascade" screening of first-degree relatives to screen for FH. Reverse cascade screening includes recommending cholesterol testing for first-, second-, and, when possible, third-degree biological relatives, for detection of familial forms of hypercholesterolemia. The yield is high given the autosomal dominant inheritance of FH.

4.3 Using Risk Enhancers to Personalize Risk

PCEs may overestimate risk in groups with higher socioeconomic status or those receiving consistent screening and preventive care [32]. On the contrary, PCEs may underestimate risk in those with lower socioeconomic status or with chronic inflammatory conditions such as HIV and rheumatologic disease [33]. It is important to understand that risk equations such as the PCEs predict average population risk, and while recommended as the first step in ASCVD risk estimation, they alone cannot personalize the risk decision for an individual. Patient characteristics will modify population risk estimates and therefore must be considered when evaluating individual risk.

To personalize risk, the current guideline recommends evaluation of risk-enhancing factors when treatment decision is unclear. Risk-enhancing factors are evidence-based characteristics, outside of traditional risk factors, which are associated with increased risk of developing ASCVD. The presence of risk-enhancing factors in patients, especially with borderline or intermediate risk, may convey higher baseline risk and more strongly favor initiation of treatment. Risk-enhancing factors are summarized in Table 2. The presence of risk-enhancing factors in patients at intermediate risk favors statin therapy.

4.4 Reclassifying Risk with Coronary Artery Calcium Scoring

There is an extensive body of evidence demonstrating that direct measurement of subclinical atherosclerosis, particularly with coronary artery calcium (CAC), predicts future ASCVD events. The CAC score has been shown to be the best discriminator of risk among serum biomarkers, traditional risk factors, and nontraditional risk markers including ankle-brachial index, high-sensitivity C-reactive protein levels, and family history of ASCVD [34]. CAC improves statistical risk reclassification of patients in primary prevention [35] and can effectively guide risk-based selection of appropriate prevention therapies, such as initiation of statin therapy [36]. The relationship of CAC and incident ASCVD across 10 years was highlighted

in an analysis of the Multi-Ethnic Study of Atherosclerosis (MESA) cohort [37]. In this study, a CAC score of zero Agatston units (AU) was associated with a low ASCVD risk for the subsequent 10 years. A CAC score ≥ 100 AU signified at least a 7.5% 10-year risk of ASCVD regardless of age, gender, or ethnicity.

The 2018 cholesterol guidelines support CAC measurement as an effective tool to reclassify risk in a large proportion of patients classified at intermediate (7.5% to <20%) 10-year risk by the PCE. In these patients, if the CAC score is ≥100 AU or is at or above the 75th percentile, the guidelines recommend statin therapy. If the CAC score is 1–99 AU, 10-year ASCVD event rates in MESA [37] were 3.8% in patients 45–54 years of age, 6.5% in those 55–64 years of age, and 8.3% in those 65–74 years of age. Therefore, as the reclassified effect of a CAC score of 1–99 AU is only modest, the guidelines favor statin initiation only in adults >55 years of age after a risk discussion.

Intermediate-risk patients with a CAC score of 0 AU have a low subsequent 10-year event rate (<5%) [38]. This score suggests limited benefit from starting a statin, and therefore guidelines support withholding therapy in this group. Nearly half of patients in the intermediate-risk group will have a CAC score of zero [36]. The zero CAC score in MESA was the strongest negative predictor with a diagnostic likelihood ratio (DLR) of 0.41 for coronary heart disease and 0.54 for cardiovascular disease. Of note, DLR for the CAC score increases with age, and therefore measuring CAC can be particularly useful in older adults. In adults 76–80 years of age, the guidelines state it may be reasonable to measure CAC to avoid statin therapy in those with a score of zero. It is important to highlight that a CAC score of zero does not imply zero risk. The score should always be interpreted in the context of patient's known risk factors. The guidelines do not recommend CAC testing in high-risk patients (those with a 10-year ASCVD risk ≥20%), including those with familial hypercholesterolemia. In these patients, risk will remain in a statin-benefit group regardless of CAC score. The guidelines also do not recommend CAC testing in certain subgroups: persistent smokers, DM, strong family history of ASCVD, and chronic inflammatory conditions such as HIV. These subgroups have been demonstrated to have higher ASCVD risk regardless of CAC score [39–41], perhaps due to noncalcified plaques.

5 Special Populations to Consider

5.1 Hypertriglyceridemia

Patients with hypertriglyceridemia can be classified into two groups based on risk for adverse events. Patients with severe elevations, those with fasting triglyceride (TG) levels ≥1000 mg/dL, are at increased risk for pancreatitis. These patients require TG lowering with drug therapy. TGs can be reduced by implementing a very-low-fat diet, avoidance of refined carbohydrates and alcohol, consumption of omega-3 fatty acids, and fibrate therapy.

In those with moderate elevations (fasting or nonfasting TG 175–499 mg/dL), there is concern for increased ASCVD risk. In these patients, the guidelines recommended initially to decrease TG levels through lifestyle interventions such as diet and exercise. Clinicians were guided to search for secondary causes of elevated TGs: DM, chronic liver or kidney disease and/or nephrotic syndrome, and hypothyroidism. In addition, medications should be reviewed and those that elevate TGs should be discontinued, if possible. The guidelines also state that it is reasonable to calculate the ASCVD risk score for patients with moderate elevations in TG. If the score is ≥7.5% and TGs are persistently elevated (≥175 mg/dl or 2 mmol/L), initiation of statin therapy is reasonable. In this case, statin therapy is given to decrease ASCVD risk, not to simply lower TG level.

Since the guidelines, the REDUCE-IT trial of icosapent ethyl, a highly concentrated form of modified EPA, found a 25% reduction in cardiovascular events and a 20% reduction in cardiovascular death in statin-treated patients with either ASCVD or higher-risk patients with DM to an LDL-C < 100 mg/dL but with TG levels 135–499 mg/dL [42]. The mechanisms underlying the risk reduction are not entirely clear. It does not appear that the risk reduction is solely based on lipid lowering, as the magnitude of benefit was consistent across all TG levels. Although this RCT was not part of the 2018 cholesterol guidelines, it is included in discussion as it may inform clinician judgment in patients with moderate elevations of TG.

5.2 Sex and Race Considerations

The PCE included sex and race in the 10-year risk calculation. Clinicians should note that the same risk factors in a middle-aged African American woman lead to a higher ASCVD 10-year risk score than her white counterpart. The 2018 guidelines include a separate section that outlines how race and ethnic characteristics/factors may influence risk for ASCVD and should be considered risk-enhancing factors. For example, patients of South Asian descent have a higher risk of developing heart disease than the general US population. Patients with Japanese ancestry, meanwhile, are more likely to be sensitive to statins and may require lower doses. The guidelines also recognize that individuals who identify as Hispanic fall into a diverse population; individuals from Puerto Rico have an increased risk for ASCVD compared to those from Mexico.

Women also require assessment of unique risk-enhancing factors for determining ASCVD risk in primary prevention. Female-specific risk conditions, which include premature menopause and certain pregnancy-related conditions, have been associated with increased long-term risk of ASCVD. Premature menopause (age before 40 years) and preeclampsia appear to similarly increase ASCVD risk. The other pregnancy-related conditions (gestational diabetes, gestational hypertension, and preterm delivery) are recognized as increased lifetime CVD risks but were not classified as risk-enhancing factors.

Lipid management in women of childbearing age is complicated by the uncertain effect of statins on the fetus. All women of childbearing age who are treated with statin therapy should be counseled concerning contraception. If planning pregnancy, women should stop statin 1–2 months before pregnancy is attempted. If pregnancy is identified, statin should be stopped. Lipid profiles are known to be altered with pregnancy, and therefore pregnant women with underlying genetic lipid disorders should seek expert guidance.

5.3 Primary Prevention in Adults >75 Years of Age

Unlike secondary prevention, there is less direct evidence for benefit of cholesterol lowering among patients >75 years in primary prevention. PCE risk scores always exceed 7.5% in this age group and therefore are not useful in identifying those where benefit would outweigh negative aspects or risks. There is evidence supporting use of CAC in patients 76–80 years of age to reclassify risk, with a CAC score of zero being helpful to support a decision to avoid statin therapy. The value of statin therapy in this age group is being addressed by current ongoing trials (i.e., STAREE trial). The use of other risk-enhancing factors as described earlier can also aid in the treatment decision.

5.4 Children and Adolescents

With increasing age, there is concern for increased statin-related adverse events including liver and muscle injury. Statins have been estimated to increase the risk of myopathy typically by 1 case per 10,000 patients treated with statins per year; this risk can be increased by drug interactions and major comorbidities that are more common in older people. A meta-analysis of published data for participants older than 65 years in statin trials reported no increased risk of less severe muscle-related adverse events [43]. The CTT Collaboration is undertaking a prespecified analysis of reported adverse events in the statin trials from original trial records, including examining whether age directly influences the small increase in risk of DM and whether statins adversely influence cognition. However, three large-scale RCTs (Heart Protection Study, PROSPER, and HOPE-3) used validated indicators of cognitive function and found no decrease in cognitive function in those assigned statins versus those assigned placebo. The current guidelines introduced a IIB recommendation in adults 75 years of age or older without ASCVD, indicating it may be reasonable to stop statin therapy when functional decline (physical or cognitive), multimorbidity, frailty, or reduced life expectancy limits the potential benefits of statin therapy.

Highlighting the concept that atherosclerosis begins in childhood and adolescence, the 2018 guidelines include special recommendations for children age

0–19 years. Identifying and treating high cholesterol early may reduce the lifetime risk for cardiovascular disease. A long-term follow-up of six epidemiological cohorts recently showed that earlier in life risk factor exposure, including elevated LDL-C and blood pressure, increases ASCVD events independent of later adult exposure [44]. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study demonstrated that measurement of ASCVD risk factors predicts future subclinical atherosclerosis as assessed by noninvasive tests during a 15-year interval [45]. Thus, in the pediatric age group, it is important to detect FH. For those without FH but elevated cholesterol, it is an important time to emphasize improved lifestyle.

The new guideline suggests elective cholesterol screening is appropriate for children as young as 2 who have a family history of heart disease or high cholesterol. In those without a family history, an initial screening test can be considered between the ages of 9 and 11 and then again between 17 and 21. It is essential that those found to have elevated cholesterol adhere to a healthy lifestyle, become aware of the risk of high cholesterol levels, and are provided treatment as appropriate. Several recommendations focus on those more severely affected with elevated LDL-C. It is reasonable to initiate statin therapy in children and adolescents ≥10 years of age, with primary elevations of LDL-C persistently ≥190 mg/dL or ≥160 mg/dL and with a clinical presentation consistent with FH, after a lack of an adequate response to 3–6 months of lifestyle therapy.

5.5 Other Special Populations

The 2018 cholesterol guidelines also addressed lipid issues in children and those with chronic inflammatory disorders or HIV and chronic kidney disease (CKD). In children and adolescents, they recommend testing to identify both severe elevations of LDL-C and dyslipidemia related to multiple lifestyle factors. They endorse nonfasting lipid testing for initial screening purposes. For those with lipid abnormalities, they endorse lifestyle counseling. For those with severe hypercholesterolemia with a clinical presentation consistent with FH, they recommend statin therapy if they don't respond to 3–6 months of lifestyle therapy. Chronic inflammatory conditions or HIV enhance a patient's risk of ASCVD.

Their effect on risk can be considerable. For example, in individuals with RA, the risk of an MI has been estimated to be similar to that of an adult with DM or one who is about 10 years older without RA. Thus, if the patient's ASCVD risk estimate is ≥7.5% over 10 years, it is reasonable to begin moderate-intensity statin therapy. Finally, the guidelines highlight CKD as a risk-enhancing factor for ASCVD. In clinician-patient risk discussion with intermediate-risk patients, the presence of CKD favors initiation of statin therapy. Although statin therapy is not recommended for those with advanced CKD requiring chronic dialysis based on RCT evidence, the guidelines noted it was reasonable to continue the statin.

6 Conclusion

The 2018 AHA/ACC/Multisociety Cholesterol Guidelines build upon fundamental principles proposed in the 2013 guidelines emphasizing ASCVD risk and the importance of RCTs in identifying groups of patients shown to benefit from both lifestyle and pharmacologic reduction of LDL-C. They continue the important guidance from ATP I through ATP III that LDL-C and ASCVD risk factors should be measured, evaluated, and treated based on the appropriate evidence in adults. The updated guidelines support cholesterol lowering to decrease ASCVD risk across the entire lifespan with intensive lifestyle intervention, as well as a shared decision model between the clinician and patient regarding statin and non-statin pharmacotherapy for those at highest risk. The guidelines provide the clinician with a personalized approach to ASCVD risk assessment, starting with a validated population-based risk calculator and further individualizing this score with risk-enhancing factors and, in specific cases, reclassifying risk with a CAC score. This personalized risk assessment focuses the risk discussion on specific patient characteristics and creates a framework to intensify cholesterol-lowering interventions for those patients found to be at greatest risk for ASCVD who may benefit most from statin intervention, as well as indicate those who may safely defer this therapy. In secondary prevention, therapy decisions are likewise personalized. Those at "very high risk" are shown to have greater absolute ASCVD risk and hence more aggressive therapy including non-statins such as ezetimibe and PCSK9 inhibitors recommended for this group. Finally, new to the guidelines are sections on unique features of women and other special populations crucial to appropriate assessment and treatment of ASCVD risk, cost-effectiveness considerations, and racial/ethnicity factors.

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Blood Pressure and Hypertension Management

Keith C. Norris and Bettina M. Beech

Summary

- The prevention and management of hypertension remains a significant public health problem.
- For patients with elevated blood pressure, initiation of nonpharmacologic therapy should be instituted to include smoking cessation in tobacco users, daily walking and/or exercise three times a week, and a vegetable-rich diet. In many cases the addition of pharmacologic intervention will be needed if the goal blood pressure is not achieved with nonpharmacologic interventions.
- The most recent recommendations for the management of high blood pressure by the American College of Cardiology/American Heart Association include classifying a blood pressure level of 130–139/80–89 mmHg as Stage 1 hypertension and a blood pressure level ≥140/90 mmHg as Stage 2 hypertension.
- For persons with blood pressure of ≥130/80 mmHg an estimated 10-year atherosclerotic cardiovascular disease risk of ≥10%, concurrent initiation of pharmacologic therapy with lifestyle management is recommended, whereas all those with blood pressure ≥140/90 mmHg are recommended for pharmacologic therapy.

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- Optimal blood pressure control necessitates an appropriate sensitivity to, and an understanding of, demographic, socio-cultural, and other factors. Such an understanding can enhance adherence and overcome many of the barriers to blood pressure control and improved cardiovascular health.

1 Introduction

High blood pressure (HBP) or hypertension is a major risk factor for cardiovascular (CV) and related diseases, as well as premature death in the USA and worldwide. The prevention and management of hypertension remains a significant public health problem as hypertension affects over a billion people globally and is one of the most commonly diagnosed chronic diseases in the USA, affecting one in three adults [1]. Given the high prevalence, it is not surprising that hypertension is also the most common reason for a physician office visit for chronic medical conditions [2]. Hypertension is commonly recognized as: (1) an untreated systolic blood pressure (SBP) of 130 mm Hg or higher, or diastolic blood pressure (DBP) of 80 mm Hg or higher, (2) taking antihypertensive medicine, or (3) being told at least twice of having the condition by a health professional [1].

Hypertension is a complex polygenic disorder with the collective effect of all identified blood pressure (BP) loci accounting for only less than 4% of BP variability [3]. Some patients with systemic hypertension will have a specific identifiable cause for the elevated systemic blood pressure termed secondary hypertension, accounting for 5–10% or even more of the cases of systemic hypertension [3, 4]. Secondary causes of hypertension include primary hyperaldosteronism, renal disease, obstructive sleep apnea, substance abuse, medications, endocrine disorders, and others [3, 4]. Patients with secondary hypertension usually exhibit suggestive constellations of signs, symptoms, and/or laboratory abnormalities on initial evaluation and should undergo further evaluation for a specific cause of hypertension.

Hypertension has additional implications for clinical management and economic consequences. Data from the National Health and Nutrition Examination Survey (NHANES) 2013–2016 found that while 64.7% of US adults with hypertension were aware of their condition, only 53.4% received pharmacologic treatment and only 24.7% had their SBP controlled to <130 mmHg [1]. These findings are particularly concerning since cardiovascular mortality risk nearly doubles for every 20 mmHg increase in systolic blood pressure above 115 mmHg [5]. Further, costs associated with clinic visits, medication, and the treatment of comorbidities associated with hypertension are staggering. The estimated direct and indirect cost of hypertension for 2014–2015 was $55.9 billion, while the cost associated with CV disease was over $350 billion [1]. The annual mean additional medical cost for a person with hypertension was $1920 compared to a person without hypertension [1].

Despite numerous challenges in the management of hypertension, remarkable progress has been made over the past half century in improving BP control and reducing its complications. Unfortunately, recent indicators have raised concerns about population-level reversals in CV improvements, which require the prioritization of

lifestyles changes (e.g., improved diet, regular physical activity, smoking cessation) to prevent or delay the onset of hypertension. Sustained lifestyle changes may not only reduce BP levels but also reduce CV risk [6]. This chapter will provide a summary of target blood pressure level recommendations but will mainly focus on the management of hypertension, with a focus on how to effectively achieve these targets across populations and with individual patients.

2 Definition of High Blood Pressure

According to the recent recommendations for Prevention, Detection, Evaluation, and Management of High Blood Pressure by the American College of Cardiology/*American Heart Association* (ACC/AHA), BP measurements should be categorized as normal, elevated, stage 1, or stage 2 hypertension to help guide the prevention and treatment of high BP (Table 1) [7]. In addition to the revised definition of hypertension, the ACA/AHA recommends estimating 10-year risk of atherosclerotic CV disease (ASCVD) to establish the BP threshold for treatment using of the ACC/AHA Pooled Cohort Equations (http://tools.acc.org/ASCVD-Risk-Estimator/) [7].

3 New Blood Pressure Target Recommendations

Most guideline committees prior to 2017 recommended treatment for hypertension to a target blood pressure level of <140/90 mmHg. Recent randomized trials have prompted new recommendations for hypertension by the ACC/AHA that include a new target SBP level of <130 mmHg [3]. Like many clinical recommendations, the major caveats (which are often overlooked once the guidelines are disseminated), include CV risk, age, and comorbidities including ASCVD risk [3]. This new BP target represents a significant departure from the 2014 recommendations of a target SBP level <140 mmHg by the panel members appointed to the Eighth Joint National Committee on the Prevention, Detection, Evaluation, and Treatment

Table 1 Categories of blood pressure (BP) in adults

Blood pressure level	Normal	Elevated	Stage 1 hypertension	Stage 2 hypertension
Systolic blood pressure	<120 mmHg	120–129 mmHg	130–139 mmHg	≥140 mmHg
	and	and	or	or
Diastolic blood pressure	<80 mmHg	<80 mmHg	80–89 mmHg	≥90 mmHg

Based on data from Ref. [7]
Individuals with a systolic blood pressure and diastolic blood pressure in two categories should be designated to the higher blood pressure category. Blood pressure should be based on an average of ≥2 careful readings obtained on ≥2 occasions

of High Blood Pressure [8]. These more recent ACC/AHA guidelines were influenced in large part by the results from the Systolic Blood Pressure Intervention Trial (SPRINT) [9]. SPRINT enrolled 9361 participants and found that, compared to participants assigned to the <140 mmHg goal, those assigned to the lower target SBP of <120 mmHg, had a significantly lower hazard ratio (HR) for the primary composite outcome of CV events and death (25%), as well as all-cause mortality (27%) [9]. Although the low SBP target in SPRINT was <120 mmHg, several concerns arose for extending this finding to general clinical recommendations. These include the use of unattended BP measurements which may underestimate the BP levels in clinical settings [10], increased rates of adverse events [9], exclusion of persons with diabetes or poor record of adherence, and data from observational studies and meta-analyses that suggest rates of CV events and death may increase with SBP levels <120 mmHg [11, 12]. Based on these and a myriad other studies, a target SBP of <130 mmHg was agreed upon [3, 13].

The 2018 European Society of Cardiology/European Society of Hypertension BP treatment target recommendations are less aggressive than the ACC/AHA BP Guideline recommendation [3, 14]. Their approach is to first lower BP to <140/90 mmHg but then strive for <130/80 mmHg if tolerated in adults <65 years (130–140/90 mmHg in adults ≥65 years) (Table 2). In the 75–80 years of age or older

Table 2 A summary of key recommendations for the treatment of high blood pressure from several professional organizations

Guideline	BP target in general adult population	Qualifications for BP (mmHg) targets
Panel members appointed to the Eighth Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (2014) [8]	<140/90	Age ≥60: <150/90
American Diabetes Association 2015 Standards of Medical Care [15]	<140/90	
National Institute for Health and Clinical Excellence (2019) [16]	<140/90	Lack of evidence for people >80 years
American Academy of Family Physicians (2014) [17]	<140/90	Age ≥60 years, goal SBP <150 mmHg and goal DBP <90 mmHg
American Diabetes Association Standards of Medical Care (2019) [18]	<130/80 if CVD risk >15% and BP target can be safely attained	<140/90 if low CVD risk (10-year risk <15%)
European Society of Cardiology and the European Society of Hypertension (2018) [14]	<140/90	<130/80 if treatment is well tolerated
Australian National Heart Foundation (2016) [19]	<140	<120 (>15%; 5-year CVD risk)
Hypertension Canada (2018) [20]	<120/80 (High risk CVD)	Low risk CVD SBP <140 DM <130/80
American College of Cardiology/American Heart Association (2017) [3]	<130/80	Age ≥65 years – use clinical judgment

CVD cardiovascular disease, *BP* blood pressure, *SBP* systolic blood pressure

group, a goal of lower than 140 mmHg might be reasonable and if well-tolerated, a further titration to lower than 130 mmHg could be considered [21]. However, there should not be any urgency in pursuing this goal. Older patients should be monitored closely for adverse effects, such as orthostatic hypotension, syncope, and changes in cognition and renal function.

4 Diabetes and Hypertension

Hypertension and type 2 Diabetes (T2DM) are highly prevalent worldwide [2], increase the risk of cardiovascular disease, and lead to premature morbidity and mortality while exacting exorbitant healthcare costs [22]. Data from NHANES 2013 to 2016 estimates 37.6% of US adults have prediabetes, 9.8% have diagnosed DM, and 3.7% have undiagnosed DM [1]. According to data from NHANES 2011 to 2016, even when the consensus SBP target was <140 mmHg, nearly 37% of adults with prediabetes had hypertension and 50% of adults with diabetes who were taking antihypertensive therapy did not meet treatment goals from the 2017 ACA/AHA BP guidelines [1]. Many patients with DM have concomitant hypertension [23], and the combination of both conditions appears to be more deleterious than either alone [23]. Because persons with DM have a high prevalence of hypertension and because of the link between DM and hypertension to premature CVD and other related diseases, BP control in persons with DM is a major clinical and public health issue [18, 23].

The benefit of a SBP target of <120 mmHg versus <140 mmHg on the reduction of cardiovascular events was assessed in two large randomized clinical trials: The Systolic Blood Pressure Intervention Trial (SPRINT) and the Action to Control Cardiovascular Risk in Diabetes Blood Pressure Trial (ACCORD-BP). Findings from the SPRINT trial indicated a significant benefit of intensive SBP on reducing CV events in adults without T2DM. In contrast to the SPRINT findings, the Action to Control Cardiovascular Risk in Diabetes Blood Pressure Trial (ACCORD-BP) randomized over 4700 study participants with T2DM to intense control to HbA1c <6.0% versus less intense control to HbA1c 7.0–7.9% and standard BP therapy (target SBP <140 mmHg) or intensive BP therapy (target SBP <120 mmHg) and found no difference between BP groups in the primary composite outcome of CV events and mortality despite a significant reduction in stroke incidence [24]. However, the intensive glucose lowering arm of the main ACCORD trial was stopped early due to excess deaths [25]. A post-hoc analysis of ACCORD data found participants in the less intense control to HbA1c 7.0–7.9% had a significantly reduced hazard of the primary composite outcome, similar in magnitude to those in the lower SBP arm (<120 mmHg versus SBP <140 mmHg), similar to the SPRINT Trial [26]. In addition, a re-analysis of ACCORD participants who would have met eligibility criteria for SPRINT (other than the exclusion for T2DM) that was restricted to those in the less intensive glycemic arm found a significantly beneficial association between strict SBP control and CVD outcomes (HR 0.79, 95% CI 0.65–0.96) [27]. While

there are no long-term intervention trials examining BP control inpatients with pre-diabetes, an analysis of 4193 patients with angiography-proven stable, newly diagnosed coronary artery disease followed for nearly 6 years found CV events did not differ between patients with prediabetes and normal glucose but when stratified by BP those with prediabetes or diabetes and elevated BP (<130/80 mmHg) had significantly increased CV events [28]. Thus, while the ideal BP goal in persons with DM remains controversial and there is even less data for pre-diabetes, emerging evidence supports a SBP less than 130 mmHg for persons with either prediabetes or diabetes [29].

In part, these findings led to recommending a target SBP of <130 mmHg [3, 20] while others continue to recommend a target SBP <140 mmHg) [14, 16]. The position of the ACC/AHA is, unless contraindicated, that target BP should be <130/80 mmHg for adults with T2DM since the majority of this population has a 10-year risk for atherosclerotic CV disease that is equal to or exceeds 10%, and are therefore considered to be at increased risk of CV events [3].

4.1 Generalizability of Clinical Trials and Patient-Centered Approach

Although several randomized controlled BP clinical trials have been conducted, differences in study design (such as inclusion and exclusion criteria), outcomes (e.g., differing BP goals and achieved BP levels), medications, and patient characteristics make the creation of clinical guidelines using these heterogeneous studies an art rather than a science and complicate the application of the guidelines to a given patient [30]. The specific inclusion and exclusion criteria of SPRINT may limit extrapolation to a more general population with hypertension, and many of the prior hypertension studies conducted BP measurements that were more consistent with the methods used in clinical practice [10]. After their review of SPRINT and other studies the ACC/AHA arrived at a recommended target SBP of <130 mmHg, which is higher than the actual low target SPRINT SBP of <120 mmHg [3]. Indeed, a recent analysis by Anderson et al. [31] examined data from the 2013–2014 and 2015–2016 NHANES data to identify the generalizability of SPRINT and ACCORD trial eligibility criteria to adults classified as having hypertension and recommended to receive pharmacotherapy according to the 2017 ACC/AHA guideline [3]. Using the 2017 ACC/AHA guideline they estimated that over 107 million US adults would be classified as having hypertension of which nearly 59 million would need intensified pharmacotherapy. They found nearly 45% did not meet trial inclusion criteria because of low CVD risk, and over one quarter met at least 1 exclusion criterion. Most younger adults (<50 years) would not have met trial inclusion criteria due to low cardiovascular risk, while most older adults who met the high CV risk inclusion criteria also met trial exclusion criteria. They concluded that while the 2017 ACC/AHA guideline substantially expanded the number of adults diagnosed as having hypertension and the number eligible for treatment, the inclusion/exclusion criteria

for SPRINT and ACCORD, two of the major trials driving the new guidelines were representative of less than one-third of the general population.

As noted earlier, the ACC/AHA guidelines also reinforce that clinicians use a patient-centered approach to the management of hypertension [31]. Active involvement of patients in their own care and increasing the quality of care using a range of blood pressure management tools are deemed essential for patient engagement [32]. Kalra et al. (2017) suggested the use of the 5T's to guide a patient-centered care approach to hypertension: (1) Technique of measurement; (2) Threshold for intervention; (3) Targets to be achieved; (4) Tools to be used; and (5) Tactics to be followed [32].

5 Strategies for Hypertension Management

The approach to treating blood pressure in patients with hypertension requires an understanding of both the recommended nonpharmacologic and pharmacologic interventions as well as the major CVD risk factors (Table 3). This may require certain lifestyle changes by the patient and education to ensure appropriate understanding of factors that can improve or worsen their condition. Meeting recommendations for both nonpharmacologic and pharmacologic interventions cannot only improve risk factors for CVD but also reduce premature morbidity and mortality.

5.1 Blood Pressure Measurement

Using a standardized technique for BP measurement is of critical importance in the office or at home to make well-informed clinical decisions [34]. It can be performed using an auscultatory device (one that requires a stethoscope) or an automated BP device designed for the office setting. Automated BP devices can take multiple consecutive readings in the office with the patient sitting and resting alone or with an observer present. Either attended or unattended automated BP measurement effectively predicts awake ambulatory blood pressure monitoring (ABPM) and may reduce the chance of inducing white coat hypertension [35]. The ACC/AHA highlights six points to consider in the appropriate measurement of BP: (1) properly preparing the patient, (2) use the proper technique for BP measurements, (3) take the proper measurements needed for diagnosis and treatment of elevated BP/hypertension, (4) properly document accurate BP readings, (5) average the readings, and (6) provide the BP readings to patient [3]. There should be adequate initial and booster training of healthcare professionals with periodic review of their performance to ensure quality and consistency of the BP measurement [3, 16]. Additional key points to consider in the appropriate measurement of BP include: (1) palpate the radial or brachial pulse to ensure the pulse is regular before measuring BP, as automated devices may not accurately measure BP in the setting of an irregular

Table 3 Overview of hypertension management

Assess blood pressure to confirm hypertension	
Appropriate measurement of blood pressure	
Ambulatory blood pressure monitoring to assess for white coat hypertension or masked hypertension	
Determine 10-year atherosclerotic cardiovascular disease risk (http://tools.acc.org/ASCVD-Risk-Estimator/) [7].	
Assess for comorbidities (e.g., diabetes mellitus, congestive heart failure, kidney disease)	
Nonpharmacological approach	
1. Smoking cessation	
2. Physically active – strive for >10,000 steps a day (5000 steps/day for those ≥65 yo)	
3. Restrict daily alcohol intake to 1 oz in men and 0.5 oz in women	
4. Reduce dietary intake of salt to <3 gm/day – may require 24 hour urine assessment to confirm [33]	
5. Discontinue nonsteroidal anti-inflammatory drugs (NSAIDs), including over the counter	
6. Identify level of kidney function to select proper antihypertensives, particularly diuretics	
7. In obese hypertensive patients initiate weight loss and a reduced-calorie diet	
Pharmacological approach	
1. Ensure optimal dosing regimens or appropriate antihypertensive drug combinations	
2.The currently recommended first-line medications include renin-angiotensin-aldosterone system blockers, calcium channel blockers, or diuretics.	
3. Many patients require two or more antihypertensive drugs to achieve target BP, but may be less if a high level of adherence to both pharmacological and nonpharmacological treatments	
3. If patients require >3 antihypertensive drugs to achieve target BP, with evidence of good adherence to both pharmacological and nonpharmacological treatments	
5. Combining angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) should be avoided	
6. Endothelin receptors antagonists are not currently recommended	
Common CVD risk factors in patients with hypertension	
Relatively nonmodifiable risk factors	*Modifiable risk factors*
Family history	Current cigarette smoking, secondhand smoke
Male sex	Diabetes mellitus
Low socioeconomic/educational status	Dyslipidemia/ hypercholesterolemia
Chronic kidney disease	Overweight/obesity
Obstructive sleep apnea	Unhealthy diet
Psychosocial stress	Physical inactivity/low fitness

pulse (e.g., atrial fibrillation), and if pulse is irregular, BP should be manually measured using direct auscultation over the brachial artery; (2) ensure that BP measuring devices are properly validated, maintained, and regularly recalibrated according to manufacturers' recommendations; and (3) provide a standardized environment including a relaxed, temperate setting, with the person quiet and seated, and the arm outstretched and supported, and always use a BP cuff size that is appropriate for the person's arm when measuring BP in the clinic or in the home [3, 16]. Utilization of

the correct cuff size is critical for accurate blood pressure measurement [36]. If a cuff size is too small, measurements of SBP and DSP tend to be elevated to a small or moderate degree. Conversely, large cuff sizes result in small decreased measurements [37].

5.2 Debate on Blood Pressure Measurement

It has been noted that SPRINT participants were assessed using unattended automatic BP, a method not used in other randomized controlled BP trials [10]. This method may underestimate BP values in standard clinical trial protocols as well as conventional office BP readings by as much as 16 mmHg [10]. While the potential to underestimate exists, a post-hoc analysis of SBP values in SPRINT participants stratified into four groups found BP levels did not differ between: (1) those who were either alone during the entire BP measurement process ($n = 4082$), (2) those who were never alone ($n = 2247$), (3) those who were alone for pre-measurement resting ($n = 1746$), and (4) those who were alone only for BP measurement ($n = 570$). These findings provide some assurance that attended or unattended BP values in SPRINT were similar, and therefore relatively comparable to other randomized controlled BP trials [38].

5.3 Ambulatory Blood Pressure Monitoring (ABPM)

While measurements made in the clinical setting should be used for screening purposes, clinic measures can be fraught with error and should not be singularly relied upon for diagnosing hypertension. The proper diagnosis of hypertension requires integration of home or ambulatory blood pressure monitoring (ABPM) to assess for white coat hypertension and masked hypertension (Table 4) [35]. White coat hypertension is identified when consistently elevated BP office readings do not meet the out-of-office diagnostic criteria for hypertension. By contrast, masked hypertension is identified when blood pressure is consistently elevated from out-of-office BP measurements do not meet office-based criteria for hypertension [35]. The diagnostic

Table 4 Office and out-of-office blood pressure patterns based

	Normotensive	Sustained hypertension	Masked hypertension	White coat hypertension
Office/clinic/healthcare setting	No hypertension	Hypertension	No hypertension	Hypertension
Home/nonhealthcare/ ambulatory blood pressure monitoring setting	No hypertension	Hypertension	Hypertension	No hypertension

Based on data from Ref. [7]

criteria for ABPM to qualify as hypertension includes: (i) 24-hour mean SBP and DBP of ≥125/75 mmHg, (ii) a daytime (awake) mean BP of ≥130/80 mmHg, or (iii) a nighttime (asleep) mean of BP of ≥110/65 mmHg [3]. One final point to consider is the role of ambulatory BP and whether office BP measures should be even lower than recommended targets to account for the high prevalence of masked hypertension, which has been reported in up to 40% of patients [39]. In a subset of over 500 participants assessed from the third follow-up cohort of the Australian Diabetes, Obesity, and Lifestyle Study 3, masked hypertension was found in 21% of adults [40]. Zhao and colleagues [41] found masked hypertension in over 25% in a cohort of 266 adults with DM. Importantly, masked hypertension was recently reported to have an increased risk of all-cause and CV mortality compared to sustained hypertension, which did not differ in magnitude by the presence or absence of DM [42]. Thus, the high prevalence of masked hypertension is yet another reason to consider the lower BP target of <130/80 mmHg from office readings in persons with hypertension, including those with DM.

5.4 Therapeutic Lifestyle Changes

Therapeutic lifestyle changes are particularly important in persons with hypertension because many of the major risk factors for hypertension are behavioral and modifiable. Healthcare providers should use evidence-based tools such as brief motivational interviewing or the 5A's (Ask, Advise, Assist, Assess, Arrange) to ask patients with suspected or diagnosed hypertension about their smoking status, diet and exercise patterns, provide lifestyle advice, and participate in local initiatives or services that provide support and promote healthy lifestyle change [16]. The identification and effective communication of risk-attributable behaviors (such as dietary intake, physical inactivity, excessive alcohol intake, and smoking) should engage and encourage patients to be proactive in the implementation of therapeutic lifestyle changes.

Substantial evidence indicates that diet is the most powerful modifiable risk factor with the most robust effect on blood pressure, largely because of its impact on obesity which strongly predicts hypertension [43]. While numerous commercial diets purport to be effective for weight loss, the scientific literature has shown that the Dietary Approaches to Stop Hypertension (DASH) is the most effective approach to reduce excess weight gain and reduce high blood pressure. The DASH study with a diet enriched in fruits and vegetables and low in sodium led to a 7.1 mmHg lower SBP in participants without hypertension, and 11.5 mmHg lower SBP in participants with hypertension compared to control diet with a higher sodium content [44]. A combination of DASH diet plus weight management significantly reduced clinic-measured BP by 16.1/9.9 mmHg compared to only 11.2/7.5 mmHg reduction by DASH diet alone; and 3.4/3.8 mmHg for the usual diet control group ($P < 0.001$) [45]. Although a goal of 10,000 steps per day is commonly promoted to improve CV health, there is limited evidence regarding its association with improved longevity [46]. In addition,

it was not clear if it is the number of daily steps or step intensity that may influence health outcomes. A recent analysis by Saint-Maurice et al. examined mortality in over 4000 NHANES participants (2003–2006) who wore an accelerometer for up to 7 days and found an increasing number of daily steps up to 12,000 a day was significantly associated with lower all-cause mortality, while step intensity was not, after adjusting for total steps per day [47]. Thus, increasing daily steps in contrast to step intensity is appears to be an effective healthy lifestyle approach.

Stress reduction may also be effective. Among 113 patients treated with antihypertensive drugs, participants randomly assigned to CALM-BP treatment (consisting of rice diet, walks, yoga, relaxation, and stress management) did as well as those assigned to a DASH diet plus exercise control group (consisting of DASH and walks), reinforcing the benefits of stress reduction strategies [39]. A summary of practical suggestions for the effective implementation of therapeutic lifestyle changes is listed in Table 5.

The recommendations for therapeutic lifestyle changes, such as weight control, dietary salt reduction, regular physical activity, stress reduction, smoking cessation, and adherence to clinic visits and pharmacotherapy, should be provided in specific detail with a patient-centered approach, making it possible to overcome some of these common barriers to therapeutic lifestyle changes (Table 6), and achieve successful implementation. This may frequently necessitate the inclusion of additional healthcare professionals (e.g., dietitian, social worker, pharmacist) and/or the inclusion of family members or close friends as part of a team approach.

The Mediterranean Diet is a second pattern of eating that shows promise for improving endothelial function and protective effects against hypertension [40, 41]. Similar to the DASH diet, the main components of the Mediterranean diet

Table 5 Key lifestyle changes to optimize blood pressure control

Healthy diet
Rich in fruit, vegetables, whole grains, and low-fat dairy products, with reduced content of saturated and total fat, low sodium, and high potassium
Regular physical activity
Increase physical activity as part of the daily routine by undertaking an enjoyable physical activity for 30–45 min per day for 3–5 days per week *Or 10,000 or more steps a day (5000 steps/day in those ≥ 65 yo)*
Weight maintenance
Monitor body weight and maintain a healthy body mass index
Maintain weight by making permanent changes in the daily diet
Stress reduction
Develop coping skills for specific stressors in work and/or home environment with meditation, relaxation, yoga, biofeedback, etc.
Moderate alcohol intake
Men: ≤2 drinks daily; Women: ≤1 drink daily
Smoking cessation
Offer advice and referral for intervention if needed to help smokers to stop smoking *Ensure smoke-free environment*

Table 6 Key approaches to achieve healthy dietary changes

Consider culturally appropriate nutritional substitutions
Eat more broiled (grilled) and steamed foods
Eat more grains, fresh fruits, and vegetables
Eat fewer fats and use healthier fats, such as olive oil
Eat fewer processed foods, fast foods, and fried foods
Read labels and pay attention to the sodium, potassium, and fat content of foods
Do not season foods with smoked meats, such as bacon and ham hocks
If lactose intolerant, try lactose-free milk or yogurt, or drink calcium-fortified juices or soy milk
Limit alcohol consumption to <2 beers, 1 glass of wine, or 1 shot of hard liquor per day
Limit the intake of sugar-sweetened beverages and juices

(MedDiet) are vegetables, fresh fruit, whole grains, fish and seafood, legumes, nuts, extra virgin olive oil, and red wine with limitations on red and processed meats [42, 48]. A paucity of international observational and intervention studies have explored the influence of the MedDiet on blood pressure and found that it resulted in inconsistent findings [49]. The Greek European Prospective Investigation into Cancer and Nutrition (EPIC) study demonstrated that the MedDiet score was significantly and negatively associated with systolic and diastolic blood pressure among a cohort of over 20,000 adult participants who were not diagnosed with hypertension [50]. After 6-years of follow-up, adherence to the MedDiet was related to small changes in mean levels of SBP and DBP among 9408 educated adults who participated in a Spanish prospective cohort study. A third observational population-based cohort study conducted in Athens, Greece, with 3042 adults with excess body weight showed that SBP (not DBP) was independently, negatively, but only modestly associated with the MedDiet [51].

In general, the paucity of randomized controlled dietary intervention studies resulted in small, but significantly lower SBP. The Prevencion con Dieta Mediterranea (PREDIMED) study was conducted in two Spanish centers with 7447 adults 55–80 years old to compare the MedDiet with a low-fat control diet, 80% of whom were diagnosed with hypertension. No changes in SBP were found in both intervention groups at the 4-year follow-up, however, DBP decreased by 1.5 and 0.7 mmHg, respectively [52]. Domenech et al. evaluated the PREDIMED dietary intervention with three arms using 24-hour ABPM to assess control of BP among 235 study participants 55–80 years old, most of whom were diagnosed with hypertension [52]. Participants were randomized to the MedDiet coupled with either extra virgin olive oil (e.g., oil that is free of defects of flavor or odor as measured by chemical and sensory standards) or mixed nuts compared to a control diet designed to reduce fat intake. Compared to the control group, at the 1-year follow-up, participants randomized to the extra virgin olive oil and mixed nuts groups had a 4.0 and 4.3 mmHg lower mean SBP, respectively, and both had 1.9 mmHg lower 24-hour mean DBP. Olive oil is hypothesized to be the most significant component of the

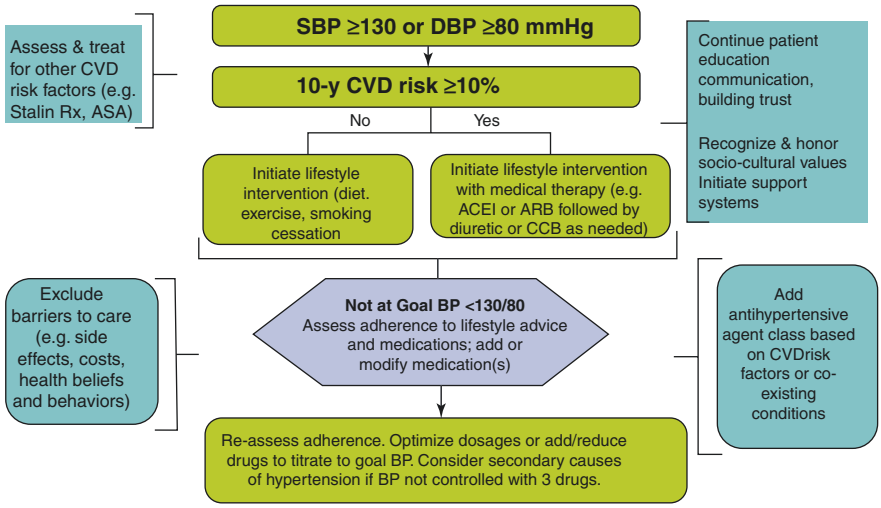
MedDiet by virtue of the vasoprotective effect of polyphenols and their reported ability to increase endothelial synthesis of nitric oxide and the response mediated by endothelium-derived hyperpolarization factor [49, 53, 54].

Lastly, a recent 12-month randomized clinical trial, the New Dietary Strategies Addressing the Specific Needs of Elderly Population for Healthy Aging in Europe (NU AGE) was conducted to assess the effects of a Mediterranean-style dietary pattern on BP and arterial stiffness. Blood pressure was measured in adults 65–79 years of age (N = 1294) and arterial stiffness was measured in a subset of 225 participants. Adults were either randomized to an intervention group that received individually tailored standardized dietary advice and commercially available foods to support adherence to the Mediterranean diet or to a control group encouraged to continue their regular diet, supplemented with national dietary advice. Follow-up assessments demonstrated a significant reduction in SBP (−5.5 mmHg; 95% CI, −10.7 − 0.4; p = 0.03) with an intervention effect that favored men (−9.2 mmHg; p = 0.02), but not women (−3.1 mmHg; p = 0.37) [41].

Over the past 5 years, interest in plant-based diets has increased in the USA. In general, the goal of a plant-based diet is to increase the intake of nutrient-dense plant foods while simultaneously reducing the consumption of processed foods, added sugars, oils, and animal-based foods. A 2014 meta-analysis of 7 randomized control trials and 32 observational studies showed that compared to an omnivorous diet, vegetarian diets lower both SBP and DBP [55]. Specifically, in observational studies, vegetarian diets were associated with an average of 6.9 and 4.7 mmHg lower systolic and diastolic blood pressure; and among randomized clinical trials, 4.8 and 2.2 mmHg, respectively. In regards to CV outcomes, a Mediterranean diet has also been associated with a lower risk of heart failure, stroke, all-cause and/or CV mortality in most [56–61], but not all studies [62]. The consistent results across studies provide robust evidence for the benefits of plant-based diets on cardiovascular health.

5.5 Pharmacologic Treatment

As a health professional, it is critical to ensure optimal dosing regimens and/or appropriate antihypertensive drug combinations when appropriate, using the classes of antihypertensive medications that have been shown in randomized clinical trials to most effectively reduce CVD complications. The recommended first line medications include renin-angiotensin-aldosterone system (RAAS) blockers, thiazide-type diuretics, and calcium channel blockers (CCBs) [3]. At recommended dosages there is comparable BP reduction with each of these classes, but differences exist in individual patient response to treatment and there is the need to consider comorbidities in selecting an antihypertensive drug [3, 63] (Fig. 1). The currently recommended initial treatment is to start with a RAAS blocker followed by either a diuretic or a CCB. Even with recommendations for lifestyle changes it is estimated that more than 50% of persons with hypertension will require two or more antihypertensive medications to achieve goal BP [6].



BP – blood pressure; SBP– systolic blood pressure; DBP- diastolic blood pressure; CVD – cardiovascular disease
ACEI – angiotensin converting enzyme; ARB - angiotensin receptor blocker; CCB – calcium channel blockers; ASA – aspirin

Fig. 1 Algorithm for treating elevated blood pressure

The use of BP-lowering medications is also recommended for primary prevention of recurrent CV disease events in adults with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk of 10% or higher and an average SBP ≥130 mm Hg or an average DBP ≥80 mmHg [7]. Similarly, the use of BP-lowering medication is recommended for primary prevention of CVD in adults with no history of CVD and a lower estimated 10-year ASCVD risk (<10%) but at a higher BP level: a SBP of ≥140 mmHg or a DBP ≥90 mmHg [7]. For secondary prevention of recurrent CV disease events in patients with clinical CVD, the use of BP-lowering medications is also recommended, typically when the average SBP is ≥130 mmHg or average DBP is ≥80 mmHg [7] (Fig. 1).

6 Combination Therapy

In most patients whose SBP is ≥15 mmHg above their goal, a single-agent therapy is not likely to lower BP to goal. Also, in such situations combination therapy with two or more drugs from different classes has a greater likelihood of achieving goal BP than increasing the dose of a single agent [64]. When multiple drugs are needed for BP control, therapy with either a long-acting ACE inhibitor or ARB (should *not* be used together) in concert with a diuretic or long-acting dihydropyridine calcium channel blocker should be considered. In any patient whose SBP is more than 20 mmHg systolic, or DBP is more than 10 mmHg above goal, combination therapy

with two first-line antihypertensive agents of different classes is suggested as initial treatment alongside lifestyle advice [7, 65].

If BP remains uncontrolled with the use of two antihypertensive medications, then adding a third medication that is from the third class of antihypertensive agents, should be instituted: (i) ACE inhibitor or ARB, (ii) thiazide-like diuretic, (iii) long-acting dihydropyridine calcium channel blocker. If a long-acting dihydropyridine calcium channel blocker is not tolerated due to side effects such as peripheral edema, a non-dihydropyridine calcium channel blocker (e.g., diltiazem or verapamil) can be used instead. If a thiazide-like diuretic is not tolerated or is contraindicated, the use of a mineralocorticoid receptor antagonist (e.g., spironolactone or eplerenone) should be considered.

While these are general recommendations, in several instances one of the above three drug classes cannot be used due to contraindication or intolerance, or due to coexisting medical conditions there may be a strong reason for other options such as a beta blocker, alpha blocker, or direct arterial vasodilator. Of note, the concomitant use of beta blockers and non-dihydropyridine calcium channel blockers should be avoided because drugs from these classes each have negative cardiac inotropic effects. If a patient's BP is not controlled on reasonable doses of a combination of three agents that include a diuretic and the patient is considered adherent, the patient is considered to have drug-resistant hypertension. Such patients warrant an evaluation for secondary causes of hypertension and referral to a specialist.

6.1 Drug Resistant Hypertension

A patient is considered to have drug-resistant hypertension if their BP is not controlled on three antihypertensive agents that include a diuretic despite appropriate BP measurement including assessment of home BP, adherence to non-pharmacologic treatment, and exclusion of substances that may interfere with BP control (e.g., NSAIDs, sympathomimetic drugs) [66, 67]. The addition of, or change from, a thiazide diuretic to chlorthalidone or a mineralocorticoid receptor antagonist, loop diuretics (if chronic kidney disease is present), and the addition of other medications with different mechanisms of action (e.g., beta blocker, alpha agonists, peripheral vasodilators, rauwolfia alkaloids such as reserpine) may be needed. A referral should be made to a specialist for further evaluation if enhanced treatment BP is not controlled after 6 months; assessment of secondary causes of hypertension such as primary aldosteronism, chronic kidney disease, renal artery stenosis, obstructive sleep apnea, or pheochromocytoma should also be considered [66, 67]. Treatment with new device therapy such as renal nerve ablation therapy and carotid baroreceptor activation showed early promise, but unfortunately long-term controlled trials have not shown proven benefit of these devices in treating resistant hypertension [66, 67].

To that end, concern has been raised regarding the number of additional medications needed to achieve the lower SBP target in SPRINT. However, an important and

frequently overlooked aspect of SPRINT is that the usual study goal of <140 mmHg was achieved with ~1.8 antihypertensive medications/day (for achieved SBP of 134 mmHg) [31], in comparison to ~3 antihypertensive medications/day in many other hypertension trials with a higher BP target (<140/90 mmHg) and an achieved SBP of 130–140 mmHg [68]. In fact, even the lower SBP goal (<120 mmHg; achieved SBP of 121 mmHg) was actually attained with only ~2.8 antihypertensive medications/day [31]. This suggests that the manner of blood pressure measurement, additional nonpharmacologic factors such as enhanced behavioral changes to reinforce medication adherence and lifestyle changes, and/or pharmacologic measures such as the use of the longer acting diuretic chlorthalidone [69] may have contributed to achieving the lower BP target among SPRINT participants with the avoidance of excessive medications use. Chlorthalidone is a diuretic with a longer half-life than thiazide diuretics (approximately 40 hours vs 10 hours) with greater antihypertensive efficacy [70] and enhanced clinical outcomes [69, 71]. While SPRINT results heavily influenced the ACC/AHA BP guidelines, it is important to remember the recommendations are for a SBP target of <130 mmHg and not the SPRINT low BP target of <120 mmHg [3].

6.2 Fixed-Drug or Polypill Antihypertensive Combinations

Fixed-dose, single-pill combination medications should be used when possible to reduce patient pill burden and to enhance medication adherence. Fixed antihypertensive drug preparations [72–79] or polypills which are fixed-dose combination of medications with proven benefits for the prevention of CV disease usually include aspirin or a statin (e.g., atorvastatin, amlodipine, losartan, and hydrochlorothiazide). Some designed more directly for blood pressure control (thiazide, beta blocker, and angiotensin converting enzyme inhibitor) have also been reported as useful [80, 81]. In fact, a polypill-based strategy has led to greater reductions in SBP and LDL cholesterol levels than were observed with usual care even in a socioeconomically vulnerable minority population [81].

6.3 Emerging Issues for Reducing CV Risk in Patients with Diabetes

Most of the traditional trials assessing hypertension control in patients with DM utilized more traditional diabetes agents such as insulin, metformin, sulfonylurea, and/or thiazolidinediones [26]. Newer classes of diabetic medications such as the glucagon-like peptide-1 (GLP1) receptor agonists and the sodium-glucose co-transporter 2 (SGLT2) inhibitors have demonstrated cardioprotective and renoprotective effects [82, 83]. However, it is not clear if these newer antidiabetic agents

may be associated with different outcomes based on the degree of BP control. The LEADER trial found that outcomes by level of glycemic control did not differ and outcome differences by BP control were not reported [83]. What the impact of newer DM agents may be on SBP targets in persons with T2DM and hypertension remains to be elucidated.

7 Potential Strategies for Improving Medication Adherence to Achieve Effective Blood Pressure Control

Broadly, lack of adherence may come in several forms, such as receiving a prescription but not filling it, changes in the frequency of medication doses, missing office visits and others (Table 7). For example, between 25% and 30% of the 3358 participants taking antihypertensive medication in the Jackson Heart Study reported not taking ≥1 of their prescribed antihypertensive medications within the 24 hours prior to their baseline study and follow-up examination visits [1]. For these study participants poor adherence was associated with 26% higher likelihood of having a SBP ≥140 mm Hg or DBP ≥90 mm Hg compared to those with good adherence [1]. Varying adherence interventions have yielded mixed results. Pladevall et al. randomized 877 patients with uncontrolled hypertension to a multifactorial intervention group in which physicians counted patients' pills, provided educational information or usual care to patients, and designated a family member to support adherence behavior [84]. Intervention patients were nearly twice as likely to be adherent at 6 months and almost half as likely to have uncontrolled SBP. However, after 5 years follow-up there was no difference in long-term CV events [84]. Thus, further studies are needed to assess additional adherence approaches on long-term outcomes.

Adherence to blood pressure control can be categorized into five major groups of key risk factors: (1) patient-centered, (2) therapy-related, (3) healthcare system, (4) social and economic, and (5) disease related (Table 7) [85–87]. Several of these risk factors for adherence to blood pressure control are behavioral and modifiable. The identification and communication of the risk attributable to behaviors (such as dietary indiscretion, physical inactivity, excessive alcohol intake, and smoking), particularly within the context of established CVD burden, should engage and encourage the patient to be proactive in risk reduction strategies [88].

Another key component to blood pressure adherence is effective communication. Effective communication necessitates compassion and concern by the healthcare provider to engender a sense of trust. Other factors that are more difficult to address directly, but equally important to assess and integrate into a comprehensive care plan, include insurance status and social support (Table 7). Lack of insurance is associated with lower rates of BP control among treated, but not among untreated, persons with hypertension, likely related to differences in appropriate treatment intensification or adherence, rather than differences in rates of treatment initiation [89]. Assessing a

Table 7 Categories of factors that influence adherence

Patient-centered factors	Demographic factors: *age, race/ethnicity, gender, education, marital status*
	Psychosocial factors: *beliefs, motivation, attitude*
	Patient-prescriber relationship: *trust, confidence, respect*
	Health literacy: *effective communication*
	Patient knowledge
	Physical difficulties
	Tobacco, smoking, alcohol intake or substance abuse
	Forgetfulness: *disease or medication related*
	History of good compliance: *highly motivated, self-efficacious*
Therapy-related factors	Route of administration
	Treatment complexity
	Duration of the treatment period
	Medication side effects
	Degree of behavioral change required
	Change in one's daily routine
	Taste of the medication
	Requirements for drug storage
Healthcare system factors	Lack of accessibility
	Long waiting time
	Difficulty in getting prescriptions filled
	Unhappy clinic visits
	Trust or distrust of the provider or the health system
Social and economic factors	Inability to take time off work
	Inability to coordinate childcare or eldercare
	Cost of therapy
	Adequacy of community assets to support healthy cardiovascular lifestyle
	Presence or absence of effective social support
Disease factors	Disease symptoms or lack of symptoms
	Severity of the disease: *impact on memory, impact on implementing healthy cardiovascular lifestyle*
	Depression: *disease related, medication related, other*

patient's insurance medication coverage and adjusting therapy accordingly can play an important role in enhancing adherence. Other healthcare system level factors are highlighted in Table 7.

Lack of adherence to CV lifestyle recommendations and antihypertensive medications not only causes personal hardship due to accelerated morbidity and mortality, but societal hardship from increased healthcare costs. Pittman et al. reported patients with high adherence were more likely to be male and older, have higher

numbers of coexisting chronic diseases, lower copayments for antihypertensive medications, and fill a greater percentage of prescriptions by mail order. Patients with high levels of adherence had significantly lower adjusted odds of CVD-related hospitalizations, emergency department visits, and adjusted healthcare costs compared to the moderate and low adherence groups [90]. Similar findings were reported in a cohort of nearly 60,000 Canadian patients with essential hypertension between 45 and 85 years of age with no evidence for symptomatic CV disease [91].

Special consideration for optimizing adherence needs to recognize the substantial diversity of patients with hypertension in the USA which necessitates an appropriate sensitivity to and understanding of socio-cultural factors such as education, socioeconomic status (SES), family support, insurance profile, and religious and health beliefs/behaviors to achieve targeted SBP. The high prevalence of low educational attainment and high unemployment as well as increased rates of being under- or uninsured and reduced access to quality healthcare further impact cardiovascular health in the USA [92]. These conditions predispose to reduced quality of care, psychosocial stress, elevated BP, and worse outcomes [93–96].

8 Conclusion

Hypertension treatment should be driven, in part, by not only the prevalence of coexisting cardiovascular risk factors but the prevailing socioeconomic context that is integrated into an effective real-world treatment plan for an individual patient. Thus, in addition to selecting the most appropriate pharmacotherapies, achieving optimal outcomes necessitates an appropriate sensitivity to, and an understanding of, each patient's unique sociocultural and economic aspects to maximize effective access to care, adherence to treatment, and scheduled follow-up. Optimal hypertension control necessitates an appropriate sensitivity to, and an understanding of, demographic and sociocultural factors such as race/ethnicity, gender, age, employment rate, income levels, leisure time availability, poverty, family support, education, medical insurance status, and others that may act as barriers to a recommended care plan and adherence to that plan. When these issues to unravel many of the barriers to hypertension control are integrated into a comprehensive approach that includes lifestyle recommendations and guideline-informed use of antihypertensive medications, we increase the value of BP care with an increased likelihood of appropriate BP control and improved cardiovascular outcomes with reduced healthcare costs.

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Cardiodiabetology: Reducing Risks to Optimize Cardiovascular Disease Outcomes

Nathan D. Wong and Yehuda Handelsman

Summary

- Atherosclerotic cardiovascular diseases, including coronary heart disease, stroke, heart failure, and peripheral arterial disease, along with microvascular disease (retinopathy, neuropathy and chronic kidney disease), are principal causes of morbidity and mortality in persons with diabetes.
- Diabetes is associated with great heterogeneity in cardiovascular disease risk, warranting cardiovascular risk assessment, including global risk scoring and consideration of risk-enhancing factors and subclinical atherosclerosis.
- Few persons with diabetes are at recommended targets for all major cardiovascular risk factors, including LDL-cholesterol, blood pressure, HbA1c, nonsmoking status, and body mass index.
- The treatment approach for diabetes involves consideration of cardiovascular risk assessment, lifestyle modifications: diet and exercise, weight control and avoidance of cigarette smoking; cholesterol, blood pressure, and glucose management; and for higher risk patients, antiplatelet therapy.
- Newer medications for diabetes, including SGLT2 inhibitors and GLP-1 receptor agonists, also reduce cardiovascular events independent of glycemic control. Both classes prevent further kidney function deterioration while the SGLT2 inhibitors reduce heart failure hospitalizations.
- A multidisciplinary team is required to address the myriad of cardiovascular risks in persons with diabetes.

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1 Introduction

Diabetes mellitus (DM), in particular type 2 DM, is increasing in prevalence worldwide, fueled largely by the obesity epidemic as well as unhealthy lifestyles. Nearly 500 million adults have diabetes, a number expected to increase to 700 million by 2045. Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in persons with DM, due principally to coronary heart disease, stroke, heart failure, and peripheral arterial disease. While type 2 DM has traditionally been referred to as a coronary heart disease (CHD) risk equivalent, it actually presents with a great heterogeneity in CHD and CVD risk which is dependent on many factors such as severity of accompanying risk factors, duration of diabetes, and the presence of risk-enhancing factors and subclinical atherosclerosis, thus warranting the importance of risk assessment. However, while DM is not necessarily a CHD risk equivalent, those with DM do have a markedly higher risk for CVD events. Persons at recommended levels and/or treatments for blood pressure, lipids, and glucose, as well as at non-smoking status and ideal body weight, have significantly lower rates of adverse cardiovascular outcomes than those who are not. Few persons with type 2 DM, however, are at target recommendations for all these measures, warranting the need for improved coordination of care to ensure that not only microvascular complications are minimized by glucose control, but also CVD risks are managed aggressively to prevent adverse CVD outcomes. Thus, cardiovascular risk assessment, blood pressure, cholesterol, glucose management, as well as proper dietary and exercise strategies and weight control, smoking cessation, and, as appropriate, antiplatelet therapy for people at higher risk, comprise the key strategies to manage CVD risk in persons with DM.

This chapter will review the epidemiology of DM and CVD, approaches for CVD risk assessment, the role of composite risk factor control, and the key strategies for CVD risk reduction in DM, including the evidence and recommendations for newer therapies aimed to reduce CVD risk in DM.

2 Epidemiology of Diabetes and Cardiovascular Disease

Latest estimates from 2019 indicate 463 million (9.3%) adults worldwide aged 20–79 years are living with diabetes, a number expected to rise to 578 million (10.2%) by 2030 and to 700 million (10.9%) by 2045. Current annual deaths due to complications from diabetes are estimated to be 4.2 million and annual healthcare expenditures exceed 750 billion US dollars [1]. China, India, and the United States have the greatest number of cases of diabetes with 116.4 million, 77.0 million, and 31.0 million cases, respectively [1].

Cardiovascular disease is the most common cause of death among patients with diabetes, according to data from death certificates. Heart disease accounts for approximately 55% of all deaths and cerebrovascular disease is responsible for another 10% of deaths [2].

Acute diabetes-related complications are the next most common cause of death, accounting for 13% of deaths. Pneumonia/influenza, malignant neoplasms, and other causes account for the remaining deaths [2]. Data from the Emerging Risk Factors Collaboration shows diabetes to confer a 2.0-fold increased risk of coronary heart disease, while the risks for ischemic and hemorrhagic stroke are increased 2.3- and 1.6-fold [3]. Recent data from a population of 1.9 million persons demonstrated the most common initial manifestations of CVD in adults with diabetes mellitus (DM) were peripheral arterial disease (16.2%) and heart failure (14.7%), followed by stable angina, nonfatal myocardial infarction, and stroke [4]. Moreover, among cardiovascular patients, data from the Glucose Tolerance in Patients with Acute Myocardial Infarction study, Euro Heart Survey, and the China Heart Survey show 34–45% have diabetes and another 35–37% have prediabetes, indicating the vast majority of cardiovascular patients have abnormal glucose tolerance [5]. It has also been shown that upon admission for an acute coronary syndrome approximately 15% of patients are newly diagnosed with T2DM [6] and some two-thirds of patients meeting criteria for DM based on fasting glucose are discharged from hospital inappropriately undiagnosed for DM [7].

We previously showed among US adults from the National Health and Nutrition Examination Survey mortality from CHD, CVD, and all causes to increase in a stepwise gradient among those who were disease free, or had metabolic syndrome, diabetes, and prior CVD, with the highest rates seen for those who had both DM and CVD, indicating this combination to be a very high-risk condition (Fig. 1). Of interest, however, all-cause mortality is similar in those with DM without CVD compared to those with CVD without DM, suggesting these conditions to be risk equivalents for all-cause mortality [8]. The Framingham Heart Study demonstrated that diabetes is a stronger risk factor for CVD outcomes in women compared to men. While diabetes is associated with a 2.2-fold greater risk of all CVD outcomes in men (absolute rate 76/1000), the respective increase in risk was 3.7-fold in

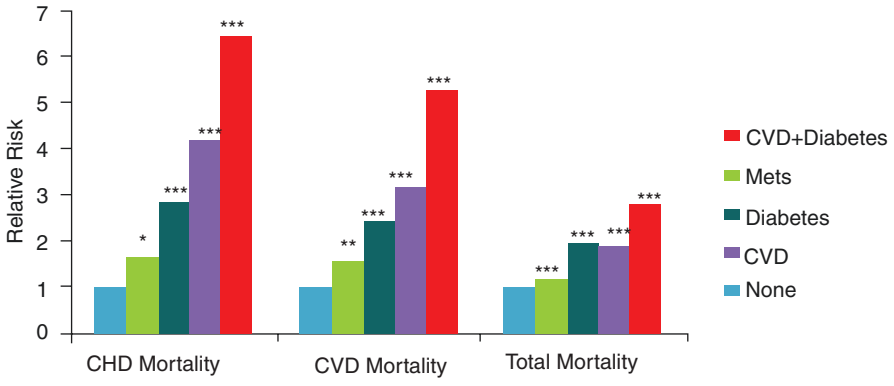

Fig. 1 Metabolic syndrome and diabetes in relation to CHD, CVD, and total mortality: US men and women ages 30–74. * $p < .05$, ** $p < .01$, **** <.0001 compared to none. (Based on data from Ref. [8])

women (absolute rate 65/1000). In particular, the sex difference for the relative risk associated with DM was substantial for peripheral artery disease (3.4 in men and 6.4 in women; absolute rate 18/1000 for both) and heart failure (4.4 in men and 7.8 in women; absolute rate 23 and 21/1000, respectively) [9]. The presence of chronic kidney disease (CKD) with diabetes increases the risk of many cardiovascular complications (myocardial infarction, stroke, heart failure, peripheral arterial disease, and death) by at least another twofold [10].

3 Cardiovascular Risk Assessment in Diabetes

The work of Haffner and colleagues [11] showing that among Finnish men those with DM without a prior myocardial infarction (MI) had a similar risk of future MI as those with a prior MI but without DM helped promulgate the concept that DM was a risk equivalent for CHD. This was also adopted by the Third Adult Treatment Panel of the National Cholesterol Education Program in 2001 [12]. However, several years later, a meta-analysis of over a dozen studies examining this issue showed that those with DM without a prior MI had a 43% lower risk of future CHD compared to those with a prior MI without DM [13]. In an analysis of US adults [8], it was shown that DM (without CVD) carried a lower risk of CHD and CVD mortality than those with preexisting CVD (without DM). Moreover, it has been shown utilizing global risk assessment with the Framingham risk equations that among US adults with DM from NHANES, nearly a third of men and half of women did not reach CVD risk equivalent status and were at intermediate or lower risk (<20% 10-year risk of CVD events) [14]. Finally, data from the Multiethnic Study of Atherosclerosis examining CHD and CVD event rates, according to levels of coronary calcium in adults with DM or metabolic syndrome, show a tenfold variation in event rates (Fig. 2). For example, in those with DM with a 0 calcium score, CHD event rates were 0.4% per year, compared to 4% per year in those with calcium scores of 400 or greater [15]. Most recently, Rana and colleagues showed, among a large registry of DM patients from Kaiser Permanente, DM patients with a duration of DM of 10 years or more to have a risk similar to those with preexisting CHD [16]. Thus, while those with DM are clearly at higher risk of CVD events than those without DM, some are at clearly higher risk than others, warranting quantitative risk stratification.

Key risk factors in persons with DM that promote CHD risk include elevated low-density lipoprotein cholesterol (LDL-C), low high-density lipoprotein cholesterol (HDL-C), elevated blood pressure, and elevated triglycerides. The UKPDS showed among 2693 persons with DM, important predictors (of a first CVD event) were in order of importance: LDL-C, HDL-C, A1c, systolic blood pressure, and cigarette smoking [17]. Thrombogenic and inflammatory factors include C-reactive protein, intereukin-1, fibrinogen, and PAI-1, all of which are increased in DM [18]. Diet, physical activity, tobacco smoking, obesity, and excess alcohol consumption can also influence risk. Nonmodifiable factors include age, sex, and family and

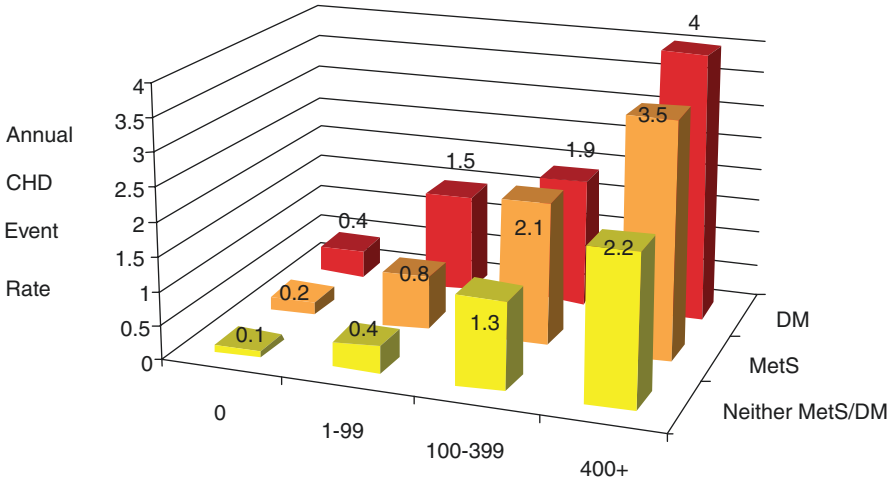

Fig. 2 Annual CHD Event Rates (in %) by Calcium Score Events by CAC Categories in Subjects with DM, MetS, or Neither Disease [15]. (Courtesy of Nathan D. Wong, PhD)

personal history of CVD [19]. In the Swedish National Diabetes Register a glycated hemoglobin level outside the target range was the strongest predictor of stroke and acute myocardial infarction, and patients who were younger than 55 years had the highest excess risk [20] Patients with type 1 DM are also at risk for ASCVD. The strongest predictors for death and cardiovascular outcomes were glycohemoglobin, albuminuria, duration of DM, systolic blood pressure, and LDL-C [21]. Risk factors frequently cluster together and in persons with DM, among those with hypertension, hyperlipidemia, and obesity, over 35% have two of these factors and another 21% have all three [22]. Long ago the MRFIT study showed risk of mortality varies fourfold (from 31 to 125 per 10,000 person years) comparing those with DM who have no risk factors to those who smoke and have elevated cholesterol and blood pressure [23].

The 2018 AHA/ACC Multisociety Guideline for Management of Blood Cholesterol [24] recognizes the importance of risk stratification in persons with DM. The following "risk-enhancing factors" can be used to inform the treatment decision regarding initiating or intensifying statin therapy: long duration (≥10 years for type 2 diabetes mellitus or ≥20 years for type 1 diabetes mellitus), albuminuria ≥30 mcg of albumin/mg creatinine, eGFR <60 mL/min/1.73 m^2, retinopathy, neuropathy, and an ankle brachial index of <0.9. While at least a moderate-intensity statin is recommended for those with DM aged 40 and over, it is recommended the Pooled Cohort Risk Calculator be used to determine the 10-year ASCVD risk, which if over 20%, recommends the use of a high-intensity statin with ezetimibe if needed to reduce the LDL-C by at least 50%. However, neither this risk calculator nor the Framingham risk calculators were derived from exclusive DM samples and treat DM as a binary factor in the equation, without consideration for other factors such as HbA1c or duration of DM. Specifically, the UKPDS risk score (Fig. 3),

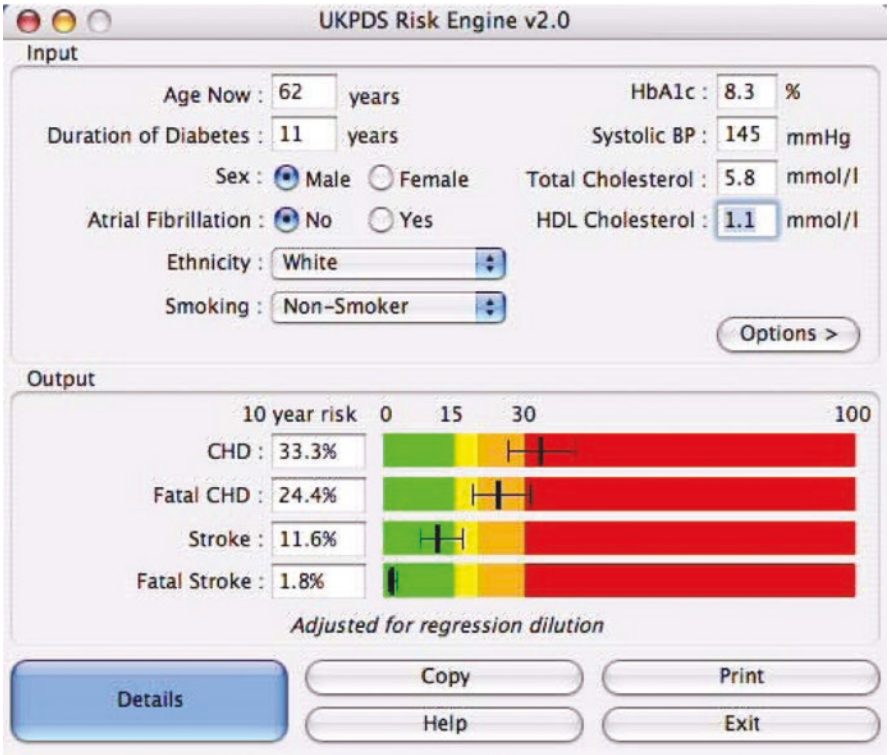

Fig. 3 UKPDS risk engine. T2DM specific risk calculator. Based on 53,000 patients years of data from the UK Prospective Diabetes Study. Risk estimates and 95% confidence intervals in individuals with type 2 diabetes not known to have heart disease. (Based on data from: http://www.dtu.ox.ac.uk/riskengine [24])

which was derived from the large UKPDS diabetes sample, does calculate the 10-year risk of fatal and nonfatal MI and stroke and includes factors such as duration of DM, HbA1c, and even the presence of atrial fibrillation [25]. There have also been attempts to develop other risk scores for those with DM in the United States, such as from the ACCORD cohort [26]. There is a need for a DM Pooled Cohort Risk Score for calculating the risk of total CVD and its major components which will help to more precisely quantify CVD risks in patients with DM in the future.

4 Evidence for Multiple Risk Factor Control to Reduce Cardiovascular Risk

Glycemic and cardiovascular risk factor control in persons with DM remains suboptimal. Studies examining composite control of multiple risk factors note this remains poor with little improvement over the past decade. A recent report from

the US Diabetes Collaborative Registry Analysis of 74,393 US adults with DM [27] showed 74% of patients have a HbA1C <7% (<8% if with ASCVD), 40% had blood pressure <130/80 mmHg), 49% to have an LDL-C <100 mg/dL (<70 mg/dL if with ASVD), and 85% were nonsmoking. Only 13% of patients, however, were at target for all four measures. Moreover, an analysis of NHANES 2013-2016 [28] showed similar results with 56%, 51%, and 49% at targets for HbA1c, blood pressure, and LDL-C cholesterol, respectively, but only 17% at guideline target for all three. With the addition of proportion nonsmoking (84%) and with BMI <25 kg/m^2 (9%), fewer than 10% were at all five targets. Moreover, composite target achievement tended to be worse for those with preexisting CVD compared to those without (20% and 10%, respectively, for HbA1c, LDL-C, and BP control together).

The Intensified Multifactorial Intervention in Patients With Type 2 Diabetes and Microalbuminuria (STENO-2) trial is among the few trials designed specifically to examine the impact of comprehensive risk factor control (lipids, blood pressure, glucose, diet, exercise) on cardiovascular and mortality outcomes. The primary trial involving 7.8 years of follow-up showed a 53% reduction in the composite CVD endpoint of CVD death, myocardial infarction, stroke, revascularization, and amputation by the end of the trial [29]; however, of note, a further 13-year follow-up report showed mortality to be 40% lower in the intensively treated group [30], suggesting a possible legacy effect beyond the original trial from comprehensive CV risk factor management that occurred during the trial. Moreover, in the Bypass Angioplasty Revascularization Investigation 2 (BARI 2D) trial of DM subjects with CAD, those who had a greater number of risk factors controlled to optimal levels (nonsmoking, blood pressure, non-HDL-cholesterol, HbA1c, and triglycerides) had a decreased risk of MI, stroke, and death [31] (Fig. 4). Finally an analysis from a pooled cohort of more than 2000 subjects with DM without CVD at baseline from the MESA, Jackson, and Atherosclerosis Risk in Communities (ARIC) prospective studies [32] showed lower CHD and CVD event

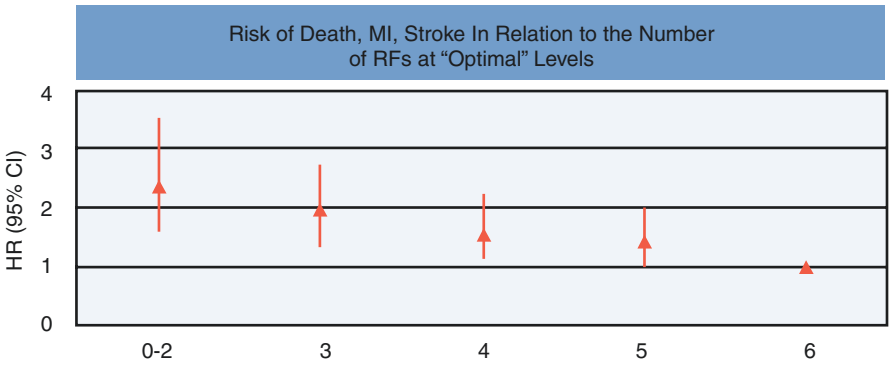

Fig. 4 Risk of death, myocardial infarction, and stroke in relation to the number of risk factors at optimal levels: BARI-2D study. (Reprinted from Bittner et al. [31]. With permission from Elsevier)

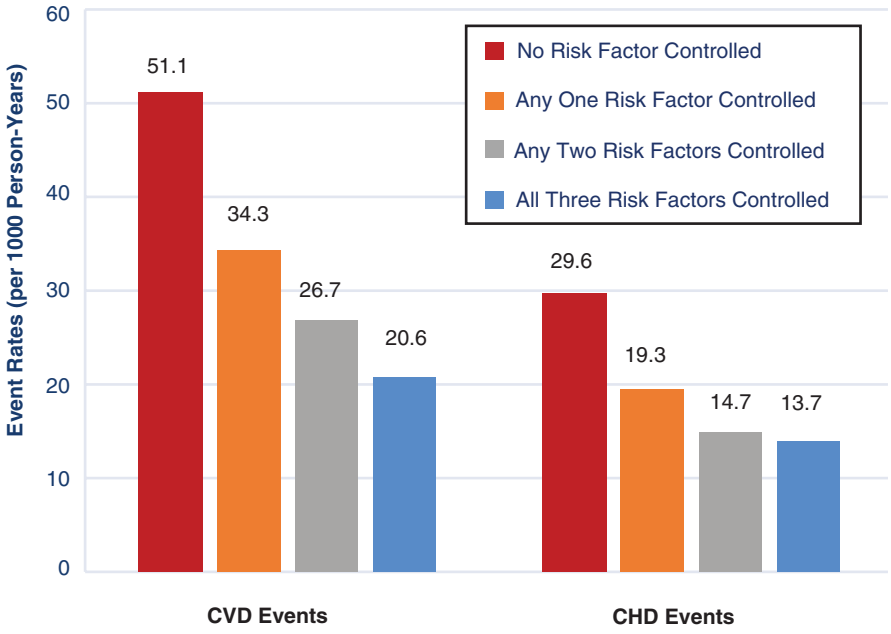

Fig. 5 CVD and CHD event rates by number of risk factors at target among HbA1c, LDL-C, and blood pressure: pooling of ARIC, JACKSON, and MESA study DM subjects. (Courtesy of Nathan D. Wong, PhD)

rates the more the number of risk factors at target (Fig. 5), and that those who had HbA1c <7%, blood pressure <130/80 mmHg, and LDL-C <100 mg/dl had a 62% lower CVD event risk and a 60% lower CHD event risk after adjustment for age, sex, ethnicity, and other risk factors. Findings were also robust in African Americans who comprised about half of the cohort. These data together show the importance of composite risk factor control in persons with DM in optimizing CVD risk reduction. Improved efforts to coordinate control of these multiple risk factors are needed given the currently poor state of risk factor control among US adults with DM.

5 Cardiovascular Risk Management in Diabetes

The management of CVD risks in persons with DM involves a comprehensive approach addressing: (a) assessment of CVD risks (as discussed above), (b) lifestyle management, (c) statins and other lipid-lowering drugs, (d) blood pressure management, (e) hyperglycemia management, and (f) aspirin therapy for those at highest risk. Each of these will be addressed in the following sections, including the most recent recommendations for management.

6 Lifestyle Management

The Diabetes Prevention Program (DPP) was highly successful in showing a lifestyle program involving diet to reduce weight by 7% and physical activity of 150 minutes per week resulted in a 58% reduction in risk of developing DM among persons with pre-DM, which was even more effective than the 31% risk reduction provided with metformin therapy over usual care [33]. Lifestyle management of DM was examined in the LOOK AHEAD trial to reduce CVD events in persons with established DM and after 9 years of follow-up there was no macrovascular or death benefit seen. However, there was improvement in systolic blood pressure, LDL-C, and HDL-C, although with diminishing group differences over time [34].

Diet and Weight Management Importantly, the PREDIMED trial in more than 8000 persons with DM or multiple risk factors for CVD implemented a Mediterranean diet intervention and showed a striking 30% reduction in risk of future CVD events in those who consumed such a diet supplemented by either extra virgin olive oil or nuts, compared to a standard low-fat diet [35]. The importance of weight loss in reducing cardiometabolic risk factors cannot be overemphasized; a 15% weight loss resulted in substantial improvements in many risk factors including systolic (10.5%) and diastolic (9.3%) blood pressure, serum glucose (16.5%), triglycerides (44.8%) and total cholesterol (11.8%). These results indicated that generally a 5–10% weight loss is sufficient to improve CV risk factors [36]. The ACC/AHA Guideline on Lifestyle Management [37] is in line with other medical societies (the ADA and AACE), and recommends a dietary pattern that emphasizes intake of vegetables, fruit, and whole grains; includes low-fat dairy products, poultry, fish, legumes, non-tropical vegetable oils and nuts; and limits the intake of refined sugar, sugar-sweetened beverages, and red meats.

Physical Activity It is also recommended that persons with or without diabetes perform at least 150 min/week of moderate-intensity aerobic physical activity (50–70% of maximum heart rate), spread over at least 3 days per week with no more than 2 consecutive days without exercise, and in the absence of contraindications, adults with type 2 diabetes should be encouraged to perform resistance training at least twice per week.

Cigarette Smoking Cessation Both in those with and without DM, cigarette smoking is an important risk factor for CVD events. The methodology for smoking cessation is similar for those with and without DM and focuses on the 5As [38], which should be addressed at each patient visit by the provider and involves: (1) Asking and documenting current tobacco use, and if a user, (2) Advising in providing a strong personalized message to quit, (3) Assessing readiness to quit in the next 30 days, and if ready (4) Assisting in negotiating a plan to quit, which should involve the STAR plan which involves setting a quit date, telling family, friends, and coworkers, anticipating challenges: withdrawal, breaks, and removing tobacco from the house, car, etc., and may also involve pharmacotherapy, providing social support

and educational materials, and (5) Arranging follow-up to check the plan and adjust medications if necessary, which may involve calling the patient before and after the quit date, weekly follow-up for 2 weeks then monthly, asking about difficulties, building upon successes, and seeking a commitment to remain tobacco free. In a recent quitter, it is important to prevent relapse by congratulating the patient, providing encouragement, discussing benefits experienced by patient, and addressing weight gain, negative mood, and lack of support. If the patient is not yet ready to quit, increase motivation relevant to the personal situation, address short and long-term environmental risks, potential benefits of quitting, identify barriers and solutions, repeat motivational intervention, and reassess readiness to quit. Finally, avoidance of second-hand smoke, which can substantially increase CVD risks in a nonsmoker, as well as other nicotine-based products (e.g., vaping products and chewing tobacco) should be a priority in all patients.

7 Blood Pressure Control

The UKPDS [39] showed the importance of tighter blood pressure control (then defined as <150/85 mmHg) compared to less tight control (then defined as <180/105 mmHg) in reducing both microvascular and macrovascular events, resulting in a significant 37% reduction in microvascular disease, 34% reduction in retinopathy progression, 37% reduction in vision deterioration, 44% reduction in stroke, and 56% reduction in incident heart failure; the composite of any diabetes-related endpoint and all-cause mortality was reduced a significant 32%. The UKPDS and other studies led guidelines committees to recommend a target blood pressure of <130/80 mmHg for persons with DM, which was lower than that for the general population (<140/90 mmHg) for many years. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Blood Pressure Trial [40] involving 4733 patients with DM, however, found that more intensive BP control with a target of <120 mmHg systolic compared to <140 mmHg systolic did not provide incremental benefit for the primary composite CVD endpoint of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death; however, there was a 41% relative risk reduction in stroke, although stroke event rates were low. This study prompted some societies to recommended treatment initiation and target levels of BP to <140/90 mmHg in those with DM.

More recently, while the SPRINT trial of persons without ASCVD or DM who had a systolic blood pressure of ≥130 mmHg showed 25% reductions in CVD events in high risk persons without DM, a recent sub-analysis of SPRINT-eligible persons in ACCORD with DM, while a post-hoc analysis, did show a significant and similar 21% reduction in CVD events [41]. Other recent meta-analyses of persons with DM showing lower BP levels are related to lower risks for CVD outcomes motivated the most recent 2017 ACC/AHA blood pressure guideline committee to recommend a universal target of <130/80 mmHg for most persons, including those with DM [42–44]. They note initial therapy may consist of most classes of

hypertensive medication, including diuretics, ACE inhibitors, angiotensin receptor blockers, and calcium channel blockers.

8 Cholesterol and Lipid Management

The Cholesterol Treatment Trialists Collaboration involving a meta-analysis of 14 statin trials comprising 18,686 persons with DM showed a 21% reduction in CVD events per mmol/l (39 mg/dl) reduction in LDL-C [45], which is similar to those without DM. Clinical trials of fibrate therapy, including the Bezafibrate Intervention Program (BIP), FIELD (evaluating fenofibrate), and finally ACCORD Lipid (evaluating the addition of fenofibrate to statin therapy) failed to meet their primary endpoint (though showing trends of benefit in subjects with atherogenic dyslipidemia, which is appropriate for fibrates – namely, high triglycerides and low HDL-C) [46]. Thus, there have been limited recommendations for the use of fibrate therapy in persons with DM to reduce CVD risks; the AACE suggests reducing elevated triglycerides to 150–200 mg/dl (1.6–2.2 mmol/l) [47], although such therapy is still indicated for those with very high TG to reduce the risk of pancreatitis. Also, while the IMPROVE-IT trial including participants within 10 days of an ACS randomized to ezetimibe or placebo in addition to simvastatin met its primary endpoint [48], a post-hoc analysis showed that the entire benefit was attributed to those with DM who had a significant 14% reduction in risk from the addition of ezetimibe, whereas those without DM showed no benefit [49]. In the FOURIER trial involving evolocumab assigned to persons with prior ASCVD, while showing similar relative risk reductions in those with and without DM (17% and 13%, respectively), there was a greater absolute risk reduction in those with DM (2.7%) resulting in a very favorable number needed to treat of 37 [50]. Most recently, the REDUCE-IT trial of icosapent ethyl (IPE- pure eicosapentaenoic acid) showed persons with either preexisting CVD or DM plus at least one additional CVD risk factor showed a 25% lower risk of subsequent CVD events over nearly 5 years of follow-up, on top of statin therapy in those with higher triglycerides (135 mg/dL or higher) and relatively well-controlled LDL-C levels (40–99 mg/dL). There was a similar reduction in risk in those with (23%) and without (27%) DM [51].

The recent 2018 AHA/ACC – Multisociety Cholesterol Management guidelines [24] recommend for adults with DM aged 40–75 years treatment with a moderate intensity statin. In those persons with DM who have two or more other risk factors, a high-intensity statin is recommended, and if 10-year ASCVD risk exceeds 20%, a high-intensity statin combined with ezetimibe is recommended to reduce LDL-C levels by at least 50%. In those persons with preexisting CVD who also have DM and other high-risk conditions (such as CKD, hypertension, cigarette smoking, or coronary revascularization), or multiple CVD conditions, if despite maximally tolerated statin and ezetimibe the LDL-C still remains at 70 mg/dL or higher, the addition of a proprotein convertase/subtilisin kexin type 9 (PCSK9) monoclonal antibody can be considered. Other guidelines such as those of the American Association of Clinical

Endocrinologists (AACE) [47] and the ESC-EAS 2019 Lipid Guidelines [52] have LDL-C goals which are <100 mg/dL for lower risk persons with DM, <70 mg/dL for those with DM who have multiple risk factors alone, and <55 mg/dL for those with DM who have established ASCVD. Also, for those with DM who have triglycerides of 135 mg/dL or higher and other risk factors for CVD, who have well-controlled LDL-C on statin therapy, the American Diabetes Association [53] and the AACE have recently recommended IPE- icosapent ethyl to further reduce ASCVD risk [47].

9 Newer Diabetes Therapies and CVD Risk Reduction

Epidemiologic studies show that for every 1% lower HbA1c level, there is a 14% lower risk of myocardial infarction, 21% lower risk of diabetes-related death, 37% lower risk of microvascular complications, and 43% lower risk of amputation or peripheral arterial disease-related death [54] Until 2015, cardiovascular outcomes trials involving glucose-lowering therapy in persons with DM had failed to meet their primary endpoints. The well-known UKPDS trial of intensive glucose control resulted in a borderline no-significant reduction in CVD events, except for the metformin subgroup in overweight and obese individuals where there was a significant reduction [55]. Moreover, neither the ACCORD [56], ADVANCE [57], nor VADT [58], all trials examining intensive versus standard glucose control, showed significant reductions in CVD outcomes; in fact, the ACCORD trial showed a significantly higher risk of cardiovascular mortality, despite a reduction in risk of nonfatal myocardial infarction. ADVANCE [57] or VADT [58], however, showed neither benefit nor increased risk for any endpoint. The adverse outcomes in ACCORD were later attributed to those who were assigned to intensive control but failed to respond in lowering their A1c. Outcomes trials of the thiazolidinediones rosiglitazone and pioglitazone failed to reduce their composite CVD endpoints; however, a principal secondary MACE endpoint was significantly reduced in the PROACTIVE trial involving pioglitazone [59]. Of interest, however, a meta-analysis of UKPDS, ACCORD, VADT, ADVANCE, and PROACTIVE showed an overall significant 15% reduction in CHD events in the intensive compared to standard treatment groups [60].

An increased risk of myocardial infarction from a meta-analysis of trials involving the thiazolidinedione rosiglitazone [61], while later refuted in the RECORD outcome trial [62], prompted the Food and Drug Administration in 2008 to require that manufacturers of newer diabetes medications would need to demonstrate cardiovascular safety within certain point estimates and limits of uncertainty [63]. This fueled the design and execution of numerous cardiovascular safety and outcomes trials of newer diabetes drugs over the past decade. The first of these contemporary trials involved the DPP4 inhibitors, which showed overall cardiovascular safety, though failed to show benefits in cardiovascular outcomes. An unanticipated finding in one of the DPP4i studies (saxagliptin) showed an increased risk of developing heart failure hospitalization [64].

Newer DM therapies include the sodium glucose co-transporter 2 (SGLT2) inhibitors which reduce glucose reabsorption in the proximal tubule thereby increasing urinary excretion, as well as the GLP1 receptor agonists, which stimulate insulin release and inhibit glucagon release, thus reducing blood glucose. These therapies also reduce weight and improve blood pressure. The SGLT2 inhibitors appear to have hemodynamic and diuretic effects and the GLP1 receptor agonists seem to impact the vasculature, specifically the endothelium. Both classes have anti-atherosclerotic benefits, reduce intrahepatic fat, and have favorable effects on the kidneys. The SGLT2i class reduces, in particular, heart failure hospitalization [65].

The breakthrough in cardiovascular outcomes trials of DM therapies came with the release of the EMPA-REG trial [66] involving randomization of over 7000 patients with DM to empagliflozin versus placebo in addition to usual care therapies in persons with known CVD. This trial demonstrated a 14% reduction in the primary composite outcome of MACE-CVD death, nonfatal myocardial infarction, and stroke. The result was primarily driven by a dramatic 38% reduction in CVD death. Other secondary outcomes were a 32% reduction in all-cause mortality, and a 35% reduction in hospitalization for heart failure. As a result, the FDA approved empagliflozin to reduce CV death in people with DM and established CVD, independent of glycemic levels and/or goals. The second SGLT-2 CVD outcomes trial to report was CANVAS involving canagliflozin versus placebo on top of standard of care administered to over 4200 patients with DM both with and without CVD, but with elevated risk due to other risk factors [67]. CANVAS, like EMPA-REG, showed a 14% reduction in the primary composite CVD outcome, and while not showing significant reductions in each individual MACE component, it received an FDA indication to reduce MACE: nonfatal MI or stroke and CV death, also independent of glucose level. Further, CANVAS demonstrated a significant 32% reduction in hospitalization for heart failure and prevention of renal function deterioration. Finally, the largest of the SGLT-2 CVD outcomes trials, DECLARE [68], involving over 17,000 patients with DM (about two-thirds being primary prevention with other risk factors but not CVD), had two co-primary endpoints for which the composite of heart failure hospitalization (HHF) and CVD death was significantly reduced by 17%, but the composite MACE outcome showed a nonsignificant 7% risk reduction. As a result, dapagliflozin is now indicated to reduce HHF in both primary and secondary prevention.

The LEADER trial [69] involving liraglutide was the first GLP-1 receptor agonist trial to report on CVD outcomes. This trial enrolled over 9000 patients randomized to liraglutide versus placebo on top of standard of care and included patients both with and without preexisting CVD and with other risk factors. The trial showed an overall 13% reduction in the primary composite endpoint of 3 point MACE: nonfatal MI, nonfatal stroke, and CV death; there were no statistically significant reductions in individual endpoints of myocardial infarction or stroke, but cardiovascular and all-cause mortality were significantly lower in the liraglutide group. The results of LEADER led the FDA to indicate liraglutide to reduce 3 point MACE in people with DM and established CVD. SUSTAIN-6 evaluated the efficacy of semaglutide and included a similar study population of DM patients with and without

known CVD and was designed as a CV safety trial; however, it showed a 24% reduction in the primary composite CVD outcome driven primarily by a 39% reduction in nonfatal stroke, without significant reductions in nonfatal myocardial infarction or CVD death. However, as all these three components of MACE trended positively, the FDA approved semaglutide to reduce 3 point MACE in persons with DM and established CVD [70]. The PIONEER-6 trial [71] also evaluated semaglutide but in its oral form (both liraglutide used in LEADER and semaglutide used in SUSTAIN-6 were injectable preparations), which had similar entry criteria and endpoints as SUSTAIN-6. Again, a safety trial, PIONEER-6, with a 21% relative risk reduction met its primary endpoint safety but not for superiority. While nonfatal MI or nonfatal stroke were not reduced significantly, the component of CVD death was significantly reduced by 51%.

Without a doubt, there is great interest in these therapies, particularly the SGLT2-inhibitors, as a new class of therapies for heart failure and for chronic kidney disease, irrespective of DM status. There are numerous ongoing trials involving these therapies both for patients with heart failure with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF). The first of these trials, DAPA HF, involving dapagliflozin, recently reported a significant 26% reduction in risk of the composite of cardiovascular death, subsequent HF hospitalization, or urgent HF visit with a 4.9% absolute risk reduction, translating to a number needed to treat of 21 [72]. Finally, the CREDENCE trial involving canagliflozin showed among patients with CKD (eGFR of 30–89 ml/min/1.73 m^2 and albuminuria >300 mg/24 hours, all treated with renin angiotensin system blockade) a 30% reduction in the composite of end stage renal disease, doubling of serum creatinine, or renal or CVD death [73]. Also, in the DECLARE trial in patients with DM (described above) there was a significant 24% reduction in the composite renal outcome (≥40% decrease in estimated glomerular filtration rate, new end-stage renal disease, or death from renal or cardiovascular causes) [68]. Both empagliflozin and dapagliflozin are in further trials to evaluate their efficacy in patients with medium to severe CKD, with or without diabetes.

10 Guidelines for Glycemic Control

The American Diabetes Association Standards of Diabetes Care [74] has noted that a reasonable HbA1c target for most adults with diabetes is <7% with a target of <6.5% which may be considered if it can be done without undue side effects or adverse events. A less stringent target of 7.5% or even 8% may be appropriate for those with a history of advanced microvascular or macrovascular complications, severe hypoglycemia, or anticipated short life span. Targets can be more stringent than 7%; in fact, the AACE [75] recommends a target of 6.5% or less if it can be achieved safely, especially without hypoglycemia, and where there is a short disease duration, long life expectancy, absence of important comorbidities or vascular complications, a positive patient attitude, good resources, and an adequate support system.

For persons with DM with established ASCVD, heart failure, kidney disease, or with multiple risk factors, the American College of Cardiology published a consensus decision pathway [65], whereby along with guideline-directed medical therapy, the addition of an SGLT-2 inhibitor or GLP-1 receptor agonist with proven CVD benefit can be considered part of the clinician-patient treatment decision. An SGLT2 inhibitor may be preferred in cases where there is a desire to reduce heart failure hospitalization or reduce blood pressure, whereas a GLP1 receptor agonist is preferred if weight loss is desired or when the eGFR is under 45 ml/min/1.73 m^2. However, neither of these drugs are approved to reduce blood pressure or promote weight loss. There are also other considerations where an alternative agent might be considered (Table 1). Other recent guidelines include those from the American Heart Association, noting that a GLP-1 receptor agonist or SGLT-2 inhibitor may be considered in patients with DM and multiple risk factors in addition to metformin therapy [76]. Most recently, the American Diabetes Association Standard of Medical Care 2020, although still requiring metformin as first line, noted that one of these therapies can be considered irrespective of current or target HbA1c level since the benefit does not depend on this [53]. Other guidelines including the 2019 ESC-EASD CVD in DM [52] and the 2020 AACE DM management algorithm [75] state that patients with DM and risk factors or established CVD have to be on one of these agents not only independent of A1C but also independent of background antihyperglycemic medications. In other words, they can be prescribed directly on top of diet and exercise. The AACE also recommends the SGLT2i dapagliflozin and others once they have data to manage patients with HF and reduced ejection fraction, and the SGLT2i canagliflozin and others once they have available data to manage people with DM and moderate to severe kidney disease. Per AACE,

Table 1 Patient and clinician preferences and priorities for considering SGLT2 inhibitors with demonstrated CV benefit versus GLP-1Ras with demonstrated CV benefit

Consider using an SGLT2 inhibitor first when patient and clinician priorities include:	Consider using a GLP-1RA first when patient and clinician priorities include:
Reducing MACE and CV death	Reducing MACE and CV death
Preventing heart failure hospitalization	Substantial weight loss
Reducing blood pressure	Once weekly (subcutaneous) dosing[a]
Orally administered therapies	Therapy when eGFR consistently <45 ml/min/1.73m^2
Consider alternative agents if: Significant CKD History of prior amputation, severe peripheral arterial disease, neuropathy, or diabetic foot ulcers (avoid canagliflozin) History of recurrent genital candidiasis History of diabetic ketoacidosis History of osteoporosis (avoid canagliflozin)	Consider alternative agents if: Persistent nausea, even at low doses History of pancreatitis History of gastroparesis History of MEN2 or medullary thyroid cancer History of proliferative retinopathy (semaglutide)

Adapted from Das et al. [65]. With permission from Elsevier

[a]Semaglutide administration recently available in the USA; MEN2 = multiple endocrine neoplasia type 2

based on all SGLT2i & GLP1-RA cardiovascular outcome trials, these drugs may improve or at least prevent reduction in kidney function. Of note, although the contemporary GLs focus on CVD prevention independent of glycemic levels, the ADA, AACE, and EASD all continue to recommend management of hyperglycemia to goal to prevent short-term microvascular and long-term macrovascular complications.

11 Aspirin Therapy

While prior analyses of subgroups of DM subjects from earlier clinical trials showed beneficial effects of aspirin therapy on reducing CVD events [77–79], other clinical trials did not [80–83]. Most recently, the ASCEND trial [84] of over 15,000 persons with DM but without prior CVD showed 100 mg of daily aspirin to result in a significant 12% reduction in the primary CVD endpoint; however, this was largely counterbalanced by a 29% relative risk increase in bleeding, with the resulting net clinical benefit essentially null. Even those at higher (>10% CVD risk in 10 years) did not derive greater clinical benefit. The American Diabetes Association guidelines note that aspirin may be used in higher-risk primary prevention DM, but serious consideration should be given to the possible risks of serious bleeding and the overall net clinical benefit [74]. Lower-risk patients with DM are not recommended for aspirin therapy.

12 The Cardiodiabetes Care Team

In order to maximize opportunities for CVD risk reduction in patients with diabetes, a comprehensive cardiodiabetes care team (Fig. 6) is needed [85]. While the primary care provider cares for most patients with diabetes, it is critical that there first be sufficient resources for proper lifestyle management, including having registered dietitians and/or exercise physiologists in particular on the team to manage the often complex lifestyle issues common in these patients. The endocrinologist should be consulted when challenges are faced with glycemic control and when questions arise about whether to add to or replace existing therapies with newer agents proven to reduce CVD risk. Also, since approximately a third of patients with DM have some form of CVD, consultation with the cardiologist, neurologist, or other specialists as appropriate is needed to ensure adherence to cardiovascular therapies along with those aimed to control DM.

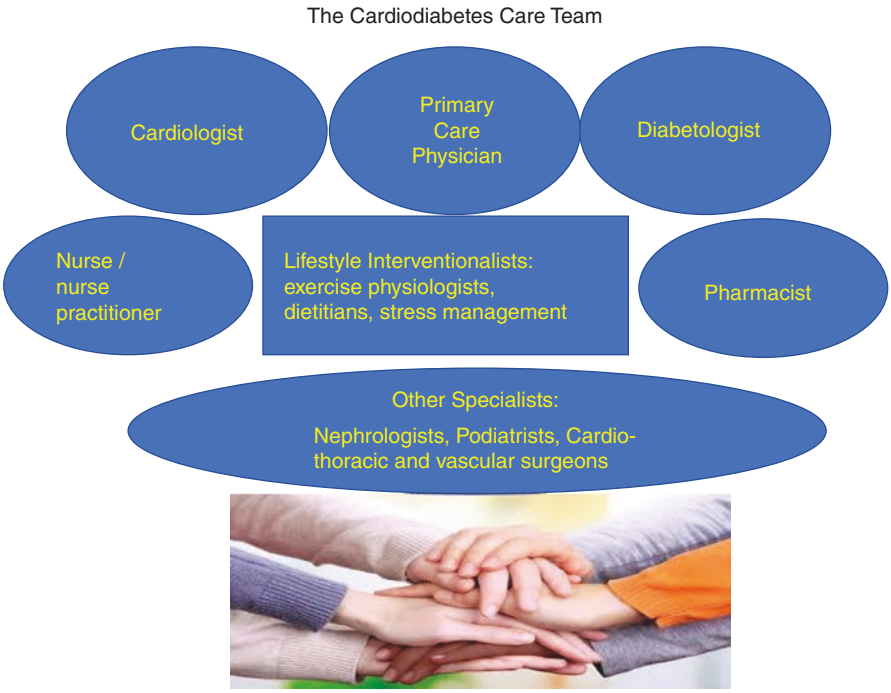

Fig. 6 The cardiodiabetes care team [85]. (Courtesy of Nathan D. Wong, PhD)

13 Conclusions

The prevalence of DM continues to increase both in the United States and worldwide, warranting greater efforts not only to prevent its rapid rise, but also to reduce the complications resulting from it. With ASCVD the major cause of morbidity and mortality in persons with DM, and the continuing poor state of control of the multiple risk factors associated with CVD in patients with DM, there is a continuing urgent need to better coordinate the identification and management of these risks. With more aggressive recommendations for blood pressure control, specific guidelines focusing on statin therapy and consideration for newer nonstatin therapies in higher-risk patients, as well as newer diabetes medications that have been proven to improve cardiovascular outcomes, in particular heart failure, there are significant opportunities to enhance our ability to optimize CVD risk reduction in such persons. Finally, a coordinated multidisciplinary team of healthcare providers focusing on the common goal of reducing CVD and other complications in patients with DM is essential.

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Antiplatelet Therapy

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Summary

- Three new randomized trials have demonstrated that aspirin therapy for primary prevention does not provide a significant benefit when weighed against the risk of significant bleeding.
- In large randomized trials of secondary prevention, aspirin results in a 25% reduction in serious vascular events.
- Dual antiplatelet therapy with a $P2Y_{12}$ inhibitor and aspirin is the mainstay of treatment after acute coronary syndromes and percutaneous coronary intervention.
- Clopidogrel resistance is an increasingly recognized phenomenon that underscores the importance of newer antiplatelet agents such as prasugrel and ticagrelor.
- The combination of aspirin and low-dose rivaroxaban in patients with established stable atherosclerotic disease reduced the combination of cardiovascular death, stroke, or nonfatal MI by 24%.

1 Introduction

Platelet activation plays a central role in the development of atherothrombosis [1], and, thus, antiplatelet therapy is a cornerstone of cardiovascular disease prevention and treatment. Initial platelet activation and rapid platelet amplification occurs in response to potent agonists such as thromboxane A2, adenosine diphosphate (ADP),

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and thrombin [2]. Our understanding of these pathways has led to the development of pivotal pharmacotherapies for treating cardiovascular disease. For example, the thromboxane inhibitor aspirin has resulted in substantial reductions in cardiovascular morbidity, and some have estimated that it could avert 100,000 vascular deaths per year [3]. In this chapter, we review the mechanism of action, primary and secondary prevention trial data, and guidelines for antiplatelet agents currently in widespread use.

2 Aspirin

2.1 Mechanism of Action

Acetylsalicylic acid, or aspirin, is the most widely used antiplatelet agent in the prevention and treatment of cardiovascular disease. Aspirin exerts its principal antiplatelet effect by acetylating a serine residue on the cyclooxygenase (COX) or prostaglandin H synthase enzyme and thus irreversibly inhibiting the action of this enzyme [4]. Following exposure to aspirin, the anucleate platelet is largely unable to synthesize COX during its 7–10-day lifespan [5]. COX enzymes, which exist in at least two isoforms, are responsible for production of prostaglandins and thromboxane from arachidonic acid. Preferential inhibition of COX-1 results in decreased production of thromboxane A2, a potent mediator of platelet aggregation [6]. Other potential mechanisms of action include inhibition of intrinsic nitric oxide synthase (iNOS) [7] and inhibition of transcription factors involved in inflammation [8, 9] (Fig. 1).

2.2 Secondary Prevention

The salutary effect of aspirin for the secondary prevention of cardiovascular disease is well-established. The first small studies to examine this relationship in patients with a history of myocardial infarction were suggestive of a mortality benefit but yielded statistically inconclusive results [10–12]. More convincing evidence arose from the Antiplatelet Trialists' Collaboration (ATC), a meta-analysis of 31 randomized trials of antiplatelet therapy primarily with aspirin in patients with prior myocardial infarction, stroke, transient ischemic attack (TIA), or unstable angina [13]. Among 29,000 patients, the investigators demonstrated a 25% reduction in the odds of suffering a recurrent vascular event in those patients treated with antiplatelet therapy [13].

In a second iteration of this collaborative, the authors demonstrated an 18% reduction in the odds of vascular death among high-risk patients, as defined by history of myocardial infarction, stroke, TIA, or unstable angina [14]. Although intuited from smaller randomized studies [15], the benefit of aspirin in the setting of an acute myocardial infarction was persuasively demonstrated in the Second International Study of Infarct Survival (ISIS-2) [16]. In this large international

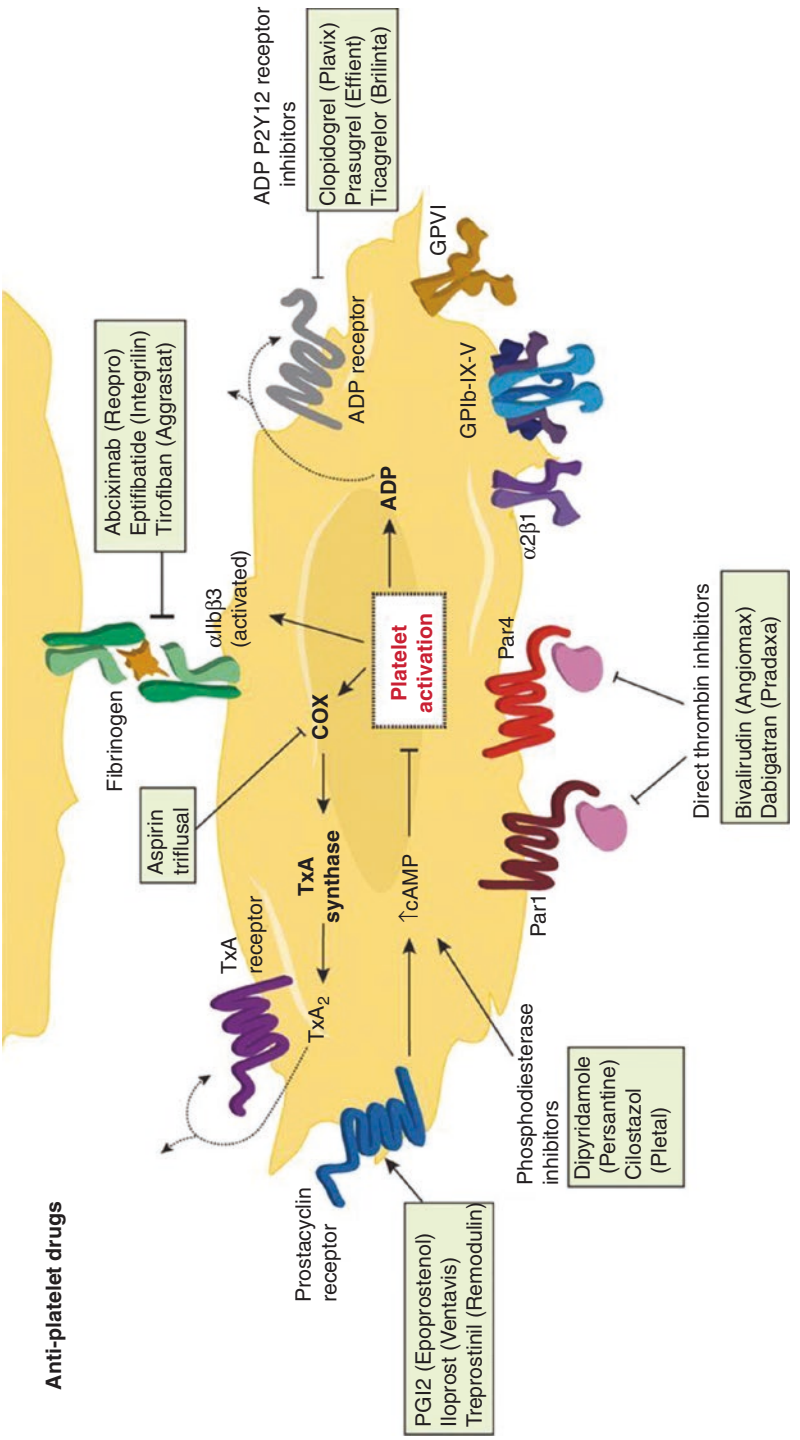

Fig. 1 Platelet targets of various antiplatelet therapies. (Adapted from Metharom et al. [9]. With permission from Wolters Kluwer Health, Inc.)

trial of 17,187 patients presenting with a suspected acute myocardial infarction, a 162.5 mg daily dose of aspirin administered daily for 1 month significantly reduced early cardiovascular mortality compared with placebo (9.4% vs. 11.8%, respectively) [16]. The protection afforded by aspirin was also shown to extend to patients with unstable angina in a study of 1266 male veterans [17]. In this randomized, placebo-controlled trial, a daily 324 mg buffered aspirin administered for 12 weeks resulted in a 51% relative reduction in myocardial infarction or death [17]. Similar results emerged from the Research Group on Instability in Coronary Artery Disease (RISC) investigators, which demonstrated a 57–69% reduction in the endpoint of myocardial infarction or death in 796 men with unstable angina or non-Q wave myocardial infarction treated with low-dose aspirin [18].

The benefits of early aspirin therapy after an ischemic stroke were elucidated in two large randomized trials of patients with acute stroke: the Chinese Acute Stroke Trial (CAST) [19] and Ischemic Stroke Trial (IST) [20]. Among over 20,000 patients enrolled in CAST, 160 mg of aspirin given within 48 hours of an ischemic stroke prevented 6.8 deaths or recurrent nonfatal strokes per thousand patients treated [19]. In a two-by-two factorial open-label design, IST investigators examined the effects of subcutaneous heparin or 300 mg of aspirin or both, administered within 48 hours of an ischemic stroke. Aspirin was associated with 11 fewer deaths or recurrent stroke per thousand patients treated [20]. When these trials were analyzed together, this benefit was slightly offset by an excess of two cases of intracranial hemorrhage per thousand patients treated [21].

Treatment with aspirin has also been an essential adjunct in patients undergoing coronary revascularization. Among patients undergoing coronary artery bypass grafting (CABG), preoperative and early postoperative aspirin administration has been demonstrated to improve both early and 1-year saphenous vein graft patency [22, 23]. After coronary intervention, aspirin has been associated with a decreased risk of the composite endpoint of death, restenosis, or myocardial infarction compared with placebo (30% vs. 41%, respectively) [24]. As might be expected, the addition of aspirin to thrombolytic therapy also results in reduced rates of recurrent ischemia and infarct-related artery reocclusion [25].

The ATC provided irrefutable evidence in favor of aspirin for secondary prevention with a meta-analysis of 195 trials including more than 135,000 patients [26]. They found similar risk reduction with antiplatelet therapy among high-risk patients, which also extended to patients with stable angina, atrial fibrillation, and peripheral arterial disease [26]. In stable cardiovascular disease, the treatment of 1000 patients with low-dose aspirin for an average of 33 months would prevent 33 cardiovascular events, 12 nonfatal MIs, 25 nonfatal strokes, and 14 deaths and cause 9 major bleeding events [27].

2.3 Primary Prevention

Aspirin for cardiovascular primary prevention has been a staple of preventive cardiology for decades. The Physicians' Health Study [28] and Thrombosis Prevention Trial [29] both demonstrated a benefit to aspirin use to prevent cardiovascular events,

but no cardiovascular mortality benefit. The Hypertension Optimal Treatment (HOT) study [30] and Primary Prevention Project (PPP) [31] were both terminated prematurely in part because data from both provided evidence in favor of aspirin for primary prevention. The Women's Health Study [32] demonstrated reductions in the risk of stroke and TIAs in the subgroup of women aged 65 and older showed a reduction in the risk of the primary endpoint of cardiovascular death, nonfatal myocardial infarction, or stroke in those treated with aspirin. While none of the above trials demonstrated a significant benefit in the primary endpoint, a meta-analysis looking at nearly 100,000 patients found a 12 and 14% reduction ($p = 0.03$ and $p = 0.01$, respectively) in cardiovascular events with aspirin in women and men, respectively [33].

Based on these data, aspirin has been recommended for primary prevention in at-risk populations from several major organizations including the United States Preventive Services Task Force (USPSTF), the American Heart Association (AHA), and the American College of Cardiology (ACC). Based on this slew of data, the USPSTF expanded their previous recommendation of aspirin use to include all men aged 45–79 to prevent MI and women aged 55–79 to prevent stroke in individuals at high risk but not outweighed by bleeding risk.

However, newer data questioned the benefit of aspirin for primary prevention. The Prevention of Progression of Arterial Disease and Diabetes (POPADAD) [34], Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) [35], Aspirin for Asymptomatic Atherosclerosis (AAA) [36], and Japanese Primary Prevention Project (JPPP) [37] all failed to show a clear benefit to aspirin for primary prevention. With these data, expert groups started to pare back their aspirin recommendations. In 2016, the USPSTF recommended aspirin for individuals with a 10-year ASCVD risk of at least 10%, a life expectancy of 10 years, and no increased risk of bleeding. For individuals aged 60–69 with similar risk, they recommended an individualized approach based on weaker evidence [38]. The European Society of Cardiology (ESC), on the other hand, gave aspirin a class III recommendation in primary prevention given the increased major bleeding risk [39]. Given the conflicting evidence of previous trials, new data were needed leading to the Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE) [40], A Study of Cardiovascular Events in Diabetes (ASCEND) [41], and Aspirin in Reducing Events in the Elderly (ASPREE) trials [42].

The ARRIVE trial was a randomized, double-blind, placebo-controlled, multicenter study of men 55 years and women 60 years and older who had average cardiovascular risk, defined as having at least cardiovascular risk factors such as dyslipidemia, current smoking, high blood pressure, or positive family history of cardiovascular disease. Patients with high risk of GI bleeding or other bleeding or diabetes were excluded from the study. The 12,546 patients were randomly assigned to 100 mg aspirin daily or placebo. Median follow-up was 60 months. The primary efficacy outcome of cardiovascular death, myocardial infarction, unstable angina, stroke, or transient ischemic attack occurred in 4.3% of the aspirin group compared with 4.5% of the placebo group ($p = 0.60$). The primary safety outcome of gastrointestinal bleeding was 0.97% in the aspirin group as compared with 0.46% in the placebo group ($p = 0.0007$). Thus, among patients with moderate risk of cardiovascular disease events, aspirin was not associated with a reduction in adverse cardiovascular events [40].

While the ARRIVE trial excluded diabetic patients, the ASCEND trial was designed to look at this higher-risk population. A total of 15,480 patients with diabetes aged 40 years and older with no known cardiovascular disease (but including those with and without risk factors) were randomized to aspirin 100 mg daily versus placebo with a mean duration of follow-up of 7.4 years. Patients with a clear indication or contraindication for aspirin were excluded from the study. The primary efficacy outcome of major adverse cardiovascular events (vascular death, myocardial infarction, or stroke/transient ischemic attack) occurred in 8.5% of the aspirin group compared with 9.6% of the placebo group ($p = 0.01$). The primary safety outcome of major bleeding (intracranial bleeding, GI bleeding, or sight-threatening eye bleeding) occurred in 4.1% of the aspirin group as compared with 3.2% of the placebo group ($p = 0.003$). When looking at the bleeding outcomes in the secondary analysis, there was no significant difference in intracranial hemorrhage, but there was a significant difference in GI hemorrhage (1.8% with aspirin versus 2.3% with placebo, $p = 0.003$) [41]. Findings were also similar in the subgroup at 10% or greater 10-year ASCVD risk, without any advantage of benefit outweighing harm.

Finally, the ASPREE trial looked at healthy individuals at least 70 years old (65 years and older for black and Hispanics) and randomized 19,114 to either 100 mg aspirin daily or placebo. Exclusion criteria included cardiovascular or cerebrovascular disease, dementia, high risk of bleeding, and contraindication to aspirin. The median duration of follow-up was 4.7 years. There was no difference in the composite primary endpoint of death, dementia, or persistent physical disability. Prespecified secondary outcomes such as CVD events were not significantly different nor did aspirin reduce MI or ischemic strokes when individual outcomes were analyzed. Similar to the other trials, there was significant increase in major hemorrhage (0.86% vs. 0.62%, $P < 0.001$). One surprising finding from this trial was an increase in all-cause death in the aspirin group by 14% (1.27% vs. 1.11% per year, HR 1.14, 95% CI 1.01–1.29). This was mostly from an increase in cancer death, in particular colorectal cancer [42–44].

Given the findings of the most recent trials, the 2019 ACC/AHA Guidelines on Primary Prevention of Cardiovascular Disease [45] changed their recommendations. In the revised guidelines, low-dose aspirin (75–100 mg) might be considered for primary prevention for select adults aged 40–70 years who are at higher ASCVD risk but not at increased bleeding risk (class IIb). Furthermore, they recommended against routine low-dose aspirin in individuals over the age of 70 and among adults of any age who are at increased bleeding risk (class III). The main primary prevention trials are summarized in Table 1 [46]. Contrary to the ACC/AHA guidelines, the American Diabetes Association (ADA) guidelines suggest that low-dose aspirin may be considered for individuals who are at increased cardiovascular risk after a discussion with the patient on the risks of bleeding [47].

2.4 Dosing

Daily aspirin doses of only 30 mg/day have been demonstrated to provide complete inhibition of platelet thromboxane synthesis [5]. Despite this observation, the optimal dose of aspirin for an individual patient is not known. Some investigators

Table 1 Major randomized trials of aspirin therapy for primary prevention

Trial	No. of patients	Population	Follow-up	Treatment	Annual events (%/year), ASA vs. control rate ratio [CI]		
					Nonfatal MI	Nonfatal stroke	Major GI bleeding
British Doctors' Trial	5139	Male physicians	6 years	500 mg ASA versus avoiding ASA	104 (0.54%) vs. 90 (0.47%) 1.15 [0.73–1.79]	61 (0.30%) vs. 27 (0.26%) 1.13 [0.72–1.77]	20 (0.10%) vs. 20 (0.10%) 1.00 [0.37–2.70]
Physicians' Health Study	22,071	Physicians	Mean of 60.2 months	325 mg ASA every other day versus placebo	129 (0.24%) vs. 213 (0.39%) 0.61 [0.46–0.81]	110 (0.20%) vs. 92 (0.17%) 1.20 [0.91–1.59]	48 (0.09%) vs. 30 (0.05%) 1.59 [0.89–2.84]
Thrombosis Prevention Trial	5499	Men aged 45–69 at high risk of ischemic heart disease	At least 5 years	Warfarin and ASA versus placebo in 2 × 2 factorial design	96 (0.58%) vs. 37 (0.83%) 0.70 [0.50–0.98]	18 (0.21%) vs. 25 (0.29%) 0.64 [0.34–1.20]	20 (0.12%) vs. 13 (0.08%) 1.54 [0.63–3.77]
Hypertension Optimal Treatment Study	19,196	50–80-year-olds with hypertension	2.5 years	ASA 75 mg versus placebo	68 (0.19%) vs. 114 (0.32%) 0.60 [0.41–0.88]	146 (0.41%) vs. 148 (0.42%) 0.98% (0.78–1.24)	114 (0.32%) vs. 62 (0.18%) 1.81 [1.22–2.66]
Primary Prevention Project	1031	Diabetics over age 50 without CVD	Median of 3.7 years	ASA 100 mg daily and vitamin E in 2 × 2 factorial design	15 (0.18%) vs. 21 (0.25%) 0.72 (0.31–1.71)	15 (0.19%) vs. 18 (0.23%) 0.84 [0.42–1.07]	6 (0.07%) vs. 3 (0.04%) 1.98 [0.36–11.02]
Women's Health Study	39,876	Women over 45 years old	10 years	ASA 100 mg on alternate days	184 (0.09%) vs. 181 (0.09%) 1.02 [0.78–1.33]	198 (0.10%) vs. 244 (0.12%) 0.81 [0.85–0.97]	127 (0.06%) vs. 91 (0.05%) 1.39 [0.98–1.97]
Prevention of Progression of Arterial Disease and Diabetes	1276	Aged 40 years or older with diabetes and ABI < 1	Median 6.7 years	ASA 100 mg and antioxidant capsule in 2 × 2 factorial design	55 (1.29%) vs. 56 (1.31%) 0.98 [0.69–1.40]	29 (0.68%) vs. 41 (0.96%) 0.71 [0.45–1.12]	28 (0.66%) vs. 31 (0.73%) 0.89 [0.53–1.50]
Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes	2539	Aged 30–85 with diabetes	Median 4.4 years	Low-dose (75 or 100 mg) ASA versus placebo	12 (0.22%) vs. 9 (0.16%) 1.35 [0.57–3.19]	22 (0.49%) vs. 24 (0.48%) 1.01 [0.60–1.72]	10 (0.18%) vs. 7 (0.13%) 1.45 [0.55–3.81]

(continued)

Table 1 (continued)

Trial	No. of patients	Population	Follow-up	Treatment	Annual events (%/year), ASA vs. control rate ratio [CI]		
					Nonfatal MI	Nonfatal stroke	Major GI bleeding
Aspirin for Asymptomatic Atherosclerosis	3350	50–75 with an ABI < 0.95 but no clinical cardiovascular disease	Mean 8.2 years	100 mg ASA daily versus placebo	62 (0.45%) vs. 68 (0.50%) 0.91 [0.65–1.28]	37 (0.27%) vs. 38 (0.28%) 0.97 [0.62–1.52]	9 (0.07%) vs. 8 (0.06%) 1.13 [0.43–2.92]
Japanese Primary Prevention Project	14,464	60–85 years old with hypertension, diabetes, or dyslipidemia	Median 5.02 years	100 mg ASA or no medication	20 (0.06%) vs. 38 (0.10%) 0.53 [0.31–0.91]	117 (0.30%) vs. 114 (0.30%) 1.00 [0.77–1.31]	103 (0.28%) vs. 31 (0.08%) 3.33 [2.22–4.98]
Aspirin to Reduce Risk of Initial Vascular Events	12,546	Men over 55 and women over 60 years with average cardiovascular risk	Median follow-up 60 months	100 mg ASA versus placebo	88 (0.28%) vs. 98 (0.31%) 0.90 [0.67–1.20]	75 (0.24%) vs. 67 (0.21%) 1.12 [0.80–1.55][a]	61 (0.19%) vs. 29 (0.09%) 2.11 [1.35–3.28]
A Study of Cardiovascular Events in Diabetes	15,480	40 years or older with diabetes and no known CVD	Mean of 7.4 years	100 mg ASA daily versus placebo	191 (0.33%) vs. 195 (0.34%) 0.98 [0.80–1.19]	227 (0.40%) vs. 244 (0.43%) 0.93 [0.77–1.12][b]	137 (0.24%) vs. 101 (0.18%) 1.36 [1.05–1.75]
Aspirin in Reducing Events in the Elderly	19,114	70 years or older (or >= 65 years and Hispanic or Black)	Median of 4.7 years	100 mg ASA daily versus placebo	171 (0.40%) vs. 184 (0.43%) 0.93 [0.76–1.15]	148 (0.35%) vs. 167 (0.39%) 0.89 [0.71–1.11]	361 (0.86%) vs. 265 (0.62%) 1.38 [1.18–1.62][c]

ASA aspirin, *CVD* cardiovascular disease, *ABI* ankle-brachial index

[a]Fatal and nonfatal

[b]Hemorrhagic and ischemic

[c]Major hemorrhage (hemorrhagic stroke, symptomatic intracerebral hemorrhage, or extracranial hemorrhage leading to transfusion, hospitalization, surgery, or death)

have speculated that higher doses of aspirin may paradoxically attenuate the antithrombotic effect of thromboxane inhibition by causing inhibition of the vasodilator prostacyclin [48]. However, a wide variety of aspirin doses ranging from 50 to 1500 mg have been demonstrated to be efficacious for prevention of cardiovascular events, and a formal comparison of several different doses has never been performed in the context of a randomized controlled prospective trial in coronary artery disease [26].

One ATC meta-analysis suggested similar reduction in vascular events across a wide range of aspirin doses [26]. In a post hoc analysis of the Clopidogrel in Unstable Angina to prevent Recurrent Events (CURE) study, increasing doses of aspirin (less than 100 mg, 101–199 mg, and greater than 200 mg daily) administered with either placebo or clopidogrel were not associated with greater clinical benefit [49]. Moreover, higher rates of major bleeding were observed with escalating doses of aspirin compared with placebo (1.9%, 2.8%, and 3.7%, respectively) [49]. A meta-analysis of 31 randomized trials including over 192,000 patients reached a similar conclusion, with the lowest risk of major bleeding events observed in patients using the lowest aspirin dose [50]. This was confirmed in an observational study of participants in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization (CHARISMA) trial [51].

In this large prospective study of patients at high risk of cardiovascular events, patients were randomized to receive clopidogrel or placebo added to background aspirin therapy (at doses less than or equal to 162 mg daily). A post hoc analysis demonstrated no significant reduction in the composite outcome of myocardial infarction, death, or stroke with increasing doses of aspirin. In fact, there was suggestion of harm in patients treated with higher doses of aspirin in addition to clopidogrel, with increased rates of cardiovascular events as well as greater incidence of bleeding, although this was not statistically significant [51]. The CURRENT-OASIS 7 trial has added to our understanding of both aspirin and clopidogrel dosing in acute coronary syndromes (ACS) [52].

Approximately 25,000 patients with ACS treated with an early invasive strategy were randomized in a two-by-two factorial design to double-blind conventional clopidogrel dosing (300 mg loading dose followed by 75 mg daily) versus high-dose clopidogrel (600 mg loading dose on day 1 followed by 150 mg daily for 6 days and subsequent maintenance dosing of 75 mg daily) [53]. Each of these groups was further randomized in an open-label manner to high-dose aspirin (300–325 mg) or low-dose aspirin (75–100 mg) after an initial 300 mg dose of aspirin. Neither higher-dose aspirin nor higher-dose clopidogrel was superior to the lower dose in the overall population. In the subgroup of patients that underwent PCI, higher-dose clopidogrel was associated with a significant reduction in the composite of death, myocardial infarction, or stroke at 30 days [54]. Consistently, an analysis of aspirin dose in the setting of STEMI noted that the initial use of 325 mg was not superior to 162 mg for efficacy; yet, it was associated with an increased risk of bleeding outcomes [55].

2.5 Formulations

Aspirin exists in a regular form as well as in buffered and enteric-coated preparations. Aspirin is rapidly absorbed in the stomach and small intestine after ingestion, with inhibition of portal platelet COX enzyme occurring before complete systemic absorption [56]. Peak levels of aspirin in the systemic circulation occur within 40 minutes after ingestion of regular aspirin, in contrast to 3–4 hours after an enteric-coated preparation [57]. A pharmacodynamic study in 12 healthy volunteers showed that near-maximal platelet thromboxane inhibition is achieved most efficiently by chewing a 325 mg aspirin tablet, occurring over a mean of 13.6 minutes [58]. Swallowing a whole buffered tablet doubled the time required to achieve maximal platelet inhibition [58]. Although enteric-coated preparations may have theoretical benefit with respect to reducing gastric irritation and bleeding, the increased risk of gastrointestinal bleeding observed with aspirin is also due to its systemic effect. Enteric-coated aspirin does not seem to confer protection against gastrointestinal bleeding compared with buffered or regular preparations of the same dose [59, 60].

2.6 Hemorrhagic Complications

The most feared complication of antiplatelet therapy is sequelae from hemorrhage. The majority of bleeding complications arise from the gastrointestinal tract, with an estimated relative risk of 2.1 in 1 meta-analysis of 22 randomized trials comparing 75–325 mg dosages of aspirin to placebo in primary or secondary prevention studies [61]. The relative risk of intracranial hemorrhage was 1.7, with no observed differences between major bleeding and dosages of aspirin. This translated to a per annum absolute increase in major bleeding of 0.12% [61].

In a prospective, observational study of 991 patients with coronary artery disease treated with 75–300 mg of aspirin, the incidence of upper gastrointestinal hemorrhage was 1.5% over 2 years of follow-up [62]. It has been estimated that aspirin contributes to an excess of 5 cases of gastrointestinal hemorrhage per 1000 patients treated [63]. Gastric toxicity as measured by inhibition of gastric prostaglandin synthesis is thought to be dose dependent, and a 50% reduction in gastric prostaglandin is observed at doses as low as 30 mg/day [64]. Therefore, it can be expected that all doses currently used in clinical practice will confer an excess risk of gastrointestinal hemorrhage [65]. The extent to which this can be attenuated by proton pump inhibition has been examined in both asymptomatic patients and those with prior gastroduodenal ulcers.

In a prospective, double-blind study of more than 900 asymptomatic patients requiring low-dose aspirin therapy, use of a proton pump inhibitor (PPI) for 26 weeks was associated with a lower rate of endoscopic ulcers compared with placebo (1.6% vs. 5.4%, respectively) [183]. In another study of 123 patients with recent healed gastroduodenal ulcers and treated *Helicobacter pylori* infection, the combination of 100 mg of aspirin and daily lansoprazole was associated with fewer recurrent ulcer complications than aspirin and placebo over 1 year (1.6% vs. 14.8%, respectively) [66]. A similar,

randomized placebo-controlled trial of 320 patients with a recent bleeding ulcer studied the combination of clopidogrel and placebo versus 80 mg of daily aspirin and twice-daily esomeprazole [67]. Compared with aspirin and PPI, clopidogrel was associated with a relatively high rate of recurrent bleeding over 1 year (0.7% vs. 8.6%, respectively) [67]. During 12 weeks of follow-up, the histamine H_2 receptor antagonist famotidine was recently demonstrated to decrease the risk of endoscopic esophagitis and peptic ulcers compared with placebo in patients receiving 75–325 mg aspirin therapy [68].

By consensus, the American College of Cardiology Foundation, American College of Gastroenterologists, and AHA recommend reducing chronic aspirin doses to 81 mg daily with the addition of a daily-dose PPI in patients with history of gastrointestinal hemorrhage or ulcer or patients at risk of these complications, such as those maintained on chronic steroids, the elderly, or those with a history of dyspepsia [29].

Additionally, testing and treatment of *Helicobacter pylori* is advocated prior to initiation of chronic antiplatelet therapy in patients with history of peptic ulcer disease. Replacing aspirin with clopidogrel is not recommended as a strategy to reduce the risk of recurrent gastrointestinal complications [69].

2.7 Drug Interactions

Other members of the nonsteroidal anti-inflammatory drug (NSAID) family can interact in deleterious ways with aspirin. The addition of NSAIDs to aspirin potentiates the risk of gastrointestinal events. However, concomitant NSAID use may also mitigate the protective effect of aspirin. MacDonald and colleagues reported on trends in mortality in over 7000 patients with cardiovascular disease discharged from the hospital on aspirin or the combination of aspirin and ibuprofen. The latter combination was associated with an excess risk of both all-cause mortality and cardiovascular death (hazard ratios 1.9 and 1.7, respectively) [70]. The potential mechanism of this interaction was evaluated in healthy volunteers administered ibuprofen followed by 81 mg of aspirin [71]. Ibuprofen dosed prior to aspirin or several times daily blocked normal aspirin-induced platelet inhibition. However, the administration of aspirin 2 hours prior to a single dose of ibuprofen resulted in expected irreversible COX-1 inhibition [71].

Naproxen has also been demonstrated to antagonize the COX-1 inhibition of aspirin in vitro, presumably by functioning as a competitive inhibitor of the COX enzyme [72]. Amplifying concerns about NSAIDs as a class, a large Finnish case-control study demonstrated a significant increase in the risk of first myocardial infarction with use of either conventional or selective COX-2 inhibitor NSAIDs [73, 74].

2.8 Aspirin Resistance

Despite appropriate doses of aspirin, many patients develop recurrent ischemic events. This clinical dilemma has often been attributed to aspirin resistance, a broad term which encompasses the wide variety of factors thought to contribute to this

phenomenon. At the simplest level, patient nonadherence, under-prescription by physicians, interaction with ibuprofen or naproxen, and malabsorption may all play a role [75]. It is also known that platelet activation can occur via thromboxane-independent pathways [76]. One such mechanism may involve COX-independent production of the arachidonic acid derivative, 8-iso-PGF2α, a potent vasoconstrictor and platelet aggregant, released in response to oxidative stress [77].

As aspirin is a relatively weak inhibitor of COX-2, it has also been postulated that platelet COX-2, normally expressed in response to inflammatory stimuli, may result in sufficient thromboxane A2 synthesis to contribute to aspirin resistance [78]. Other genetic factors may also contribute to observed differences in platelet responsiveness. The platelet polymorphism PI ^{A2} has been associated with aspirin resistance [76]. Aspirin resistance has been observed in patients with acute myocardial infarction [79] and elicited by exercise in patients with stable coronary artery disease [80]. One systematic review of 15 studies found a wide range in the prevalence of laboratory aspirin resistance, with estimates of 5–65% [81]. The lack of a uniform definition of aspirin resistance and its measurement has limited our understanding of this entity. The gold standard test of platelet function, light transmission aggregometry, is the most precise; however it is time-consuming and unable to be performed at the bedside [82].

The implications of inadequate aspirin-induced platelet inhibition were assessed in a nested case-control study of participants in the Heart Outcomes Prevention Evaluation (HOPE) [83]. Eikelboom and colleagues found an independent association between increasing urinary thromboxane levels, a marker of aspirin resistance, and major cardiovascular events [83]. In another prospective study of 326 patients with stable cardiovascular disease, aspirin resistance, as measured by a one-time optical platelet aggregation test, was present in 5.2% of patients and associated with a significant increase in the rate of myocardial infarction, stroke, or death compared to patients not deemed resistant (24% vs. 10%, respectively) [84]. A prespecified analysis of the CHARISMA trial confirmed the findings of the HOPE substudy and revealed an increased risk of stroke, myocardial infarction, or death in patients belonging to the highest quartile of urinary 11-dehydro thromboxane B2 levels [85]. Moreover, assignment to clopidogrel did not appear to attenuate this relationship.

3 Platelet $P2Y_{12}$ Receptor Antagonists

3.1 Mechanism of Action

The thienopyridines, which include ticlopidine, clopidogrel, and prasugrel, all irreversibly inhibit platelets by binding to $P2Y_{12}$, the G protein-coupled receptor which is normally activated by ADP released from injured endothelium and red blood cells [86]. Ticagrelor is not categorized as a thienopyridine since it reversibly inhibits the $P2Y_{12}$ receptor. Via interaction with the P2Y12 and P2Y1 platelet receptors, ADP triggers a cascade of events which results in platelet aggregation and further release of ADP from the activated platelet, thus potentiating the initial response [87, 88].

3.2 Ticlopidine

Ticlopidine, first studied in humans in 1975, inhibits ADP-induced platelet aggregation in a dose-dependent manner, with an onset of action of 24–48 hours [89]. Like clopidogrel, it is a prodrug and requires metabolism by the cytochrome P450 system to an active metabolite [90]. Although many early trials provided evidence to support the use of ticlopidine in patients with established cardiovascular disease, adverse hematologic side effects and rather slow onset of action as compared to clopidogrel have curtailed widespread subsequent use. In patients taking ticlopidine, serious neutropenia has been reported in <1–3.4% [91–95] and thrombotic thrombocytopenic purpura in 0.02% [96].

Two such early trials were the Canadian American Ticlopidine Study (CATS) [92] and Ticlopidine Aspirin Stroke Study (TASS) [93]. The CATS trial, which randomized over 1000 patients with recent thromboembolic stroke to treatment with ticlopidine or placebo, demonstrated a nearly 25% relative risk reduction in the rate of vascular death, myocardial infarction, or death [92]. The TASS group compared ticlopidine to high-dose aspirin in over 3000 patients with a recent neurologic event and demonstrated a 21% relative risk reduction in the rate of recurrent fatal and nonfatal stroke favoring ticlopidine [93]. Incongruent with this were the findings of the African-American Antiplatelet Stroke Prevention Study (AAASPS), which did not show a reduction in the composite endpoint of stroke, myocardial infarction, or vascular death in Black patients treated with ticlopidine after an ischemic stroke [94].

The Swedish Ticlopidine Multicentre Study demonstrated a 29% reduction in all-cause mortality in 687 patients with established peripheral arterial disease treated with ticlopidine compared to placebo [91]. This mortality benefit was explained entirely by a reduction in fatal myocardial infarction. The early use of ticlopidine was further supported by a study demonstrating a nearly 47% relative risk reduction in vascular death among 653 patients with unstable angina treated with ticlopidine in an open-label trial [97]. The additional antiplatelet benefit of ticlopidine was later demonstrated to extend to percutaneous coronary interventions, previously beleaguered by stent thrombosis in the era of single antiplatelet therapy and oral anticoagulation [95, 98, 99]. Soon after, the Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS) suggested superiority of combination aspirin and clopidogrel compared to aspirin and ticlopidine in patients undergoing coronary stenting [100]. While not statistically powered to compare the efficacy of these two antiplatelet regimens, the combination of aspirin and clopidogrel was associated with significantly less noncardiac adverse effects when compared to ticlopidine and aspirin (4.6% vs. 9.1%, respectively) [100]. More conclusive evidence arose from a meta-analysis of both registry and randomized trial data comparing clopidogrel and ticlopidine which revealed a 50% reduction in the rate of major adverse cardiac events with combination clopidogrel and aspirin compared to ticlopidine and aspirin [101].

4 Clopidogrel

4.1 Secondary Prevention

There have been several trials of clopidogrel in the secondary prevention of cardiovascular disease (Table 2). The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study was the first large, randomized, placebo-controlled trial to test the efficacy of clopidogrel in preventing cardiovascular events [102]. This international, multicenter study included 19,185 predominately male patients with a mean age of 63. In this population with a recent myocardial infarction, stroke, or symptomatic peripheral arterial disease followed for a mean of almost 2 years, clopidogrel conferred a modest, yet statistically significant, 8.7% relative risk reduction in the rate of the composite endpoint of myocardial infarction, stroke, or vascular death when compared to a daily 325 mg dose of aspirin [102]. In subgroup analyses of patients with diabetes and prior CABG in the CAPRIE trial, clopidogrel was also more efficacious than aspirin in reducing the rate of vascular death, myocardial infarction, or stroke [103, 104].

The salutary effect of dual antiplatelet therapy with clopidogrel and aspirin in patients with acute coronary syndromes was established in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial [105]. Among 12,562 men and women with unstable angina or non-ST-elevation myocardial infarction, a 300 mg loading dose of clopidogrel followed by a daily 75 mg dose in the background of open-label aspirin therapy (75–325 mg) was associated with a lower rate of cardiovascular death, myocardial infarction, or stroke when compared to placebo (9.6% vs. 11.4%, respectively). The protective effect of clopidogrel was evident within the first 24 hours after randomization [105]. The additional early benefit of clopidogrel compared to placebo was also shown to extend to patients in the CURE study who subsequently underwent CABG [106] and PCI [107].

Evidence supporting dual antiplatelet therapy with clopidogrel and aspirin prior to PCI arose from the Clopidogrel for the Reduction of Events During Observation (CREDO) trial [108]. In over 2000 patients undergoing elective PCI, pretreatment with a 300 mg loading dose of clopidogrel followed by 1 year of dual antiplatelet therapy was associated with a nearly 27% relative risk reduction in the composite endpoint of myocardial infarction, death, or target vessel revascularization compared to placebo [108].

Based on the premise that combination therapy with clopidogrel and aspirin might attenuate cardiovascular risk beyond that observed with clopidogrel alone, the CHARISMA trial evaluated the efficacy of clopidogrel and low-dose aspirin for the prevention of major cardiovascular events [109]. Among 15,603 patients with established cardiovascular disease or multiple cardiovascular risk factors followed for a median of 28 months, randomization to clopidogrel and aspirin did not result in significant benefit with respect to the composite endpoint of stroke, myocardial infarction, or cardiovascular death compared to placebo plus aspirin [109]. However, in a subsequent analysis of patients with prior myocardial infarction,

Table 2 Summary of antiplatelet agents

Agent	Mechanism	Cardiovascular indications (class of recommendation)
Aspirin	Thromboxane A_2 inhibitor	*Primary prevention:* Can be considered for primary prevention of ASCVD in select individuals aged 40–70 at higher ASCVD but not bleeding risk (IIb) Should not be administered routinely for primary prevention individuals over age 70 (III) Should not be administered for primary prevention in anyone at increased risk of bleeding (III) *Secondary Prevention:* Recommended for all patients with coronary artery disease (I) Recommended for all patients with extracranial or vertebral atherosclerosis (I) Recommended for all patients with symptomatic peripheral artery disease (I) Can be considered in patients with asymptomatic peripheral artery disease (IIb) After PCI, 81 mg aspirin is preferred to higher doses (IIb)
Clopidogrel	$P2Y_{12}$ inhibitor (irreversible)	Recommended as an alternative to patients who are aspirin allergic (I) Recommended for SIHD status post PCI (1 month for BMS and 6 months for DES) (I) Recommended for SIHD status post CABG for 12 months (IIb) Medically managed ACS for 12 months (I) and can be considered beyond 12 months (IIb) Recommended for STEMI managed with lytics for minimum of 14 days and ideally at least 12 months (I) and can be considered beyond 12 months (IIb) Recommended for ACS status post PCI at least 12 months (I) and can be considered beyond 12 months (IIb) Recommended for ACS status post CABG for 12 months (I) Recommended for patients with symptomatic peripheral artery disease (or aspirin) (I) Recommended with extracranial or vertebral atherosclerosis (or aspirin) (I)
Prasugrel	$P2Y_{12}$ inhibitor (irreversible)	Recommend for ACS status post PCI for at least 12 months (I) and can be considered beyond 12 months (IIb)
Ticagrelor	$P2Y_{12}$ inhibitor (reversible)	Recommended for medically managed ACS for 12 months (I) and can be considered beyond 12 months (IIb) Recommended for ACS status post PCI for at least 12 months (I) and can be considered beyond 12 months (IIb)

(continued)

Table 2 (continued)

Agent	Mechanism	Cardiovascular indications (class of recommendation)
Cilostazol	Phosphodiesterase type 3 (PDE_3) inhibitor	Cilostazol is an effective therapy to improve symptoms and increase walking distance in patients with claudication (I)
Dipyridamole	Multiple mechanisms	Recommended with extracranial or vertebral atherosclerosis with aspirin (I)
Rivaroxaban	Direct Xa inhibitor	US guidelines have not been updated to include indications ESC guidelines recommend adding a second antithrombotic agent (such as low-dose rivaroxaban) to aspirin in patients with chronic coronary syndrome who are at high risk (IIa) of ischemic events and can be considered in moderate risk (IIb) of ischemic events who are not at increased bleeding risk

SIHD stable ischemic heart disease, *ESC* European Society of Cardiology, *ASCVD* atherosclerotic cardiovascular disease

symptomatic peripheral arterial disease, or stroke, combination clopidogrel and aspirin afforded a 1.5% absolute risk reduction in the composite endpoint of stroke, myocardial infarction, or cardiovascular death [110].

The additional benefit of clopidogrel among patients with STEMI has been demonstrated in two large-scale randomized placebo-controlled trials [111, 112]. The Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) enrolled 45,852 Chinese patients with an acute myocardial infarction to receive clopidogrel 75 mg daily or placebo in addition to aspirin 162 mg daily [111]. The two-by-two factorial design also evaluated the effect of intravenous followed by oral metoprolol.

Clopidogrel treatment for a mean of approximately 2 weeks was associated with a 9% odds reduction in the composite of myocardial infarction, stroke, or death, as well as a 7% odds reduction in all-cause mortality [111]. Similarly, the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY-TIMI 28) study demonstrated a 36% odds reduction in the composite endpoint of death, myocardial infarction, or angiographically occluded infarct-related artery in over 3000 patients with ST-elevation MI treated with clopidogrel and fibrinolytics [112]. This was achieved without a significant increase in the risk of major bleeding in both trials. In a prespecified analysis of patients who underwent PCI in the CLARITY-TIMI 28 study, randomization to pretreatment with a 300 mg loading dose of clopidogrel was associated with a 46% odds reduction at 30 days in the composite endpoint of stroke, myocardial infarction, or death [113].

Furthermore, the role of clopidogrel in the prevention of cerebrovascular events has been addressed in a prospective manner. Diener and colleagues studied the addition of low-dose aspirin to background clopidogrel therapy among patients with recent stroke or TIA and at least one additional cardiovascular risk factor in the Management of Atherothrombosis with Clopidogrel in High-Risk Patients (MATCH) study [114]. After 18 months of treatment, there was no statistically significant benefit of dual antiplatelet therapy with respect to stroke, myocardial

infarction, or vascular death, and an important increase in major bleeding was observed compared with clopidogrel and placebo [114].

With this background, the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) study randomized over 20,000 men and women with a mean age of 66, who had suffered a recent ischemic stroke, to receive either fixed-dose aspirin 25 mg and extended-release dipyridamole 250 mg twice daily or clopidogrel 75 mg daily [115]. The effect of telmisartan was also incorporated in a two-by-two factorial design. After a mean follow-up of 2.5 years, there was no statistical difference in the rate of the primary endpoint of recurrent stroke, nor the secondary composite endpoint of vascular death, stroke, or myocardial infarction [115].

The first prospective investigation of the role of dual antiplatelet therapy in preventing cardiovascular events in patients with atrial fibrillation came from the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE) family of studies [116, 117]. The ACTIVE-W trial enrolled over 6000 patients with atrial fibrillation and additional risk factors for stroke, with a mean CHADS 2 score of 2, to test the hypothesis that combination clopidogrel and low-dose aspirin would be noninferior to oral anticoagulation with vitamin K antagonists targeted to an INR goal of 2–3 [116]. The trial was halted prematurely as clopidogrel and aspirin was associated with an excess risk of the composite endpoint of stroke, myocardial infarction, vascular death, or systemic embolus compared to oral anticoagulation (5.6% vs. 3.9%, respectively).

The superiority of oral anticoagulation was largely driven by a significant reduction in the risk of stroke and systemic embolism [116]. As expected, maintenance of a therapeutic INR is an important proviso [118]. The superiority of oral anticoagulation over dual antiplatelet therapy in stroke prevention has also been demonstrated in relatively lower-risk subgroups of ACTIVE-W participants [119]. Despite the clear superiority of oral anticoagulation over antiplatelet therapy in high-risk patients with atrial fibrillation, there are many patients for whom the former is not appropriate. The ACTIVE-A trial, which enrolled 7554 such patients and randomized them to either clopidogrel or placebo with the background of aspirin, demonstrated a 28% reduction in the risk of stroke with clopidogrel and aspirin [117]. However, dual antiplatelet therapy resulted in a 51% increase in the risk of major extracranial hemorrhage [117]. The Secondary Prevention of Small Subcortical Strokes (SPS3) trial evaluated the role of combination of aspirin and clopidogrel in individuals with recurrent lacunar strokes and found that not only was there no significant reduction in the risk of recurrent stroke, but there was a significantly increased risk of major bleeding (HR 1.97, $P < 0.001$) and death (HR 1.42, $P = 0.004$). As such, the AHA, ACC, and Heart Rhythm Society (HRS) guidelines for management for patients with atrial fibrillation do not recommend the use of any antiplatelet agents to prevent thromboembolism [120].

Although dual antiplatelet therapy with a P2Y12 inhibitor and aspirin has become the standard of care after percutaneous coronary intervention and stent placement, the optimal duration of this therapy, particularly after drug-eluting stent placement, remains a subject of great debate. The most feared complication after stent placement is stent thrombosis, an uncommon, but highly morbid, event.

An early meta-analysis of 6675 patients enrolled in randomized trials comparing first-generation drug-eluting stents to bare-metal stents demonstrated a significant increase in the risk of late stent thrombosis in patients treated with drug-eluting stents and <6 months of dual antiplatelet therapy [121]. Although the risk of early stent thrombosis (<30 days) appeared similar, the risk of stent thrombosis after 1 year was almost 5 times greater in patients treated with drug-eluting stents [121].

Elaborating on these findings, a registry analysis of over 4000 patients receiving drug-eluting or bare-metal stents demonstrated a significantly lower rate of death or myocardial infarction in patients with drug-eluting stents treated with extended clopidogrel compared to 6 or 12 months of clopidogrel [122]. In another observational study of patients treated with drug-eluting stents, the overall rate of stent thrombosis was 1.9% during 18 months of follow-up, and the major predictor of stent thrombosis within 6 months of drug-eluting stent placement was discontinuation of clopidogrel [123].

The possibility of rebound phenomena after cessation of clopidogrel was raised in a retrospective study of over 3000 patients treated with clopidogrel after acute coronary syndromes [124]. In this Veterans Affairs cohort of patients treated with both medical therapy and percutaneous coronary intervention, an increased rate of death and acute myocardial infarction was observed in both groups of patients after cessation of clopidogrel. Interestingly, there was a grouping of events in the first 90 days after clopidogrel cessation, raising the specter of a rebound effect [124]. This is supported by in vitro upregulation of pro-inflammatory markers and increased platelet aggregation after clopidogrel withdrawal in a small study of patients with diabetes [125]. On the other hand, biological rebound is less likely with an irreversible antiplatelet agent.

To better evaluate the appropriate duration of dual antiplatelet therapy, multiple trials have since been published. One early study was the Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia (PRODIGY) study [126]. In this study, patients who received bare-metal or drug-eluting stents were randomized to either 6 months or 24 months of dual antiplatelet therapy. The study included 2013 patients who presented for elective, urgent, or emergent angioplasty and were randomized to a bare metal, zotarolimus-eluting, paclitaxel-eluting, or everolimus-eluting in a 1:1:1:1 fashion. After 30 days of treatment with DAPT, they were then randomized to either 6 or 24 months of DAPT. The composite of death from any cause, MI, or cerebrovascular accident was the primary endpoint, which occurred in 10.1% in the 24-month group and 10.0% in 6-month group ($P = 0.91$). The risks of each individual component of the primary endpoint were not different between groups, but there was a higher risk of hemorrhage in the 24-month group.

Furthermore, two additional studies have evaluated DAPT beyond 12 months in early-generation drug-eluting stents. These included the Correlation of Clopidogrel Therapy Discontinuation in Real-World Patients Treated with Drug-Eluting Stent Implantation and Late Coronary Arterial Thrombotic Events (REAL-LATE) and Evaluation of the Long-Term Safety after Zotarolimus-Eluting Stent, Sirolimus-Eluting Stent, or Paclitaxel-Eluting Stent Implantation for Coronary Lesions – Late Coronary Arterial Thrombotic Events (ZEST-LATE) trials [127]. These two trials

included over 2700 patients who received drug-eluting stents and had been free from MACE and major bleeding for a period of at least 12 months. They were then randomized to either clopidogrel and aspirin or aspirin alone. The primary endpoint of composite of MI or death from cardiac causes at 2 years was 1.8% in the DAPT group versus 1.2% in the monotherapy group ($P = 0.17$). Individual risks of MI, stroke, stent thrombosis, need for repeat revascularization, major bleeding, and death from any cause were all not significantly different between groups.

However, more recent and robust studies have better investigated the question of DAPT duration in an era of later-generation drug-eluting stents. The 2014 DAPT trial [128] evaluated patients who had undergone coronary stent placement with a drug-eluting stent. All patients received DAPT with either clopidogrel or prasugrel and aspirin for 12 months. At that point, they randomly assigned to continue their assigned DAPT regimen for a total of 30 months or were given placebo. The coprimary endpoints were stent thrombosis and major adverse CV and cerebrovascular events (a composite of death, MI, and stroke) during the 12- to 30-month period. Moderate to severe bleeding was the primary safety outcome. Of the nearly 10,000 patients enrolled, continued treatment with either clopidogrel or prasugrel reduced the rates of stent thrombosis (0.4% vs. 1.4%, $P < 0.001$) and major CV and cerebrovascular events (4.3% vs. 5.9%, $P < 0.001$). Death from any cause was 2% in the treatment group as compared with 1.5% in the placebo group ($P = 0.05$), though this was primarily related to noncardiovascular death. The risk of moderate to severe bleeding was higher in the treatment group (2.5% vs. 1.6%, $P = 0.001$).

Another more contemporary study though found that there may be harm with prolonged DAPT. The Assessment by a double Randomisation of a Conventional antiplatelet strategy versus a monitoring-guided strategy for drug-eluting stent implantation and of Treatment Interruption versus Continuation 1 year after stenting-Interruption (ARCTIC-Interruption) study was conducted. It includes over 2400 patients who were undergoing planned DES placement. After 1 year of DAPT, patients who did not have a contraindication to DAPT were randomized to either stopping their thienopyridine or continuing it for 6–18 months. The primary endpoint of death, MI, stent thrombosis, stroke, or urgent revascularization occurred in 4% of both the continued and the interrupted group at a follow-up of 17 months ($P = 0.58$). Major and minor bleeding were more common in the continuation group (2% vs. 1%, $P = 0.04$). The authors concluded that there was no benefit and potential harm with DAPT continuation.

With conflicting findings, the AHA/ACC 2016 guidelines were amended to include these data on duration of DAPT. While all patients with ACS should be treated with DAPT as a class I indication for 12 months, a class IIb recommendation was introduced to extend DAPT beyond 12 months in individuals who are not high risk for bleeding and did not have significant bleeding while on DAPT. For stable ischemic heart disease (SIHD), a class III recommendation remains in place in those undergoing medical therapy only. For those with SIHD who undergo PCI, clopidogrel is a class I indication for at least 1 month after BMS or 6 months after DES. Extending DAPT beyond 1 or 6 months, respectively, is a class IIb recommendation.

4.2 Clopidogrel Resistance

An important clinical conundrum arises from the great variability observed in platelet responsiveness to clopidogrel [129]. There is a growing body of evidence to suggest that clopidogrel resistance is associated with poorer cardiovascular outcomes. In a small study of 60 patients presenting with STEMI, clopidogrel hyporesponsiveness was observed in up to 25% of patients and associated with greater risk of a recurrent cardiovascular event over a 6-month follow-up period [130]. The pharmacogenetic factors underlying this observation have recently been further elucidated.

Approximately 80% of the prodrug, clopidogrel is metabolized to inactive metabolites [131]. The remainder must undergo hepatic metabolism via a two-step cytochrome P450-dependent process. Among healthy volunteers, Mega and colleagues recently demonstrated a 30% prevalence of the CYP2C19 allele, a genetic polymorphism which confers loss of function and hence a reduction of the active metabolite of clopidogrel [132]. The investigators also examined the relationship between presence of the CYP2C19 polymorphism and clinical outcomes among 1477 participants in the TRITON-TIMI 38 study assigned to clopidogrel treatment.

In this retrospective analysis, there was a 54% increase in the risk of the composite endpoint of myocardial infarction, cardiovascular death, or stroke among carriers of at least one CYP2C19 allele compared to noncarriers. Presence of the CYP2C19 allele was also associated with a threefold increase in the risk of stent thrombosis [132]. These findings were supported by a contemporaneous report from the French registry of Acute ST-elevation and non-ST-elevation Myocardial Infarction (FAST-MI) [133]. In patients with an acute myocardial infarction who underwent PCI, the presence of two copies of the CYP2C19 allele was associated with a greater than threefold increase in the risk of adverse cardiovascular events [133]. A recent genome-wide association study confirmed that this allele may affect clopidogrel response [134, 135].

Despite this data, the optimal management strategy for patients with apparent clopidogrel resistance is not known. The Gauging Responsiveness with a VerifyNow Assay-Impact on Thrombosis and Safety (GRAVITAS) trial was designed to investigate this phenomenon. Using a point-of-care assay, approximately 2200 patients with high platelet reactivity were randomized to conventional-dose clopidogrel versus 150 mg daily after drug-eluting stent placement for 6 months and followed for the occurrence of nonfatal myocardial infarction, cardiovascular death, or stent thrombosis [136]. In the end, the results showed that use of high-dose clopidogrel did not reduce the incidence of death from cardiovascular causes, nonfatal MI, or stent thrombosis at 6 months of follow-up [137].

Multiple other studies have investigated this further. In the Assessment by a double Randomisation of a Conventional antiplatelet strategy versus a monitoring-guided strategy for drug-eluting stent implantation and of Treatment Interruption versus Continuation 1 year after stenting (ARCTIC) trial [138], bedside platelet monitoring was evaluated. In this trial, over 2400 patients who were scheduled for coronary stenting were randomly assigned to platelet function monitoring

with VerifyNow P2Y12 and aspirin point-of-care assays compared to usual care. Interestingly, even though there were patients identified as having high platelet reactivity with both assays, adjusting treatment based on those results did not lead to a difference in the primary outcome of the composite of death, myocardial infarction, stent thrombosis, stroke, or urgent revascularization at 1 year.

In the ANARCTIC study [139], a higher-risk group was evaluated, specifically older adults who were at high risk of coronary events. Among 877 adults aged 75 or older, who received prasugrel for their $P2Y_{12}$ therapy, there was no difference in clinical outcomes with monitoring and therapy adjustment. Furthermore, the Testing Platelet Reactivity in Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy with Prasugrel (TRIGGER PCI) [140] PCI studied whether switching clopidogrel nonresponders to prasugrel could improve clinical outcomes or at the least show a reduction in treatment platelet reactivity. While it was able to show a reduction in platelet reactivity, the small trial was underpowered and did not demonstrate clinical utility.

Drug-drug interactions may also contribute to clinically observed clopidogrel resistance. A small early study of 44 patients undergoing elective stent implantation suggested such an interaction with atorvastatin [141]; later reports have refuted this [142–144]. In a small study of 45 patients randomized to either atorvastatin or pravastatin in the background of clopidogrel after ACS, neither statin attenuated clopidogrel-induced platelet aggregation after 5 weeks of treatment [142]. In fact, patients treated with statins alone had decreased platelet activity and thrombin receptor PAR-1 expression, supporting the notion of an independent statin antiplatelet effect [144].

Furthermore, there has been heightened concern about the drug interaction between clopidogrel and the widely used PPIs. In the Omeprazole Clopidogrel Aspirin Study (OCLA), 124 patients receiving coronary stents were randomized in a double-blind manner to omeprazole 20 mg daily or placebo in addition to standard clopidogrel and aspirin therapy [145]. With the use of a vasodilator-stimulated phosphoprotein phosphorylation (VASP) assay, a marker of clopidogrel-induced platelet inhibition, the investigators demonstrated greater mean platelet reactivity in patients treated with omeprazole. However, the attenuation of platelet inhibition by PPIs may not be a class effect. In another study of platelet activity in patients treated with clopidogrel and pantoprazole or esomeprazole, neither PPI was associated with a change in the mean platelet reactivity index compared to patients taking clopidogrel without PPIs [146].

In a retrospective analysis of over 8000 Veterans treated with clopidogrel after ACS, use of PPIs was associated with a greater risk of rehospitalization for ACS or death after adjustment for multiple potential confounders (adjusted odds ratio 1.25) [147]. Among patients treated with clopidogrel and PPIs, 14.6% had a recurrent hospitalization for ACS compared with 6.9% treated with clopidogrel alone [147]. The clinical significance of this interaction and its contribution to adverse cardiac events has not been addressed in the context of a randomized controlled trial until recently. In the preliminary results of the COGENT trial, there was no evidence of

cardiovascular harm from the combination of clopidogrel with proton pump inhibitors [148].

Genetic testing to better guide therapies is an evolving area of research. One gene that has been identified to play a role in an individual's platelet response is CYP2C19. Reduced function genetic variants at this location on chromosome 10 have been associated with reduced active drug metabolites of clopidogrel and prasugrel leading to diminished platelet inhibition and higher rates of adverse cardiac events [132, 133]. One trial that investigated this was a substudy of the TRITON-TIMI 38 [149]. In this trial, CYP2C19 variants were evaluated in individuals treated with clopidogrel and prasugrel and were found to be an independent predictor of the primary endpoint which was a composite of cardiovascular death, myocardial infarction, or stroke in those patients treated with clopidogrel. Cost-effectiveness of genotype-guided therapy for patients undergoing primary PCI for ACS has shown modest reduction in cost [150].

This led to the more contemporary trial evaluating whether using genomics to guide the choice of oral $P2Y_{12}$ inhibitor in patients undergoing primary PCI is warranted [151]. This randomized, open-label, assessor-blinded trial assigned patients undergoing primary PCI with stent implantation to groups based on early CYP2C19 genetic testing or standard treatment with prasugrel or ticagrelor. Individuals in the genotyping group who had loss of function variants were assigned to receive ticagrelor or prasugrel, while noncarriers were assigned to receive clopidogrel. The primary outcome at 12 months was net adverse clinical events, defined as death from any cause, myocardial infarction, definite stent thrombosis, stroke, or major bleeding. While there was no significant difference in the primary outcomes between the genotype-guided group and standard care, there was a lower incidence of bleeding in the genotype-guided group (9.8% vs. 12.5%, $P = 0.04$) as compared to standard of care.

5 Prasugrel

Prasugrel is another member of the thienopyridine family with several theoretical advantages compared to its predecessors ticlopidine and clopidogrel. While it is also a prodrug, it has an onset of action of less than 30 minutes and has been demonstrated to be ten times more potent than clopidogrel in animal models [152]. Furthermore, common genetic variants of CYP450 polymorphisms do not appear to be associated with a reduction in the antiplatelet effect of the drug [153, 154]. The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel - Thrombolysis in Myocardial Infarction (TRITON-TIMI 38) randomly assigned over 13,000 patients with moderate-high-risk ACS undergoing PCI to a 60 mg loading dose of prasugrel, followed by 10 mg daily, or a 300 mg loading dose of clopidogrel followed by 75 mg daily for up to 15 months [155]. Prasugrel was associated with a 19% relative rate reduction in the composite endpoint of cardiovascular death, nonfatal myocardial infarction, or stroke. This was

counterbalanced by a 32% increase in the rate of major bleeding in patients assigned to prasugrel [155]. A post hoc analysis by the investigators concluded that there was either no net clinical benefit or net harm in three particular subgroups: the elderly, patients with prior stroke or TIA, and those weighing <60 kg.

In a prespecified analysis of patients with and without diabetes in the TRITON-TIMI 38 study, a 30% reduction in major cardiovascular events was observed in patients with diabetes treated with prasugrel, as compared to 14% in those without diabetes [156]. There was also no significant difference in the rate of major bleeding in patients with diabetes treated with prasugrel or clopidogrel, resulting in a greater net clinical benefit compared to patients without diabetes [156]. Prasugrel has also been shown to confer benefit after stent placement with respect to ischemic complications and stent thrombosis. In a subgroup analysis of patients receiving stents in TRITON-TIMI 38, prasugrel conferred a 20% and 18% relative reduction in the rate of the primary endpoint among patients receiving bare-metal and drug-eluting stents, respectively [157]. In patients with stents, prasugrel was also associated with a 58% relative reduction in stent thrombosis [157]. In an analysis of STEMI patients in TRITON-TIMI 38, prasugrel was also more efficacious than clopidogrel with a 3% absolute risk reduction in the primary endpoint at 30 days [158, 159].

While TRITON-TIMI 38 looked at STEMI patients, questions remained about NSTEMI and UA patients. This led to the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial [160]. Here, over 7000 patients under age 75 all receiving aspirin were randomly assigned to receive either prasugrel or clopidogrel as treatment for up to 30 months, though the median follow-up time was 17 months. The primary outcome was the composite of death from cardiovascular causes, MI, or stroke. The primary endpoint occurred in 13.9% of patients in the prasugrel group as compared with 16% in the clopidogrel group ($P = 0.21$). A prespecified analysis of multiple recurrent ischemic stroke showed a lower risk with prasugrel (HR 0.85, 95% 0.72–1.00; $P = 0.04$). Rates of severe and intracranial bleeding were not significantly different between groups.

In another trial, the ideal timing of prasugrel administration was investigated since it was not clear that giving prasugrel prior to angiography would alter outcomes in patients who present with NSTEMI. We designed the Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention (PCI) or as Pretreatment at the Time of Diagnosis in Patients with Non-ST Elevation Myocardial Infarction (ACCOAST) trial investigated the matter. Over 4000 patients with a diagnosis of NSTEMI and scheduled to undergo coronary angiography within 2–48 hours were randomized. The treatment group received a 30 mg prasugrel load before PCI, while the control group received placebo. If PCI was indicated, the pretreatment group was given 30 mg of prasugrel, while the placebo group received 60 mg. The composite primary endpoint of death from cardiovascular causes, MI, stroke, urgent revascularization, or glycoprotein IIb/IIIa rescue therapy through day 7 did not differ significantly between the two groups. However, the rates of TIMI major bleeding were higher in the pretreatment group (HR 1.90, $P = 0.006$).

5.1 Guidelines

Even though there was conflicting evidence of bleeding complications in different studies, prasugrel remains a class I recommendation according to the 2013 ACC/AHA guidelines for management of STEMI or NSTEMI in patients undergoing PCI for at least 12 months [161]. It is not recommended for medically managed ACS or after lytics where clopidogrel is favored as the thienopyridine of choice, given the lack of data for prasugrel in the setting of fibrinolytic therapy. The committee also suggests that it would be reasonable to choose prasugrel over clopidogrel in patients who are not high risk for bleeding and have no history of stroke or TIA [161]. In patients scheduled to undergo elective CABG, discontinuation of clopidogrel and prasugrel for a minimum of 5 and 7 days, respectively, is recommended [162]. It is not recommended in those 75 years and older given the increased risk of fatal or intracranial bleeding.

6 Ticagrelor

Ticagrelor is a high-affinity ADP analogue that causes reversible inhibition of the $P2Y_{12}$ though unlike the thienopyridines, it does not require metabolic activation and exerts its effects by binding to and changing the conformation of the $P2Y_{12}$ receptor. It is rapidly absorbed and undergoes enzymatic degradation to an active metabolite, with properties similar to the parent compound. Plasma concentrations peak around 1–3 hours after administration. The half-life is 6–13 hours and thus requires twice-daily dosing, unlike clopidogrel and prasugrel which are once daily. Compared with clopidogrel, ticagrelor can lead to earlier and more consistent platelet inhibition and can even provide platelet inhibition to those who have already been treated with clopidogrel [163].

Ticagrelor has played a major role in how we manage ACS given the early trials showing its benefit over clopidogrel. The Study of Platelet Inhibition and Patient Outcomes (PLATO) trial was the first and largest ticagrelor trial to demonstrate its benefit. Over 18,000 patients were randomly assigned to receive either ticagrelor (180 mg loading followed by 90 mg twice daily) or clopidogrel (300 or 600 mg loading dose followed by 75 mg). Patients were followed for a median of 12 months after which the primary composite endpoint of death from vascular causes, MI, or stroke was evaluated. In the ticagrelor group, the primary endpoint occurred in 9.8% of patients as compared to 11.7% in the clopidogrel (HR 0.84, 95% CI 0.77–0.92, $P < 0.001$). MI (5.8% vs. 6.9%, $P = 0.005$) and death (4% vs. 5.1%, $P = 0.001$) were both significantly lower in ticagrelor group in the subgroup analyses. Ticagrelor was, however, associated with a higher rate of major bleeding not related to CABG though there was no significant difference in the rates of major bleeding between ticagrelor and the clopidogrel groups (11.6% vs. 11.2%, $P = 0.43$). The instances of fatal intracranial bleeding were higher with ticagrelor but less fatal bleeding from other sites.

Based on these data, ticagrelor is a class I indication for patients with ACS [161]. Substudies have further evaluated ticagrelor and have shown benefit in medically managed [164] and invasively managed ACS [165, 166].

However, until recently there was no data comparing ticagrelor to prasugrel for a head-to-head comparison in patients with ACS. It had been assumed that since prasugrel had a higher bleeding incidence, ticagrelor would be the favored drug for upfront ACS management. However, the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 5 trial investigated this. This was a multicenter, randomized, open-label trial where over 4000 patients who presented with ACS and in whom an invasive management strategy was planned were randomized to either ticagrelor or prasugrel. The primary endpoint was the composite of death, myocardial infarction, or stroke at 1 year, and the major secondary endpoint was bleeding. The primary endpoint occurred in 9.3% in the ticagrelor group but only 6.9% in the prasugrel group (HR 1.36, 95% CI 1.09–1.70, $P = 0.006$). While the individual components of death or stroke were not different between groups, myocardial infarctions were higher in the ticagrelor group compared to prasugrel (4.8% vs. 3.0%, HR 1.63, 95% CI 1.18–2.2). Major bleeding was not significantly different between groups. Given these findings, it is likely that future guidelines will tip the scale in favor of prasugrel rather than ticagrelor.

Ticagrelor monotherapy has recently emerged as a potential option for secondary prevention without aspirin. In the Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention (TWILIGHT) trial [167], this was assessed further. In this study, high-risk patients were assigned to dual antiplatelet therapy with aspirin and ticagrelor for 3 months at which point 7119 patients who have undergone PCI and who had not had major bleeding episodes were all continued on ticagrelor and were randomized to either placebo or continuing aspirin 81 mg daily. The primary endpoint was the composite of death from any cause, nonfatal MI, or nonfatal stroke. The incidence of the primary endpoint was 4.0% among those assigned to ticagrelor only and 7.1% in those assigned to ticagrelor and aspirin (hazard ratio 0.56, $P < 0.001$). Bleeding was also lower in the ticagrelor monotherapy group (1% vs. 2%, hazard ratio 0.49, confidence interval 0.33–0.74).

Use of ticagrelor beyond 12 months after PCI for secondary prevention has also been investigated. The Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) [168] investigated this question. In this study, over 21,000 patients who had had an MI in the previous 1–3 years were randomly assigned to receive ticagrelor 90 mg twice daily or 60 mg twice daily or placebo. Everyone received low-dose aspirin and they were followed by for a mean of 33 months. The primary endpoint was the composite of cardiovascular death, myocardial infarction, or stroke. While ticagrelor significantly reduced the primary endpoint with either 90 mg (15% reduction, $P = 0.008$) or 60 mg (16% reduction, $P = 0.004$) twice daily as compared to placebo, there was an increase in the rate of major bleeding with 90 mg (2.6%) or 60 mg (2.3%) compared to placebo (1.06%) ($P < 0.001$ for each). Given the findings of increased bleeding, ticagrelor is not recommended beyond 12 months for DAPT.

7 Cilostazol

Although first approved in the United States in 1999 for the treatment of intermittent claudication, cilostazol has been used as an antiplatelet agent in Asia for two decades [182]. Cilostazol exerts its principal antiplatelet effect via selective inhibition of phosphodiesterase 3 (PDE 3) in platelets and vascular smooth muscle cells [182]. This leads to increased levels of platelet cyclic AMP and ultimately results in inhibition of platelet aggregation and arteriolar vasodilation [169]. Antimitogenic effects and inhibition of adenosine uptake may also play a role in the mechanism of action of cilostazol [169]. The efficacy of cilostazol in the symptomatic management of patients with intermittent claudication has been demonstrated in several trials.

In 1 randomized, placebo-controlled trial of over 600 patients with intermittent claudication, cilostazol administered either 50 mg or 100 mg twice daily significantly improved pain-free walking distance compared with placebo [170]. In a meta-analysis of 8 randomized, placebo-controlled trials including over 2702 patients with moderate to severe claudication, cilostazol resulted in a 67% increase in pain-free walking distance and a 50% increase in maximal walking distance [171]. Furthermore, this benefit was maintained across a variety of subgroups.

With its pleiotropic effects, cilostazol may add to our armamentarium of antiplatelet therapy after PCI. Early studies of cilostazol reported a reduction in intimal proliferation and restenosis after directional coronary atherectomy and balloon angioplasty [172, 173]. In a pooled analysis of 23 trials including over 5000 patients, cilostazol was associated with a reduction in the risk of both restenosis and repeat revascularization after PCI [174].

Furthermore, a prospective, randomized trial of triple antiplatelet therapy with aspirin, clopidogrel, and cilostazol in diabetic patients receiving drug-eluting stents demonstrated reduced angiographic restenosis as well as target lesion revascularization in patients receiving triple antiplatelet therapy compared to standard dual antiplatelet therapy [175]. The protective effect of cilostazol may be in part attributable to attenuation of endothelial senescence induced by drug-eluting stents [176]. As might be expected, triple antiplatelet therapy results in more potent inhibition of ADP-induced platelet aggregation than conventional dual antiplatelet therapy [177, 178]. Despite these data, the role of triple antiplatelet therapy in current clinical practice remains uncertain.

A retrospective study from a Korean registry provides important insight in this area. In this study of 4203 STEMI patients undergoing PCI, triple antiplatelet therapy was associated with fewer major cardiac events, cardiac death, and total mortality compared to dual antiplatelet therapy [179]. The incremental benefit of cilostazol may prove to be particularly useful in patients with clopidogrel resistance. This hypothesis was tested in the Adjunctive Cilostazol Versus High Maintenance Dose Clopidogrel in Patients with Clopidogrel Resistance (ACCEL-RESISTANCE) study [180]. In this small study of 60 patients undergoing PCI, patients with high posttreatment platelet reactivity >12 hours after a 300 mg dose of clopidogrel were

randomized to receive either cilostazol 100 mg twice daily or 150 mg of daily clopidogrel. Adjunctive cilostazol was associated with greater platelet inhibition after 30 days as compared to high-maintenance-dose clopidogrel [180].

Cilostazol has also shown a role in preventing restenosis in multiple vascular beds. A meta-analysis of multiple randomized controlled trials of patients undergoing PCI found that the addition of cilostazol resulted in not only a decreased platelet reactivity but also in cardiovascular outcomes including stent thrombosis in individuals already on DAPT [181]. Similar findings have been found in different meta-analyses for both carotid stenting [182] and peripheral arterial stenting [183]. The role of cilastazole for secondary prevention is an area of continued investigation.

8 Dipyridamole

Dipyridamole has a variety of vascular effects that may contribute to its efficacy in cerebrovascular disease, where it has been widely studied. Dipyridamole inhibits adenosine uptake by red blood cells which in turn stimulates adenylyl cyclase and subsequent platelet formation of cAMP, an inhibitor of platelet aggregation [184]. An additional antithrombotic effect arises from inhibition of endothelium phosphodiesterase V (PDE V) and stimulation of nitric oxide/cGMP signaling [185]. Dipyridamole has also been shown to exhibit antioxidant and direct anti-inflammatory effects [184]. Although an early randomized trial of high-dose aspirin and dipyridamole versus aspirin or placebo did not suggest an additional benefit with respect to recurrent stroke [186], subsequent large-scale studies have provided an evidence base to support its use.

Compared to placebo, the first European Stroke Prevention Study (ESPS) found a 33.5% percent reduction in stroke or all-cause death among 2500 patients with a recent stroke or TIA treated with dipyridamole 75 mg and aspirin 330 mg three times daily [187]. The European Stroke Prevention Study 2 (ESPS 2) randomized 6602 patients with prior stroke or TIA in a two-by-two factorial design to aspirin alone (25 mg twice daily), fixed-dose aspirin (25 mg) plus dipyridamole (200 mg) twice daily, dipyridamole alone (200 mg twice daily), or placebo [188]. Compared to placebo, there were a 37% relative risk reduction in stroke observed with combination therapy, 18% reduction with aspirin alone, and 16% reduction with dipyridamole alone [188].

In the European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT), 2764 patients with recent minor stroke or transient ischemic attack were randomized in an open-label design to aspirin (30–325 mg daily) alone or aspirin plus dipyridamole (200 mg twice daily) [189]. Over a mean follow-up of 3.5 years, the rate of the primary composite endpoint of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or major bleeding was 13% in the aspirin plus dipyridamole group and 16% in patients assigned aspirin. After 5 years of follow-up, 34% of patients discontinued the combination of aspirin and dipyridamole, many because of headache [189]. The awaited Japanese Aggrenox Stroke Prevention vs.

Aspirin Programme (JASAP) is comparing fixed-dose dipyridamole plus aspirin to aspirin 81 mg daily for the secondary prevention of stroke (NCT 00311402) [190].

9 Rivaroxaban

While antiplatelet therapy has been the mainstay for management of primary and secondary prevention of cardiovascular events, anticoagulants have played little role. While anticoagulation is used for patients with atrial fibrillation and elevated stroke risk, it has shown little advantage of benefit over risk in primary or secondary prevention of cardiovascular disease. While long-term treatment with a vitamin K antagonist alone or in combination with aspirin has been shown to reduce cardiovascular events, it is associated with significant bleeding complications including an increased risk of intracranial bleeding [191]. Rivaroxaban, a direct Xa inhibitor, was thought as an agent that might be helpful in ACS given the role of Xa in mediating thrombosis. The Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction (ATLAS ACS-TIMI 46) [192] investigated in over 15,000 patients whether low-dose rivaroxaban added to standard therapy would reduce the primary endpoint of death from cardiovascular causes, myocardial infarction, or stroke at a mean follow-up of 13 months. They found that rivaroxaban lowered the primary endpoint (8.9% vs. 10.7%, $P = 0.008$), but there were higher rates of major bleeding (2.1% vs. 0.6%, $P < 0.001$) and intracranial hemorrhage (0.6% vs. 0.2%, $P = 0.009$) without a significant difference in fatal bleeding. These findings laid the groundwork for further investigation into secondary prevention with rivaroxaban.

The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial [193] investigated a dual pathway approach to secondary prevention in stable cardiovascular disease. The trial investigated low-dose rivaroxaban 2.5 mg BID or 5 mg or placebo added to aspirin therapy in individuals with stable atherosclerotic disease to determine whether there was a reduction in the primary endpoint, which included the composite of cardiovascular death, stroke, or myocardial infarction. This trial included over 27,000 patients with stable atherosclerotic vascular disease who were randomized to receive rivaroxaban 2.5 mg twice daily or 5 mg twice daily or placebo in addition to the standard of 100 mg aspirin daily. The mean follow-up was 23 months. The primary outcome occurred in fewer patients in the rivaroxaban group (4.1% vs. 5.4%, $P < 0.001$) though, as many would have predicted, major bleeding occurred in more patients in the rivaroxaban plus aspirin group (3.1% vs. 1.9%, $P < 0.001$). Unlike the ATLAS ACS, there was no significant difference in intracranial or fatal bleeding between groups. All-cause mortality was lower in the rivaroxaban group as compared with the aspirin-only group (3.4% vs. 4.1%, $P = 0.01$). Rivaroxaban 5 mg twice daily did not reduce the primary endpoint but did lead to more major bleeding events.

10 Conclusion

Platelets play a fundamental role in thrombosis and inflammation, processes germane to the development of cardiovascular disease. Inhibition of thromboxane synthesis via aspirin has formed the basis of modern cardiovascular disease prevention. Similarly, ADP inhibition by $P2Y_{12}$ receptor antagonists has proved an essential adjunct in the treatment of patients with ACS, cerebrovascular disease, and peripheral arterial disease. However, despite these therapies (Table 2), a significant number of patients experience vascular events given the multiple pathways available for platelet activation. The development of new strategies for platelet inhibition is vital to achieving greater successes in the treatment of cardiovascular disease.

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Inflammation and Atherosclerotic Cardiovascular Disease

Peter P. Toth

Summary

- The inflammation giving rise to atherosclerotic disease is a highly conserved, orchestrated, and redundant constellation of interleukins, cytokines, products of oxidation, and cell types. Inflammation involves hundreds of genes, which include cell surface receptors, intracellular signaling cascades, microRNAs, and products of secretion by numerous cell types.
- Endothelial dysfunction constitutes an important early step in vascular inflammation and is necessary in order to promote the binding and transmigration of inflammatory white blood cells (monocytes, T cells, mast cells, and neutrophils) into the subendothelial space.
- White cell participants in vascular inflammation include monocytes/macrophages/T cells, mast cells, and neutrophils, all of which play critical but very different roles.
- Platelets play prominent roles in endothelial dysfunction as well as clonal expansion in the arterial wall.
- Atherosclerosis development and progression is influenced by the cellular constituents of all layers of the arterial wall, including the intima, media, and adventitia. The extracellular matrix also plays a critical role in trapping chemically modified atherogenic lipoproteins and facilitating some forms of intercellular communication.
- Inflammation can be turned on and turned off, depending upon the balance between pro-inflammatory interleukins/cytokines and anti-inflammatory specialized pro-resolving molecules, as well as phenotypic transitioning among macrophages.

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- MicroRNAs are an important new player in vascular inflammation, and much remains to be learned about how they promote and antagonize inflammation.
- Insulin-resistant adipose tissue localized in multiple visceral and systemic tissue depots is an important source of pro-inflammatory adipokines that participate in atherosclerosis development and progression.
- The microbiome of the oral cavity and gut can also participate in the modulation of systemic inflammation. Mesenteric dysfunction can lead to leaky epithelium in the ileum and colon resulting in a chronic lipopolysaccharide leak. Gut bacteria can also produce both pro-inflammatory (e.g., trimethylamine) and anti-inflammatory (short-chain fatty acids) molecules that influence inflammatory tone.
- Despite this bewildering complexity, both an IL-1 monoclonal antibody and colchicine have been shown to reduce systemic inflammatory tone and reduce risk for cardiovascular events, findings that constitute a major milestone in our ability to begin to address the risk associated with heightened inflammation.

1 Introduction

The ancient Roman physician Celsus was the first to describe the four defining signs of inflammation: calor (warmth), dolor (pain), tumor (swelling), and rubor (redness and hyperemia) [1]. The Prussian pathologist Rudolf Virchow proposed that atherosclerosis is pathophysiologically and primarily driven by inflammation, an idea that was quite radical for its time [2, 3]. Virchow showed that atherogenesis was associated with inflammatory white blood cell (WBC) infiltration, and he argued that atherosclerotic disease represented a biochemically and histologically active process resulting in arterial wall injury, rather than one of passive lipid accumulation over time [4]. Approximately 50 years later, the pioneering cardiologist Samuel Levine observed that WBCs play a significant role in the signs and symptoms of patients who sustain a myocardial infarction (MI) (coronary thrombosis):

> In the great majority of acute cases of coronary thrombosis, there quickly develops a fever and leukocytosis. This has been noted as soon as a few hours after onset. The extent of fever and leukocytosis probably depends on the amount of infarcted cardiac tissue involved. It may be stated that infarcted tissue anywhere in the body probably liberates toxic products that produce leukocytosis and fever." [5]

This observation and its causal inference were prescient, as the leukocytosis and fever represent the post-injury inflammatory response to an MI. Subsequent investigation showed that in patients with heightened systemic inflammatory tone, such as those with rheumatologic diseases, there is a substantial increase in risk for the development of atherosclerotic cardiovascular disease (ASCVD) compared

Table 1 Prevalence of atherosclerosis with connective tissue disease (CTD)

Total	With CTD			Without CTD						
n	n	ASCVD	ASCVD rate (%)	n	ASCVD	ASCVD rate (%)	Prev. Ratio	95% CI		p[a]
Race										
African American	158,335	4661	1383	29.7	153,674	14,516	9.4	3.1	[3.0–3.3]	<0.001
White	129,132	4086	600	14.7	125,046	10,251	8.2	1.8	[1.7–1.9]	<0.001
Age										
18–34	84,520	1015	25	2.5	83,505	346	0.4	5.9	[4.0–8.9]	<0.001
35–44	44,625	1224	99	8.1	43,401	1018	2.3	3.4	[2.8–4.2]	<0.001
45–54	49,432	1814	265	14.6	47,618	3123	6.6	2.2	[2.0–2.5]	<0.001
55–64	45,728	1830	427	23.3	43,898	5545	12.6	1.8	[1.7–2.0]	<0.001
65–74	34,394	1512	550	36.4	32,882	6942	21.1	1.7	[1.6–1.8]	<0.001
75+	28,768	1352	617	45.6	27,416	7793	28.4	1.6	[1.5–1.7]	<0.001
Traditional risk factors										
None (age 35+)	181,256	2362	107	4.5	178,894	2792	1.6	2.9	[2.4–3.5]	<0.001
Diabetes	24,247	1368	591	43.2	22,879	7713	33.7	1.3	[1.2–1.4]	<0.001
Smoking	26,235	1515	599	39.5	24,720	7862	31.8	1.2	[1.2–1.3]	<0.001
Hypertension	54,603	3588	1190	33.2	51,015	14,499	28.4	1.2	[1.1–1.2]	<0.001
Hyperlipidemia	44,496	2643	1098	41.5	41,853	14,581	34.8	1.2	[1.1–1.2]	<0.001

[a]p values are derived from χ^2 tests for comparisons between CTD and non-CTD populations. Intergroup comparisons of the CTD-associated ASCVD prevalence ratios shown here indicate significantly disproportionate effect of CTD on African Americans, young adults, and those without traditional risk factors ($p < 0.001$ by χ^2 test)

to patients without these conditions [6–8] (Table 1). Even periodontal disease increases systemic inflammation enough to potentiate coronary and peripheral atherogenesis [9].

The capacity to mount an inflammatory response is essential to survival. Inflammation facilitates the clearance of pathogens and promotes wound healing. Hence, acute inflammatory responses are beneficial and necessary. However, when inflammation within a tissue becomes chronic (characterized by persistent presence of macrophage, lymphocytes, and plasma cells), it is injurious and pathogenic [10]. It is now clear that chronic inflammation plays a role in the entire causal spectrum of atherogenesis as well as acute ASCVD-related events [11, 12]. The inflammatory cascade regulating atherosclerosis is comprised of hundreds of molecules that include interleukins, cytokines, prostaglandins, leukotrienes, lipoxins, reactive oxygen and nitrogen species, lipoproteins, microRNAs, phospholipids, fatty acids, bacterial toxins and products of the gut microbiome, matrix metalloproteinases, growth factors, and a large number of enzymes and transcriptional factors, among others, that are highly regulated and integrated. The cellular constituents of the inflammatory cascade include endothelial cells, monocytes/macrophages, T cells, neutrophils, mast cells, dendritic cells, and smooth muscle cells. This chapter will provide a detailed overview of how these cell types and biomolecules interact and give rise to the complex pathophysiology characterizing atherosclerotic disease. In addition, the clinical use of inflammation-related biomarkers will be reviewed and contextualized.

2 Endothelial Function/Dysfunction

Endothelial cells perform critical functions along the luminal aspect of the vasculature [13]. In total, the vascular endothelium could cover an area of 350 m^2 and is widely considered to be an independent organ system [14]. Under normal physiological conditions, the endothelium serves as a highly selective barrier for molecular and cellular trafficking into and out of the arterial wall. Barrier integrity and the capacity for intercellular cross-talk are maintained by tight gap junctions between endothelial cells. Tight gap junctions include endothelial cell-selective adhesion molecule, VE-cadherin, activated leukocyte cell adhesion molecule-1, and intercellular adhesion molecule-2, among others [15, 16]. Endothelial cells regulate arterial tone by producing nitric oxide, prostacyclin, and endothelium-derived hyperpolarizing factor [17, 18]. These molecules induce smooth muscle cell relaxation and vasodilatation. Endothelial cells also control coagulation and thrombosis by producing tissue plasminogen activator (tPA, an enzyme that promotes plasmin formation from plasminogen) [19]. Plasmin promotes thrombolysis by hydrolyzing fibrin. Endothelial cells also produce heparan sulfate and thrombomodulin which inhibit thrombin and thereby reduce capacity for the conversion of fibrinogen to fibrin [20]. Nitric oxide and prostacyclin are both potent inhibitors of platelet activation and aggregation along the endothelial cell surface [21, 22]. Clearly, endothelial

cells tightly regulate the balance between hemostasis and thrombolysis within the cardiovascular system.

Endothelial cells exposed to such CV risk factors as elevated levels of apolipoprotein B100 (apoB) containing lipoproteins, hyperglycemia, insulin resistance, hypertension, oscillatory shear stress, cigarette smoke-related toxins, turbulent flow, bacterial endotoxins, and oxygen free radicals become dysfunctional [23, 24]. In the setting of endothelial cell dysfunction, critical changes occur which potentiate inflammation and atherogenesis: [1] there is reduced nitric oxide production [2]; increased endothelin-1 production which, combined with less nitric oxide production, increases systemic vascular resistance [3]; there is a net shift to a greater inclination for thrombosis since tPA production decreases and plasminogen activator inhibitor-1 (an inhibitor of tPA and fibrinolysis) production increases [4]; the tightness of endothelial gap junctions is reduced and their barrier function is impaired resulting in increased nonselective permeability [5]; there is an increase in the expression of pro-inflammatory adhesion molecules [11, 25].

Adhesion molecules are expressed by dysfunctional endothelium and promote the binding of platelets, monocytes, lymphocytes, neutrophils, and mast cells to their surface. Adhesion molecules include platelet endothelial cell adhesion molecule (PECAM), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1, as well as selectins E, L, and P [26, 27]. Each cell type that binds to activated endothelial cells does so by expressing a variety of integrin counter-receptors (Fig. 1) [28]. The binding of counter-receptors to endothelial surface adhesion molecules regulates a three-step process: (1) initial attachment and rolling, (2) stable arrest and migration to gap junctions, and (3) transmigration. Each step is regulated by different adhesion molecules, chemokines, and counter-receptors. Different cell types home into the subendothelial space along gradients of different chemokines: monocytes follow monocyte chemoattractant protein-1 (MCP-1); T cells follow inducible protein-10, monokine induced by interferon-γ, and T cell α-chemoattractant; mast cells follow eotaxin [11]. Transmigration (diapedesis) of monocytes can occur in two different ways [28]. The first involves cellular shape change as the monocyte rearranges its actin cytoskeleton, thereby facilitating passage in between two endothelial cells with loosened gap junctions (paracytosis). The second requires an extraordinarily complex process by which the monocyte traverses the cytosol of an endothelial cell and emerges in the subendothelial space (transcytosis). Once inside the subendothelial space, white cells create an inflammatory nidus within the arterial wall that potentiates atherogenesis.

Platelets are able to interact with both endothelial cells and leukocytes. Nitric oxide inhibits the binding of platelets to endothelial cells. However, once the endothelium becomes dysfunctional, it expresses PECAM, junctional adhesion molecules, ICAM-1, and P- and E-selectins which promote the binding and interaction of platelets with endothelial cells [29–31]. Platelets engage in the molecular transfer of a variety of inflammatory mediators, including platelet factor-4 (which participates in inflammation and wound healing) [32], thrombospondin (which can activate oxidative injury) [33], platelet-derived growth factor (a mitogen, chemoattractant for vascular smooth muscle cells, and driver of intimal proliferation) [34], and transforming growth

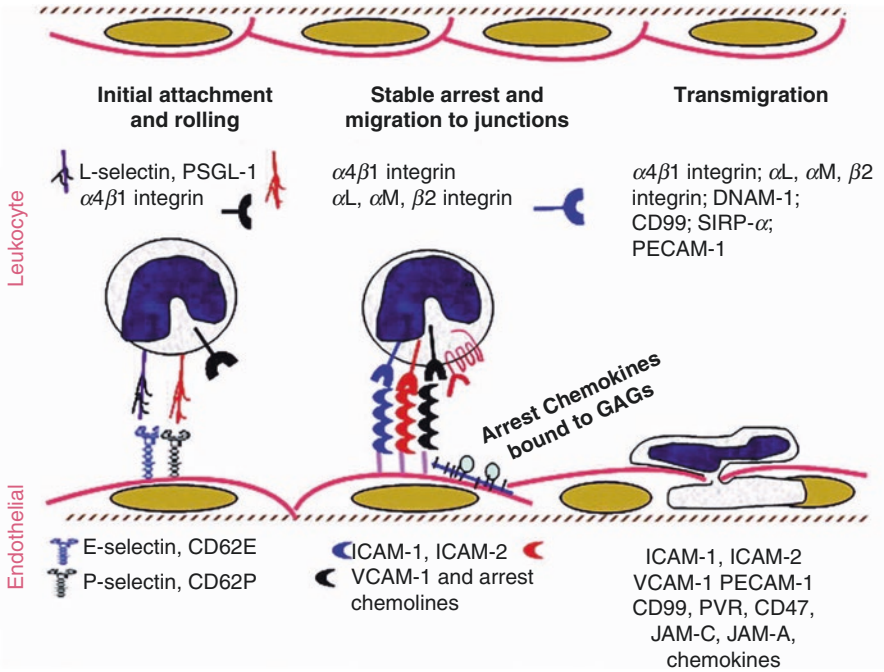

Fig. 1 The multistep process of leukocyte recruitment . Initial attachment and rolling, arrest, and migration to cell–cell borders and transmigration across the vascular endothelium, shown here for monocytes. The leukocytes initially attach via selectin-mediated mechanisms along with contributions from the α-4 and β-2 integrins interacting with their ligands VCAM-1 and ICAM-1, respectively. The next step is stable arrest; β-2 integrins become activated by arrest chemokines and trigger cell arrest at or near cell–cell junctions. Leukocytes then migrate to junctions and transmigrate across the vascular endothelium at both junctional and non-junctional locations. The symbols used to represent adhesion molecules in endothelial cells are identified below each component of the figure. (Reprinted from Rao et al. [28]. With permission from Wolters Kluwer Health, Inc.)

factor-β, (which has anti-inflammatory properties and may stabilize atherosclerotic plaque) [35], among others. Platelets can bridge a circulating leukocyte to endothelium, and platelets can also form a heterotypic aggregate with circulating leukocytes and then bind to activated endothelium, thereby potentiating inflammatory change within the endothelial cell and arterial wall [36]. These leukocyte-platelet interactions depend not only on surface receptors and counter-receptors but also on soluble, secreted cytokines released when these two cell types are in close proximity [37].

Angiotensin II exerts a broad range of deleterious effects within arterial walls. Angiotensin II is an octapeptide, induces smooth muscle cell contraction/vasoconstriction, and is produced by proteolytic cleavage of angiotensin I by angiotensin-converting enzyme. Dysfunctional endothelial cells increase their expression of the AT1 receptor which binds to angiotensin II. AT1 receptor activation induces increased expression of oxidative enzymes, including NADH/NADPH oxidase and xanthine oxidase. These enzymes potentiate oxidative stress by producing such reactive oxygen

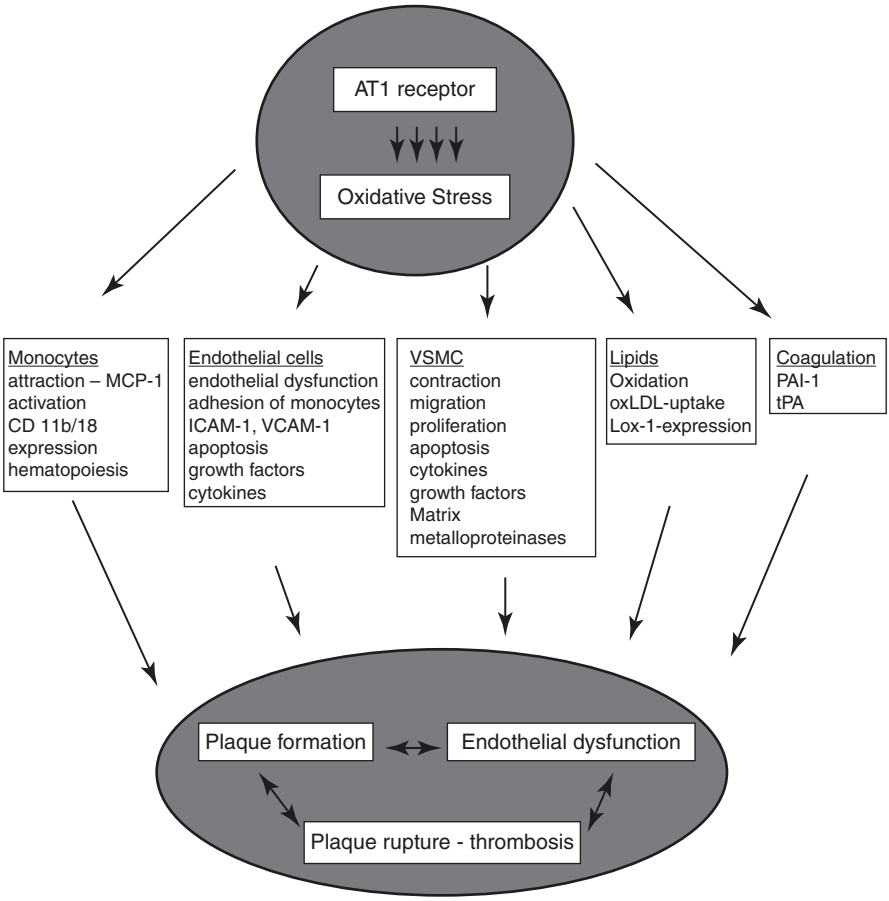

Fig. 2 AT1 receptor–induced oxidative stress AND ATHEROSCLEROSIS. AT1 receptor activation leads to the release of reactive oxygen species in various vascular cells. Oxidative stress is in turn involved in monocyte attraction and activation. This involves increased production of monocyte chemoattractant protein-1 (MCP-1). In endothelial cells, adhesion molecules that are essential for the adhesion of monocytes, such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), are induced by angiotensin II via superoxide anions. In vascular smooth muscle cells (VSMCs), numerous biological processes are induced by reactive oxygen species. AT1 receptor activation increases expression of the oxLDL receptor LOX-1 resulting in an increased oxLDL uptake. Expression of plasminogen activator inhibitor-1 (PAI-1) is increased via AT1 receptor activation predisposing to a procoagulant state. (Reprinted from Nickenig and Harrison [38]. With permission from Wolters Kluwer Health, Inc.)

species (ROS) as hydroxyl ions, hydrogen peroxide, and superoxide anion which are cytotoxic to endothelial cells and can oxidize and peroxidize lipids and phospholipids in lipoproteins [38, 39] (Fig. 2). Oxidized lipoproteins are highly atherogenic and are the preferred substrates for macrophage lipid scavenging in the subendothelial space. The ROS also quench nitric oxide which promotes greater vasoconstriction; in

addition, the interaction of ROS with nitric oxide produces peroxynitrite anions which are also cytotoxic. AII stimulates adhesion molecule expression, alters thrombolytic balance by decreasing the tPA/PAI-1 ratio, increases monocyte influx and macrophage density in the intima, promotes smooth muscle cell proliferation and migration, and increases fibroblast collagen production and deposition which alters the composition of the interstitial matrix and reduces arterial compliance [38, 40–42] (Fig. 2).

There is a burgeoning global epidemic of obesity, metabolic syndrome, and diabetes mellitus, conditions highly associated with insulin resistance. Insulin resistance is a manifestation of impaired signal transduction from the insulin receptor, which results in glucose intolerance and the genesis of a hyperglycemic milieu. Persistent hyperglycemia leads to the formation of arterial advanced glycation end products (AGEs) [43]. An AGE is formed by the nonenzymatic glycosylation of lysine residues in proteins, enzymes, and lipoproteins [44]. Once bound to receptors of advanced glycation end products, these complexes activate the inflammatory pathways controlled by the nuclear transcription factors activator protein-1 and nuclear factor kappa-B [43, 45]. The AGEs induce endothelial cell dysfunction, reduce nitric oxide availability, potentiate oxidative and procoagulatory tone, and increase adhesion molecule expression [46–48]. In addition, the AGEs increase (1) the production and deposition of adverse forms of intercellular matrix, (2) promote lipoprotein modification and trapping in the subendothelial space, and (3) augment collagen cross-linking which reduces vessel wall compliance [49].

3 Inflammatory Blood Cells and Atherogenesis

3.1 Monocytes and Macrophages

Multiple lineages of white blood cell participate in atherogenesis [50] (Fig. 3). Monocytes that gain access into the subendothelial space are heterogeneous and can have both pro- and anti-inflammatory functions in the arterial wall. This section will address the pro-inflammatory monocyte subset (increased expression of Ly6C in the mouse and P-selectin glycoprotein ligand in humans). Monocytes become resident macrophages in response to macrophage colony-stimulating factor [51]. Macrophage exiting from the arterial wall is inhibited by both VCAM-1 and the neural guidance factor netrin-1 [52]. Interestingly, migrating smooth muscle cells can transform into macrophages in a process that requires the microRNAs miR143/145 and reduced expression of myocardin [53]. Activated macrophages augment local inflammation by secreting interleukins, cytokines, matrix metalloproteinases, and ROS (Fig. 3).

Lipoproteins entering the subendothelial space can be trapped by proteoglycans comprising the intercellular matrix [54]. As the subendothelial microenvironment becomes more pro-inflammatory, it also becomes more pro-oxidative. NADH/NADPH oxidase, myeloperoxidase, and a variety of lipoxygenases can oxidatively modify the polyunsaturated fatty acid contained in the phospholipids and cholesterol esters comprising lipoproteins [55, 56]. In a hyperglycemic milieu, the

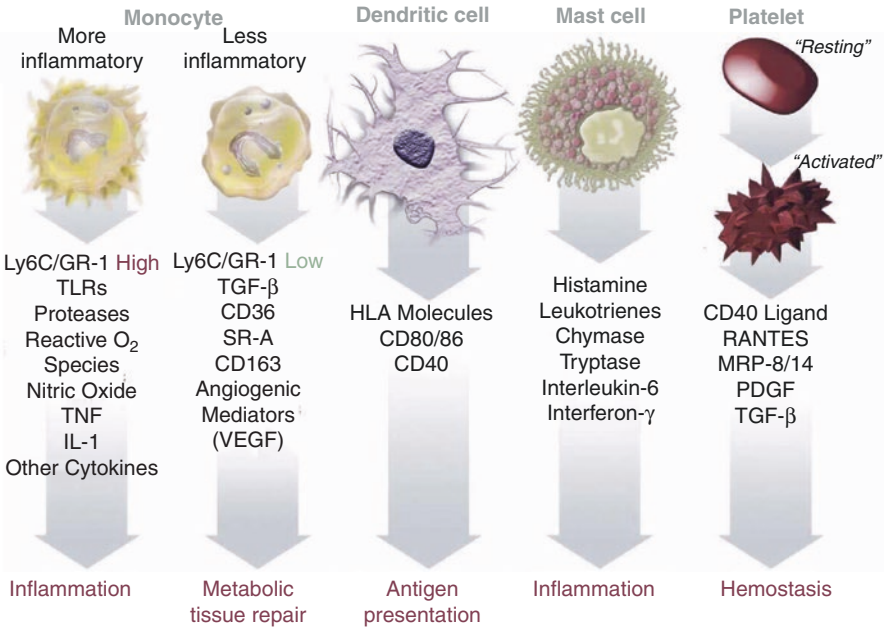

Fig. 3 Different white blood cell lineages and platelets participate in inflammation and atherogenesis . This figure summarizes some of the functions ascribed to various cellular participants in atherosclerosis. Mononuclear phagocytes represent the bulwark of the innate immune defenses in mammals. Recent work has focused on heterogeneity of mononuclear phagocytes. There is a pro-inflammatory subset distinct from a less inflammatory population of monocytes. The inflammatory subset expresses high levels of the cell-surface marker Ly6C. These inflammatory monocytes express higher levels of Toll-like receptors (TLR), and the other functions indicated, including elaboration of high levels of the cytokines tumor necrosis factor (TNF) and interleukin (IL)-1. The less inflammatory subset of monocytes express higher levels of transforming growth factor (TGF)-beta, the scavenger receptors CD36 and scavenger receptor A (SR-A), and the angiogenic cytokine vascular endothelial growth factor (VEGF). Dendritic cells express human leukocyte antigen (HLA) molecules among the other indicated structures. Dendritic cells present antigens to T cells, linking innate to adaptive immunity. Mast cells elaborate many mediators. Platelets also participate in adaptive immunity. When activated, platelets exteriorize CD40 ligand (CD40L) and release mediators including RANTES (regulated and T-cell expressed secreted), myeloid-related protein (MRP)-8/14, platelet-derived growth factor (PDGF), and TGF-beta. (Reprinted from Libby et al. [50]. With permission from Elsevier)

lipoproteins can also be glycated [57]. Many different molecular species of oxidized phospholipid are generated, and these propagate and amplify inflammation and oxidation. Macrophages exposed to oxidatively or glycatively modified apoB containing lipoproteins upregulate their surface expression of scavenger receptors [58]. These include (1) scavenger receptor A (types I–III), (2) cluster of differentiation 36 (CD36 or scavenger receptor class B member 3 (SCARB3)), (3) lectin-like oxidized LDL receptor-1 (LOX-1), and (4) scavenger receptor for phosphatidylserine and oxidized LDL (SR-PSOX) [59–62]. These receptors are used to bind and clear lipoproteins from the subendothelial space. Oxidized phospholipids in LDL particles create specific epitopes (e.g., sn-2 fatty acids that terminate in

1-palmitoyl-2-(5′-oxovaleroyl)-sn-glycero-3-phosphocholine or γ-hydroxy-α,β-unsaturated carbonyl groups) recognized by scavenging receptors [63, 64]. Oxidized phospholipids also propagate endothelial cell injury by inducing the hyperphosphorylation of VE-cadherin, a protein necessary for endothelial gap junction functionality and integrity [65]. Hyperphosphorylation of VE-cadherin causes this molecule to dissociate from paxillin and β-catenin, leading to gap junction impairment. As lipid scavenging progresses, lipid droplets form in the cytosol of macrophages, and they take on a somewhat foamy appearance, hence the designation "foam cells."

Foam cells actively secrete cytokines, interleukins, matrix metalloproteinases (MMPs or matrixins), ROS, and tissue factor [50]. The cytokines and interleukins potentiate the inflammatory response and promote the recruitment of other types of white cells. Tissue factor promotes coagulation, platelet activation, and thrombus formation on the surface of fissured or ruptured atherosclerotic plaques [66, 67] (Fig. 4). Because of their proteolytic actions, the MMPs disrupt and destabilize

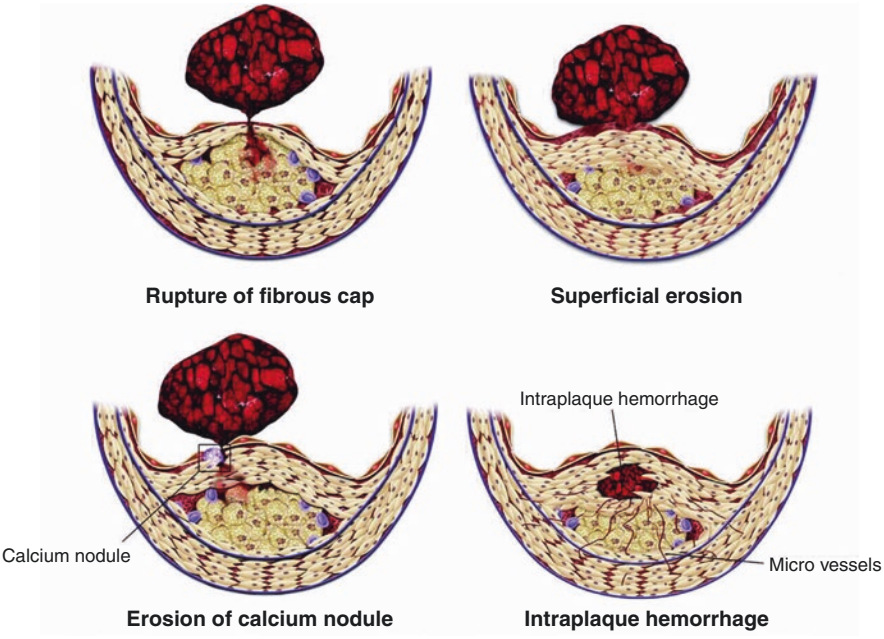

Fig. 4 Microanatomy of coronary arterial thrombosis and acute occlusion. Rupture of fibrous cap (upper left) causes some two-thirds to three quarters of fatal coronary thromboses. Superficial erosion (upper right) occurs in one-fifth to one quarter of all cases of fatal coronary thromboses. Certain populations such as diabetic individuals and women appear more susceptible to superficial erosion as mechanism of plaque disruption and thrombosis. Erosion of a calcium nodule may also cause plaque disruption and thrombosis (lower left). In addition, friable microvessels in base of atherosclerotic plaque may rupture and cause intraplaque hemorrhage. Consequent local generation of thrombin may stimulate SMC proliferation, migration, and collagen synthesis, promoting fibrosis and plaque expansion on subacute basis. Severe intraplaque hemorrhage can cause sudden lesion expansion by mass effect acutely as well. (Reprinted from Libby and Theroux [67]. With permission from Wolters Kluwer Health, Inc.)

plaque architecture by hydrolyzing the extracellular matrix (ECM) comprised of collagen, elastin, and glycosaminoglycans, among other molecular species. Plaque is particularly prone to rupture if degradation of the ECM occurs in the fibrous cap of a plaque [68]. Proteolysis of the ECM also disrupts extracellular signaling networks [69]. The proteolytic digestion products of ECM include hyaluronan, heparan sulfate, and integrin binding fibronectin, all of which stimulate immune and pro-inflammatory responses [70–72]. Migrating smooth muscle cells advance from the media into the intima by secreting MMPs and digesting ECM and the internal elastic lamina along their path [73]. One of the reasons inflamed, "hot" plaque is unstable is because there is heightened activity of MMPs.

Foam cells are a basic substrate for fatty streak and atherosclerotic plaque formation. Foam cells are distressed as excess intracellular free cholesterol is toxic. Macrophages cannot catabolize cholesterol. Foam cells can engage in defensive measures and can utilize a variety of molecular pathways for externalizing intracellular cholesterol, which include (1) exporting excess cholesterol via scavenger receptor BI, which lipidates high-density lipoprotein (HDL); (2) exporting cholesterol via ATP binding membrane cassette transport proteins A1 and G1, thereby lipidating nascent discoidal HDL and spherical HDL particles, respectively; and (3) macrophages that can secrete apolipoprotein E which becomes an auto-cholesterol acceptor on the surface of the cell [74]. If these safety systems for unloading cholesterol fail, then the macrophage is subject to other fates.

Foam cells experience endoplasmic reticulum (ER) stress [75]. The ER is the location for protein translation, sorting, and folding. During ER stress, there is an accumulation of misfolded or unfolded proteins in the ER. Cells engage in the unfolded protein response (UPR), whereby defense mechanisms are activated to reduce protein synthesis, eliminate misfolded/unfolded proteins from the ER, maintain capacity for N-linked glycosylation and disulfide isomerase activity, and increase the production of chaperone molecules that facilitate proper protein folding [76]. If the macrophage cannot normalize ER function, then the caspase pathway is activated by the transcriptional factor CCAAT-enhancer-binding protein-β, and the cell undergoes apoptosis or programmed cell death leading to the formation of apoptotic bodies [77, 78]. Apoptosis does not promote inflammation. Early in plaque development, other macrophages can engage in phagocytosis of apoptotic bodies and efficiently clear the microenvironment of debris [79]. This clearance of apoptotic bodies is highly synchronized and orchestrated and limits the cellularity of an evolving atherosclerotic plaque. Apoptotic cells produce a variety of "find me" (e.g., lysophosphatidylcholine, sphingosine-1-phosphate, fractalkine (CX3CL1), and adenosine 5′-triphosphate and uridine-5′-triphosphate) and "eat me" (e.g., phosphatidylserine, altered ICAM-1 epitopes on the cell surface, increased calreticulin exposure) molecules that promote phagocytic cell attraction and migration, target cell discovery, and engulfment/clearance [80, 81]. Apoptotic neutrophils express neutrophil-borne pentraxin-3 which promotes their recognition and removal by macrophages [82]. Lactadherin functions as a coupling molecule that facilitates the binding of apoptotic cell phosphatidylserine to vitronectin on phagocytic macrophages [83]. It is possible that deficiencies in these molecules may lead to impaired

apoptotic cell clearance. An example of this is a deficiency in the receptor tyrosine-protein kinase MER which is associated with rapid progression and enlargement of the necrotic core in experimentally induced plaques [84].

As the rate of foam cell formation and accumulation increases, the milieu within the vessel wall progressively worsens, and phagocytic capacity is eventually exceeded; the balance between foam cell apoptosis and clearance is lost, leading to progressive accumulation of lipid and apoptotic debris. The plaque now shifts into a phase where the necrotic core forms in response to impaired macrophage efferocytosis or programmed cell removal [85]. In this circumstance, macrophages undergo necroptosis (cell necrosis) which stimulates an inflammatory response, greater accumulation of necrotic core material, and lesional expansion [86] (Fig. 5).

The excess free cholesterol in macrophages can crystallize, or macrophages can phagocytose extracellular cholesterol crystals (Fig. 6). Cholesterol crystals trigger

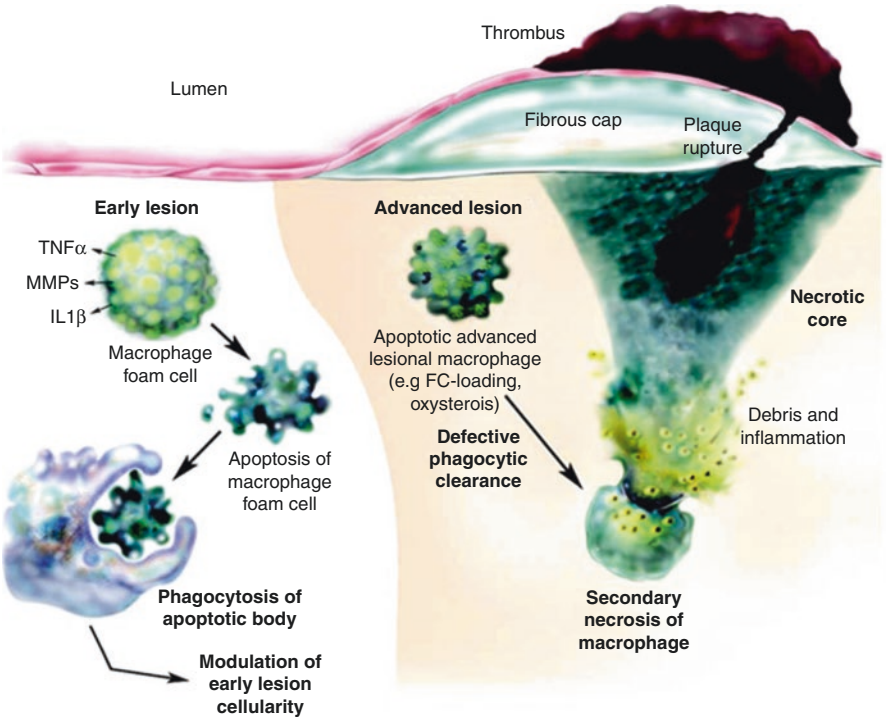

Fig. 5 The so-called "volcano" model of atherosclerotic plaque formation . In early atherosclerotic lesions (left), macrophage foam cells undergo apoptosis and are efficiently phagocytosed and cleared by other macrophages. This process controls lesion cellularity and rate of disease progression. However, in later lesions (right), apoptotic macrophages are not engulfed and cleared as efficiently resulting in a net accumulation of apoptotic and necrotic macrophages with generation of a necrotic core. This leads to the mounting of an inflammatory response which can lead to plaque instability and eventual rupture. (Reprinted from Tabas [79]. With permission from Wolters Kluwer Health, Inc.)

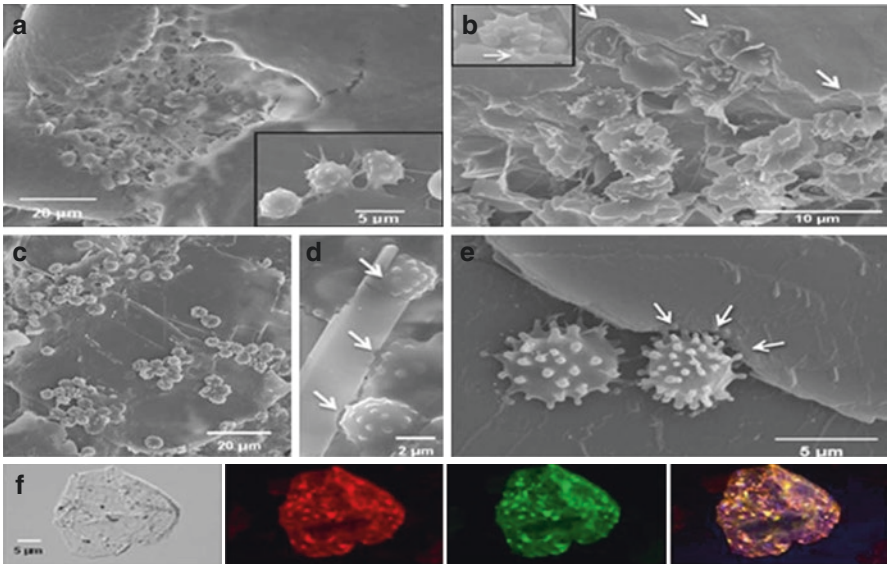

Fig. 6 Cholesterol crystals and atherosclerotic disease**.** Macrophages from coronary aspirates appear to be eroding cholesterol crystals. (**a**–**e**) Scanning electron micrographs demonstrate macrophages engaging cholesterol crystals with notched crystal matrix (arrows). Inserts demonstrate macrophage gummy attachment to the crystal edges and etching (arrow) of the crystal surface. (**f**) Confocal fluorescence microscopy demonstrates cholesterol aggregates suggestive of crystalline cholesterol (yellow-green particles stained with Cholesteryl Bodipy-C12) within the cytoplasm of aspirated macrophages. The orange-red fluorescence is a specific marker for macrophages. Cholesterol deposits can be detected in the cytoplasm using differential interference contrast (shown in gray) and fluorescence microscopy (red, green, and composite image). The unstained control did not exhibit fluorescence (not shown). (Reprinted from Abela et al. [248]. With permission from Elsevier)

activation of the nucleotide-binding domain, leucine-rich-containing family, and Nod-like receptor pyrin domain containing 3 (NLRP3) inflammasome within the cytosol [87]. An inflammasome is an intracellular sensor that is activated by danger-associated molecular signals (i.e., "DAMPS"), in this case cholesterol crystals [88]. The activated inflammasome functions as a scaffold upon which to recruit and oligomerize the inactive zymogen pro-caspase-1 to form active caspase-1. Caspase-1 converts the precursor cytokines pro-IL-1β and pro-IL-18 to IL-1β and IL-18, respectively, which the macrophage secretes to boost inflammation. Caspase-1 can also induce pyroptosis, another variant of cell death resulting in cell lysis and non-specific release of molecules that trigger inflammation [89].

Macrophages express pattern recognition receptors (PRRs) for pathogen-associated molecular patterns (PAMPs). The PRRs are a critical component of innate immunity and can recognize pathogens, lipopolysaccharides (LPS), heat shock proteins, and many other molecular motifs [90]. Among the most important PRRs are the Toll-like receptors (TLR). TLR4 is particularly important in atherosclerosis as it allows macrophages to identify oxidized LDL [91] and oxidized phospholipids [92]

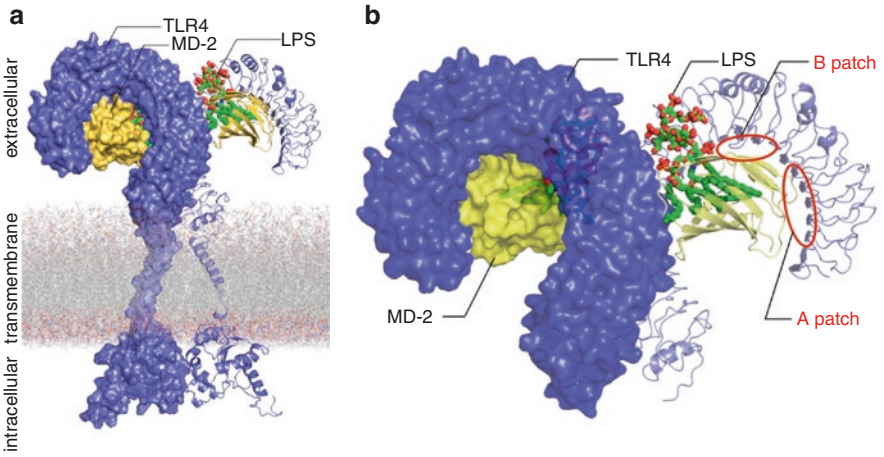

Fig. 7 Representation of the 3D structure of TLR4/MD-2/LPS . (**a**) Large-scale representation showing the intracellular, transmembrane, and extracellular domains of TLR4/MD-2 in complex with *E. coli* LPS. 3D structures correspond to the X-ray crystallographic structure for the extracellular domain (PDB ID 3FXI) and homology modeling for the transmembrane and intracellular domains. (**b**) Close-up look at the TLR4 extracellular domain (purple) along with MD-2 (yellow) and LPS (CPK colors with C atoms in green) from PDB ID 3FXI. (Reprinted from Billod et al. [93]. With permission from Creative Commons License 4.0: https://creativecommons.org/licenses/by/4.0/)

as noxious in its immediate microenvironment and then activate a defense response. TLR4 spans the cell membrane and has an extracellular LPS binding domain (where ligands bind) and a cytosolic domain (Fig. 7) that initiates a protein kinase-dependent signaling cascade [93]. Signal transmission requires myeloid differentiation primary response protein 88 and a complex series of phosphorylation reactions which result in the activation of NF-κB transcription factors and their translocation into the nucleus [90]. Macrophage activation by TLR4 is accompanied by increased production and secretion of IL-1, tumor necrosis factor-α, ROS, and other chemokines that intensify inflammation in the subendothelial space.

3.2 T Lymphocytes

CD4+ T lymphocytes also bind to stressed endothelium associated adhesion molecules and transmigrate into the intima in response to a variety of chemoattractants (e.g., interferon-inducible T-cell α-chemoattractant) which bind to the chemokine receptor CXCR3 on the surface of these cells [11, 94]. As part of the adaptive immune response, T cells patrol the intima for antigens such as oxidized LDL attached to antigen-presenting cells (macrophages and dendritic cells) [95] (Fig. 3). The PRRs on dendritic cells recognize PAMPs (such as oxidized LDL antigens) and phagocytose them, which in turn activates the cell to express major

histocompatibility complex class II (MHC II) on its surface [96]. Both dendritic cells and macrophages can present antigens to T cells via MHC II. This exposure of T-helper-1 cells (Th1) to antigen activates them to produce TNF-α, interferon-γ (IFNγ), and CD40 ligand, among other chemokines [96]. This results in endothelial cell activation and dysfunction, increased adhesion molecule expression with augmented monocyte recruitment, a prothrombotic environment, and reduced smooth muscle cell proliferation and collagen deposition. An increase in activated Th1 cell lines is associated with enhanced lesion progression and plaque instability. Antigen-dependent activation of T cells also promotes the proliferation of antigen-specific clones which augment local inflammatory tone. Th1 clones activate macrophages to boost the inflammatory response by contributing interleukins and chemokines. Th1-derived IFNγ impairs the off-loading of lipid from macrophages by inhibiting the expression of ABCA1, increasing the likelihood of cell death [96, 97]. The role of Th-2 cells will be taken up elsewhere in this chapter. T cell activation can be inhibited by transforming growth factor-β (TGF-β) [98].

In addition to a functional presence in the arterial intima, lymphocytes also infiltrate and form organized structures in the adventitia [99]. These lymphocyte aggregates are defined as adventitial aortic tertiary lymphoid organs (ATLOs) [100] (Fig. 8). They tend to associate with more severe atherosclerotic plaques. An ATLO contains a nodular center comprised of B lymphocytes (plasma cells) and dendritic cells surrounded by a rim of T lymphocytes [101]. The B cells can be triggered to produce antibodies in response to antigen presentation by dendritic cells resulting in an immune response. There is cross-talk between the endothelium and cellular constituents of the adventitia. ATLOs play a role in atherogenesis [102]. A network of small medial conduits and vasa vasorum promote the trafficking of immune cells, interleukins, and cytokines between the adventitia and intima.

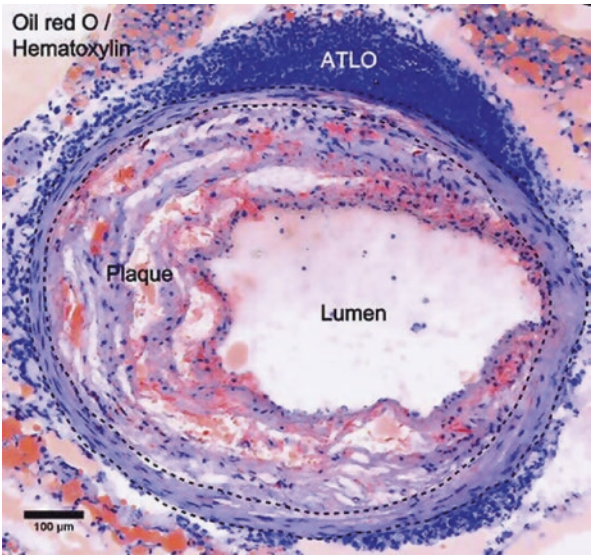

Fig. 8 Adventitial aortic tertiary lymphoid organ in atherosclerotic aorta . Oil red O/hematoxylin staining showing ATLO position in the abdominal aorta adventitia relative to media (dashed lines) and intimal plaque in aged *ApoE*$^{-/-}$ mice. (Reprinted from Luo et al. [101]. With permission from Creative Commons License 4.0: https://creativecommons.org/licenses/by/4.0/)

3.3 Mast Cells

Mast cell counter-receptors bind to adhesion molecules and follow a gradient of eotaxin into the subendothelial space [11]. Activated mast cells secrete a number of pro-atherogenic mediators:

1. Serine proteases that include chymase and tryptase. Tryptase converts the zymogens of MMPs into their enzymatically active forms. Chymase catalyzes the intravascular conversion of angiotensin I to angiotensin II. Both enzymes not only contribute to plaque formation but also influence plaque stability.
2. Histamine, which promotes increased vascular permeability.
3. Leukotrienes, macrophage inflammatory protein-1α, multiple interleukins, TNF-α, and IFNγ, which boost the intensity of inflammation [95].

3.4 Neutrophils

Neutrophils have multiple roles in host defense, including the killing of infectious organisms [103]. Recent investigation also supports roles for neutrophils in atherogenesis. Within the subendothelial space, neutrophils can produce an array of collagenases, elastases, and other MMPs [104]. Neutrophils elaborate myeloperoxidase and ROS in the subendothelial space which are cytotoxic and oxidize trapped lipoproteins [105]. Neutrophils entering the subendothelial space also potentiate injury by releasing (1) four different subsets of granules containing pro-oxidative enzymes and cytokines whose release is precisely timed in response to conditions in the prevailing histologic milieu; (2) leukotrienes such as LTB4, a potent chemoattractant; (3) cathelicidin and azurocidin, which promote monocyte influx; and (4) α-defensins which promote monocyte influx, platelet activation, and foam cell formation [106–108].

A recently discovered mechanism by which neutrophils promote atherogenesis is by forming neutrophil extracellular traps (NETs) [109] (Fig. 9). NETs are released by suicidal neutrophils and are extruded reticular structures composed of decondensed chromatin as well as nuclear, granular, and cytosolic proteins. NETs are also a means by which endothelial cells can be exposed to sudden, catastrophic concentrations of inflammatory mediators. NETosis or the process of NET formation can be induced by ROS, cytokines, cholesterol crystals, and activated platelets [110–113]. In addition to DNA, NETs contain histones (which are antibacterial), proteases, lysosomal cathepsins, α-defensins, and myeloperoxidase, among other proteins and enzymes [109]. NETs are prothrombotic and cytotoxic.

3.5 Platelets

Platelets are released megakaryocytes, have no nucleus, and participate in inflammation and coagulation (Fig. 3). The secretome of platelets includes over 300 molecules [114]. Although platelets have no nucleus, they store messenger RNAs

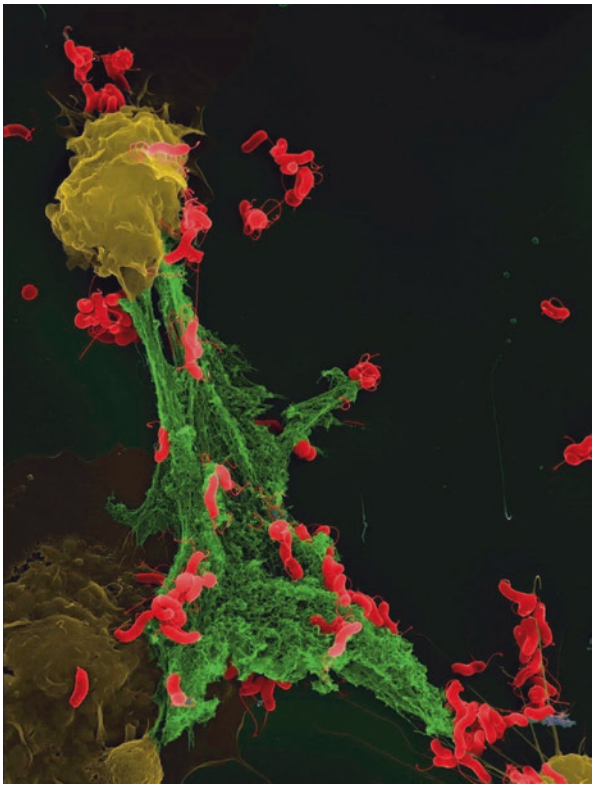

Fig. 9 Neutrophil extracellular trap (NET) formation . Scanning electron microscopy of neutrophil (yellow) disgorging a net (green) entrapping bacteria (red). (Kindly provided by Professor Volker Brinkmann, Max Planck Institute for Infection Biology, Berlin, Germany)

(mRNA) for protein translation on demand. Platelet α-granules are enriched with growth factors (platelet-derived growth factor (PDGF), epidermal growth factor, TGF-β, basic fibroblast growth factor), enzymes, chemokines (platelet factor 4, epithelial neutrophil-activating protein 78), and cytokines (IL-1β, CD40 ligand, β-thromboglobulin) and can be mobilized upon platelet activation [115, 116]. The interactions of platelets with endothelial cells and monocytes are varied and complex. Platelets bind to multiple endothelial cell surface receptors: (1) ICAM-1 via the glycoprotein IIb/IIIa receptor and fibrinogen [117]; (2) leucine-rich GPIb/IX/V (i.e., the von Willebrand receptor complex) to platelet selectin P [118]; (3) endothelial selectin P to platelet glycoprotein 1b [119]; and (4) endothelial selectin P to platelet P-selectin glycoprotein ligand-1 [116]. In an interesting twist, platelets can inhibit endothelial P secretin expression by locally secreting nitric oxide and upregulate endothelial ICAM-1 by secreting IL-1β, thereby regulating their own binding capacity to the endothelial surface [120].

Platelets are highly versatile in how they augment inflammation. Inflammation can induce the coactivation of platelets and neutrophils, precipitating increased production of human neutrophil peptide-1 (HNP-1) and regulated on activation, normal T cell expressed and secreted (RANTES). RANTES (a scaffolding molecule) and HNP-1 facilitate monocyte adhesion to activated endothelial cells and recruitment into the subendothelial space [121]. In addition to signal transmission

by cell surface receptors and granule release, platelets can interact with endothelial cells and leukocytes by direct bilateral mRNA transmission, thereby boosting local molecular biosynthetic capacity and an inflammatory response [122]. Platelet microparticles also boost the inflammatory response. These microparticles secrete microRNAs (miRNA), which are noncoding RNAs that regulate post-transcriptional gene expression. Platelet-derived miRNA-320b decreases surface expression of endothelial ICAM-1, and miRNA-223 stimulates increased phagocytic activity by macrophages resident in the subendothelial space [123–125]. Clearly, the interactions of platelets with endothelial cells and other histologic components of the arterial wall and atherosclerotic plaque are complex and highly orchestrated. Much remains to be learned about these processes and how they might be therapeutically modulated.

4 Adipose Tissue and Adipokines

Dysregulated, insulin-resistant adipocytes are important contributors to systemic inflammation and atherogenesis. Risk for insulin resistance increases as the mass and volume of visceral fat (omentum, perinephric fat, perimesenteric fat) expands. Insulin-resistant adipocytes have impaired transmission of intracellular signaling pathways when insulin binds to its receptor on the cell surface. Under normal conditions, insulin receptor substrate-1 (IRS-1) undergoes tyrosine phosphorylation to conduct insulin signaling intracellularly; however, in the setting of insulin resistance, this is disrupted, and serine residues are phosphorylated in IRS-1, which results in (1) attenuated signaling into the nucleus [126] and (2) decreased expression of glucose transport proteins, leading to hyperglycemia associated with insulin resistance. Insulin resistance is activated by c-Jun N-terminal kinases (JNK), and the insulin-resistant state promotes a large influx of pro-inflammatory white cells (neutrophils, mast cells, monocytes/macrophages, and T cells into adipose tissue) [127]. JNK activation is preceded by ER stress, UPR, and mitochondrial dysfunction (which results in derangements in energy metabolism and an increase in ROS production) within adipocytes [128].

Adipose tissue is an active endocrine organ, and adipocytes can secrete over 50 adipokines with a variety of functions. In the setting of insulin resistance, both dysregulated adipocytes and the inflammatory white cells that infiltrate adipose tissue are sources of pro-inflammatory mediators. Inflammatory white blood cells produce the interleukins, chemokines, and cytokines discussed above. Dysregulated adipocytes exacerbate insulin resistance by producing TNF-α and retinol binding protein 4 (both of which promote the conversion from tyrosine to serine phosphorylation of IRS-1) [129, 130]. Retinol binding protein 4 can also stimulate endothelial cells to express VCAM-1 and secrete IL-6 [131]. In addition to TNF-α, dysregulated adipocytes produce IL-1, IL-6, IL-8, C-reactive protein, TGF-β, PAI-1, MCP-1, angiopoietin-like protein 2 (which stimulates macrophage and endothelial cell production of inflammatory mediators) [132], chemerin (a macrophage and dendritic

cell chemoattractant), and leptin (which stimulates macrophages to produce IL-6 and IL-12 as well as TNF-α and T helper cells to produce inflammatory cytokines) [133]. These inflammatory mediators can act both locally and systemically.

Patients with insulin resistance experience substantial expansion of ectopic fat deposition in the liver, pancreas, skeletal muscle, and epicardium. This ectopic fat is also insulin resistant and pro-inflammatory [134]. Ectopic epicardial fat depots that are insulin resistant induce significant pathophysiological changes. The normal function of epicardial fat pads includes the following: (1) the triglyceride stored in this adipocyte population is a readily available reservoir of oxidizable fatty acid, which myocardium uses preferentially over glucose; (2) it protects the coronary arteries from torsional injury potentially incurred during cardiac contraction and propagation of the arterial pulse wave; (3) it is a buffer against excess circulating levels of free fatty acids by sequestering them and esterifying them to form triglycerides, thereby reducing toxic exposure; (4) it allows for positive Glagovian remodeling (ectatic expansion) of atherosclerotic plaques because adipose tissue is more compliant than myocardium; (5) it contains and protects the intracardiac nervous system (ganglia and ganglionated plexi) [135–137]. Epicardial fat pad volume (EFPV) correlates highly with the number of coronary atherosclerotic plaques, the risk of having noncalcified, calcified, and a mixture of the two types of plaque, as well as total coronary artery calcium scores [138, 139]. An EFPV that exceeds 300 cc^3 carries an odds ratio for coronary artery disease (CAD) of 4.1 ($p < 0.05$) [138]. These findings are likely a consequence of the fact that in patients with insulin resistance and CAD, the epicardial fat is showering the adventitial aspect of coronary arteries with bioactive lipids and inflammatory mediators which promotes the progressive biochemical and histologic changes that potentiate accelerated atherogenesis. Dysregulated epicardial fat is a prolific source of TNF-α, leptin, MCP-1, IL-6, resistin (an adipokine that promotes insulin resistance), and fibroblast growth factor 21 (which promotes tissue adaptation to increased fatty acid oxidation) [140], among other chemokines and cytokines [141–143]. Expanded EFPV also correlates with reduced coronary flow reserve [144], flow-mediated dilatation of the brachial artery [145], and myocardial phosphorylation potential (a measure of capacity to regenerate adenosine 5′-triphosphate by mitochondrial oxidative phosphorylation to meet intramyocellular energy demands) [146]. Finally, increased EFPV volume predisposes to increased risk for cardiac arrhythmias (particularly atrial fibrillation), ectopic foci, triggered activity, and structural and electrical remodeling [147, 148].

5 MicroRNAs and Inflammation

As previously stated, miRNAs are circulating noncoding RNAs that regulate post-transcriptional gene expression. MicroRNAs are highly conserved and bind to the 3′ untranslated region of messenger RNA (mRNA) transcripts, resulting in “RNA silencing” secondary to steric hindrance of ribosomal translation [149]. MiRNAs are produced and secreted by a large variety of cells. MicroRNAs secreted into

the circulation are resistant to hydrolysis/digestion by plasma RNases and affect the expression of gene products in target cell types. MicroRNAs are transported in plasma on microparticles and HDL particles or bound to the protein Argonaute2 [150]. Specific patterns of circulating miRNAs are identifiable in the settings of myocardial infarction, heart failure, and diabetes mellitus [150–153]. Distinct molecular miRNA signatures also develop in patients with CAD [154]. The miRNAs not unexpectedly have a very complex relationship with vascular inflammation. Numerous miRNAs can either promote or inhibit endothelial cell activation, as well as monocyte and T cell differentiation and activation, macrophage cholesterol efflux, vascular remodeling, smooth muscle cell proliferation and migration, and expansion of the vasa vasorum, among other functions [155] (Fig. 10). Many more roles of miRNAs in regulating vascular inflammation will certainly be identified. Much is also yet to be learned about the activity of these miRNAs that can be modulated for therapeutic use.

6 Inflammation and Increased Oxidative Tone

Xanthine oxidase, NADPH oxidase, cyclooxygenase, myeloperoxidase, lipoprotein-associated phospholipase A2, and 5-lipoxygenase are all found in atherosclerotic plaque and promote inflammation via ROS production and oxidative lipoprotein modification [156–158]. These processes trigger endothelial, T cell, and macrophage activation. The ROS include superoxide anion [159], hydroxyl radicals, peroxynitrite radicals, and hydrogen peroxide [160] (Fig. 11). The enzymes paraoxonase, glutathione peroxidase, thioredoxins, and superoxide dismutase convert ROS to less reactive species. Deficiencies in anti-oxidative enzymes can be associated with increased inflammation and atherogenesis [161]. The major cardiovascular risk factors (dyslipidemia, cigarette smoking, hypertension, diabetes mellitus) augment oxidative tone by upregulating the production of ROS [159]. The ROS are directly cytotoxic and are responsible for oxidizing and peroxidizing lipid and phospholipid within LDL particles [162]. Lipid peroxidation products (e.g., γ-ketoaldehydes, phosphocholine of oxidized phospholipid, malondialdehyde, 4-hydroxynonenal, and 2-(ω-carboxyethyl)pyrrole) are highly reactive [163, 164]. To illustrate, native proteins can be rendered immunogenic when they form adducts with γ-ketoaldehydes, resulting in the activation of T cells and dendritic cells [165].

7 Microbiome and Inflammation

Humans harbor a highly diverse virome and bacterial microbiome within their oropharynx and gastrointestinal tracts. It is estimated that the number of bacteria comprising the microbiome is approximately equal to the number of cells composing a human body. The oral and gut microbiomes are estimated

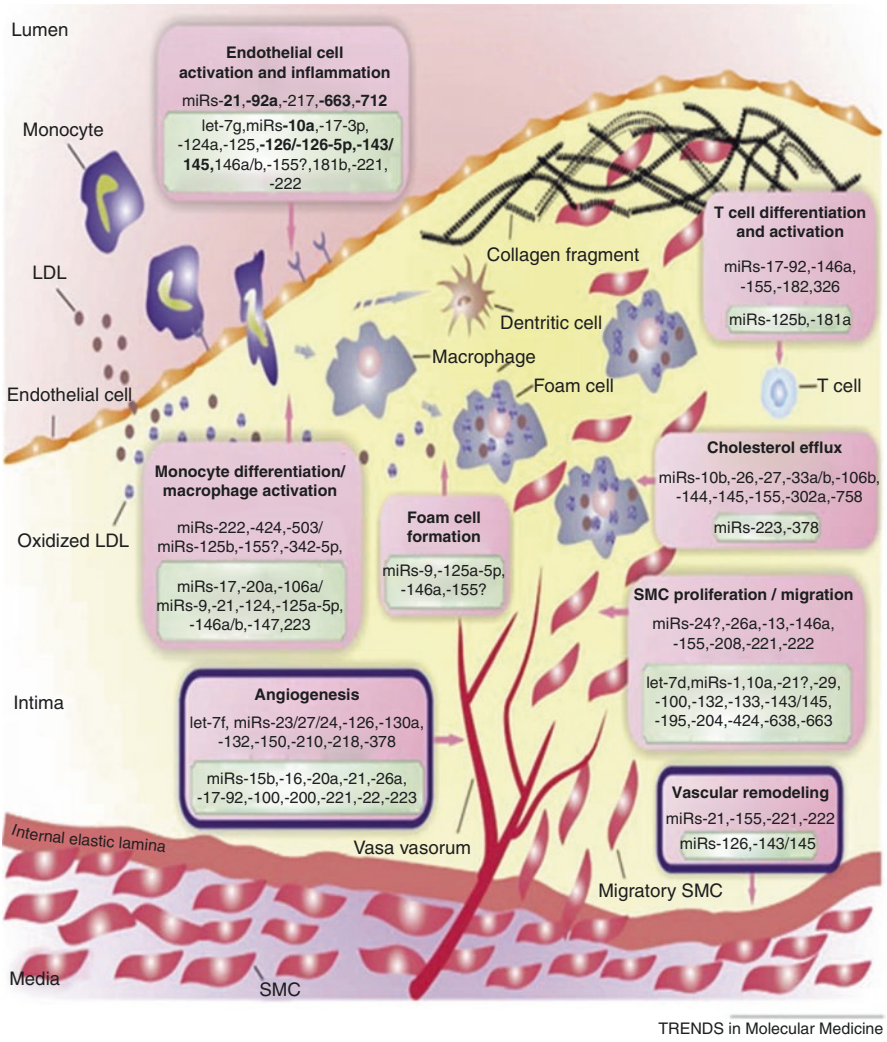

Fig. 10 MicroRNAs implicated in atherosclerosis **.** Positive/atheroprotective (in green frame) or negative/atherogenic (in red frame) effects of miRNAs on atherogenesis. Question marks indicate controversial or contradictory evidence for specific miRNAs. miRNAs in bold are regulated by blood flow/shear stress. Abbreviations: LDL low-density lipoprotein, SMC smooth muscle cell. (Reprinted from Andreou et al. [155]. With permission from Elsevier)

to consist of >700 and >1000 bacterial species, respectively, and the weight of the microbiome is approximately 1.5–2.0 kg [166]. The bacteria in both environments have been shown to potentiate inflammation and atherosclerotic cardiovascular disease (ASCVD) [167, 168]. Reductions in the colony sizes of *Bacteroides*, *Prevotella*, *Faecalibacterium*, and *Roseburia intestinalis* are associated with increased risk for ASCVD, while increased colonization

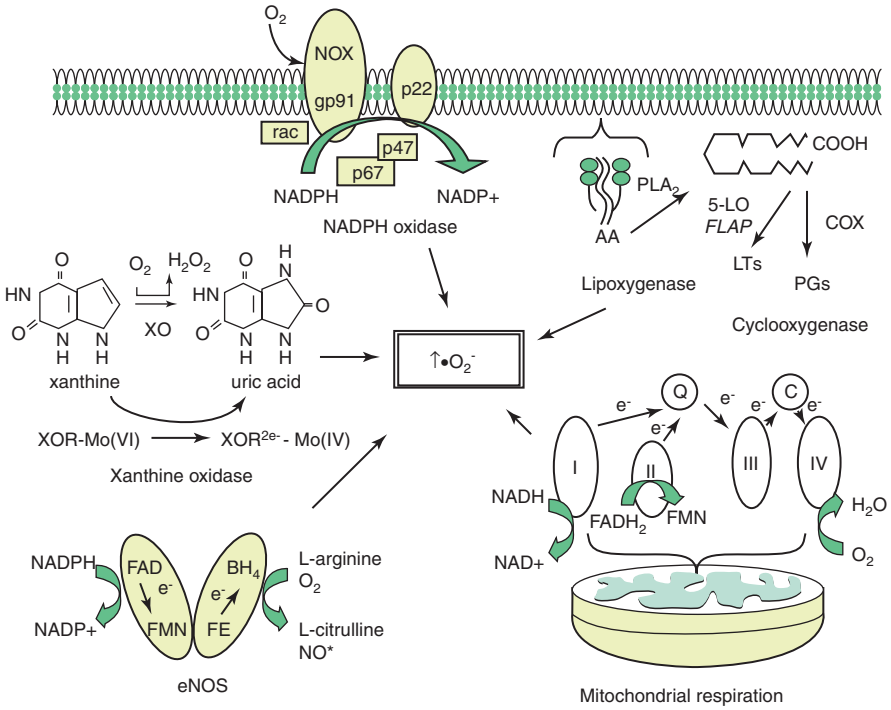

Fig. 11 Metabolic and enzymatic sources of superoxide anion in the vasculature . Superoxide anion (•O2⁻) is formed by several metabolic and enzymatic sources within the cell. NADPH oxidase is comprised of multiple membrane-bound and cytoplasmic subunits. The enzyme is activated when the cytoplasmic subunits p67 and p47 and the small G-protein Rac assemble with the membrane-bound NOX (vascular homolog of gp91phox) and p22phox. NADPH oxidase uses NADPH as a substrate and, in vascular cells, is considered an important source of reactive oxygen species (ROS) generation. The lipoxygenases and cyclooxygenases (COX) generate ROS indirectly by promoting formation of inflammatory mediators. Arachidonic acid (AA) that is cleaved from the cell membrane by phospholipase A2 (PLA2) is then metabolized by 5-lipoxygenase (5-LO) in the presence of its accessory protein (FLAP) to form leukotrienes (LTs). AA is also metabolized by the cyclooxygenases to form members of another family of inflammatory mediators, the prostaglandins (PGs). Mitochondria also generate superoxide as electrons are transferred from complex I to cytochrome oxidase during normal cellular respiration. Xanthine oxidase (XO), which converts hypoxanthine and xanthine to uric acid, is an additional source of ROS. As xanthine is converted to uric acid, two electrons are donated to molybdenum (Mo) at the active site of the enzyme, thereby reducing it from Mo(VI) to Mo(IV). Finally, endothelial nitric oxide synthase (eNOS), when substrate or cofactors are not replete, uncouples to generate superoxide in preference to NO. Abbreviations: Q coenzyme Q, C cytochrome C, NAD nicotinamide adenine dinucleotide, FAD flavin adenine dinucleotide, FMN flavin mononucleotide, FE heme iron, BH4 tetrahydrobiopterin. (Reprinted from Leopold and Loscalzo [158]. With permission from Wolters Kluwer Health, Inc.)

by Enterobacteriaceae, Lactobacillales, and Streptococci is associated with decreased risk for ASCVD [166, 169]. Among patients with gingival disease complicated by gingival bleeding, the denuded blood vessels offer oral bacteria open access to the central circulation where they stimulate elevations in C-reactive protein (CRP) and IL-6, which can lead to endothelial and white cell activation [170].

The gut microbiome induces systemic inflammation by other mechanisms as well. Gut bacteria convert the dietary quaternary amines choline and carnitine into trimethylamine (TMA) by the TMA lyases CutC/D and CntA/B, respectively [171]. TMA is a gas and diffuses down its concentration gradient across the intestinal epithelium and enters the circulation. TMA is taken up by hepatocytes and converted to trimethylamine N-oxide (TMAO) by flavin monooxygenase 3 [172]. Plasma TMAO levels correlate with foam cell formation, coronary atherosclerotic disease burden, reduced reverse cholesterol transport, myocardial infarction, peripheral arterial disease, and platelet reactivity and risk for thrombosis [173–177]. Histidine is an aromatic amino acid. Imidazole propionate is derived from histidine metabolism in the gut and has been shown to induce insulin resistance and low-grade inflammation [178]. A dysfunctional gut is associated with increased epithelial cell permeability which can allow for chronic LPS exposure from gram-negative bacteria [179, 180]. LPS binds to TLR4 and promotes intravascular macrophage activation and an inflammatory response.

The gut microbiome can also be a source of mediators that attenuate systemic inflammation. The short-chain fatty acids (SCFAs) include acetic, propionic, and butyric acids, which are composed of two, three, and four carbon atoms, respectively. The SCFAs are the products of bacterial fermentation of starches (glucose polymers) and dietary fibers that cannot be catabolized by the hydrolytic enzymes produced in the gut [181]. SCFA production occurs in the cecum and colon where they are (1) consumed as oxidizable fuel and (2) stimulate mucin production by epithelial cells. The SCFAs can also be absorbed across the colonic epithelium and subsequently taken up by the liver. The SCFAs can bind to a number of G-protein-coupled receptors on the surface of cells and activate intracellular signaling cascades. The SCFAs have been shown to attenuate the activation of T cells, monocytes/macrophages, and neutrophils with concomitant reductions in inflammatory mediator expression [182–184]. The secondary bile acid taurolithocholic acid attenuates endothelial cell ICAM-1 expression, TNF-α driven binding to endothelial cells, LPS-induced monocyte adhesion, and NF-κB activation [185]. The exploration of the impact of secondary bile acids on inflammation is in an early stage. The therapeutic implications of such findings require additional investigation.

8 Cardiovascular Biomarkers of Inflammation

8.1 High Sensitivity C-Reactive Protein

C-reactive protein (CRP) is an acute phase reactant produced by hepatocytes in response to activation by IL-1, IL-6, or TNF-α [186]. CRP was first identified in 1930, and its "C" designation arises from the observation that it binds to the capsular polysaccharide of *Pneumococcus* bacteria [187]. CRP is a pentraxin (a pentamer of CRP monomers) that participates in the opsonization and phagocytosis of infectious agents through the classical complement pathway [188]. Serum levels of CRP are elevated under the conditions of both acute and chronic systemic inflammation [189].

A high sensitivity assay for CRP (hsCRP) was developed in order to more accurately measure serum CRP in the 0–10 mg/L range [190]. hsCRP levels were initially shown to be an independent predictor of risk for acute cardiovascular events (nonfatal MI, nonfatal stroke, CV mortality) in men and women with no prior history of CVD [191, 192]. Subsequently, a large number of other prospective longitudinal cohorts confirmed that hsCRP is an independent predictor of acute CV events in the primary prevention setting [193–196] and also correlates with risk for developing diabetes [197]. hsCRP increases as the number of components of the metabolic syndrome increases [198]. hsCRP is a marker of the intensity of systemic inflammatory tone. Although for a time it was thought that CRP mediates a number of pro-inflammatory, proatherogenic effects, this is no longer held to be the case [199]. hsCRP is a validated biomarker but is not causal in the pathway for atherogenesis [200, 201]. Between 0 and 10 mg/L hsCRP, there is a continuous linear rise in risk for CVD [202]. hsCRP levels of <1.0 mg/L, 1.0–3.0 mg/L, and >3.0 mg/L are consistent with low, moderate, and high risk for CVD [203].

When evaluating CV event-free survival, elevations in hsCRP incur a level of risk commensurate with that of LDL-C [204] (Fig. 12) In the Women's Health Study, women with high LDL-C and high hsCRP had the highest risk for acute CVD events over 8 years of follow-up. [204] (Fig. 12). In contrast, women with the lowest LDL-C and hsCRP had the lowest risk for CVD events. Women with either high LDL-C and low hsCRP or low LDL-C and high hsCRP experienced a level of CVD risk between the two extremes. In a series of post hoc analyses of major secondary prevention statin trials, this concept of "dual targets" (both LDL-C and hsCRP) was affirmed. In the Aggrastat to Zocor trial (A–Z) [205], Pravastatin or Atorvastatin Evaluation and Infection Therapy trial (PROVE-IT) [206], and IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) [207], the patients with the lowest on-trial rates of CVD events were those with the lowest LDL-C and hsCRP; those with the highest rates had the highest levels of these two analytes (Fig. 13). Similarly, in two primary prevention statin trials (the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) [208] and Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER)) [209], this pattern was

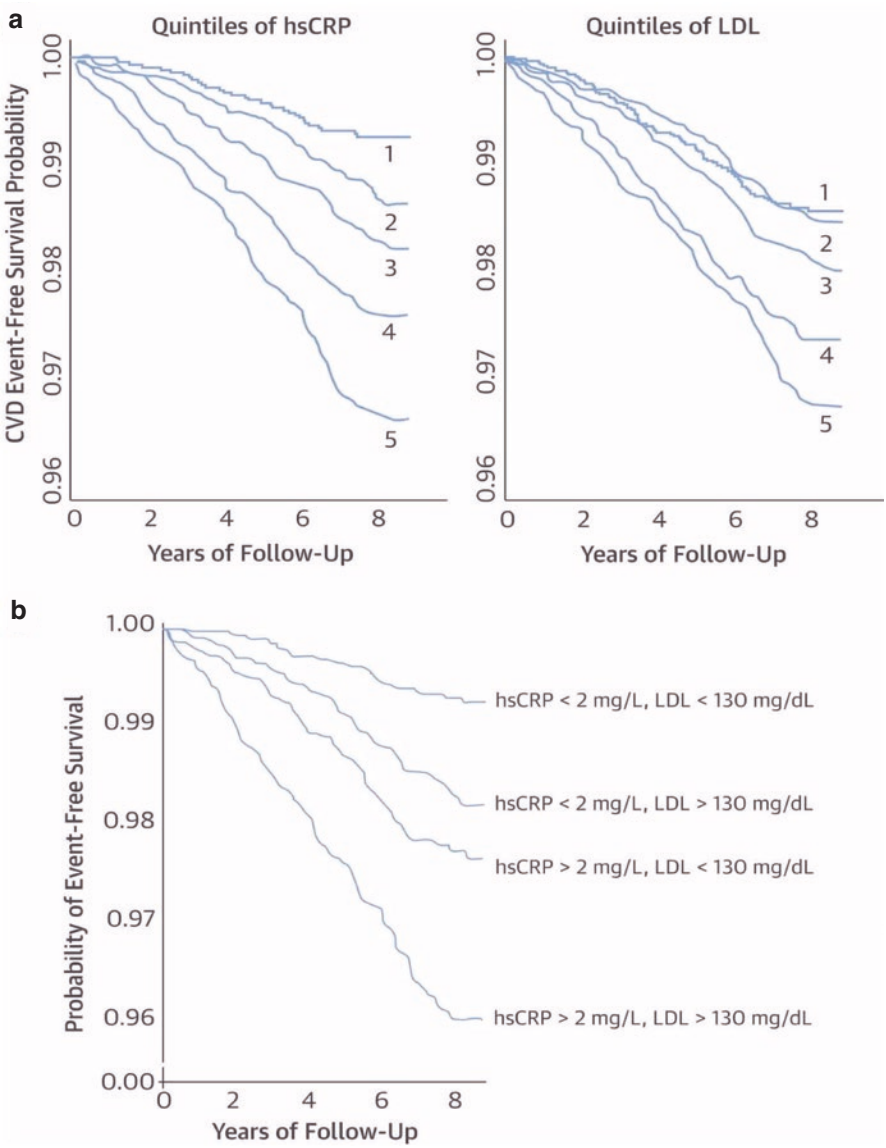

Fig. 12 Magnitude of risk associated with hsCRP is comparable with and independent of LDL-C. (**a**) Increasing quintiles of both hsCRP and LDL-C predict vascular risk. (**b**) The highest-risk patients in a primary prevention setting are those with both increased hsCRP and increased LDL-C. CVD cardiovascular disease, hsCRP high-sensitivity C-reactive protein, LDL low-density lipoprotein, LDL-C low-density lipoprotein cholesterol. (Reprinted from Ridker [202]. With permission from Elsevier)

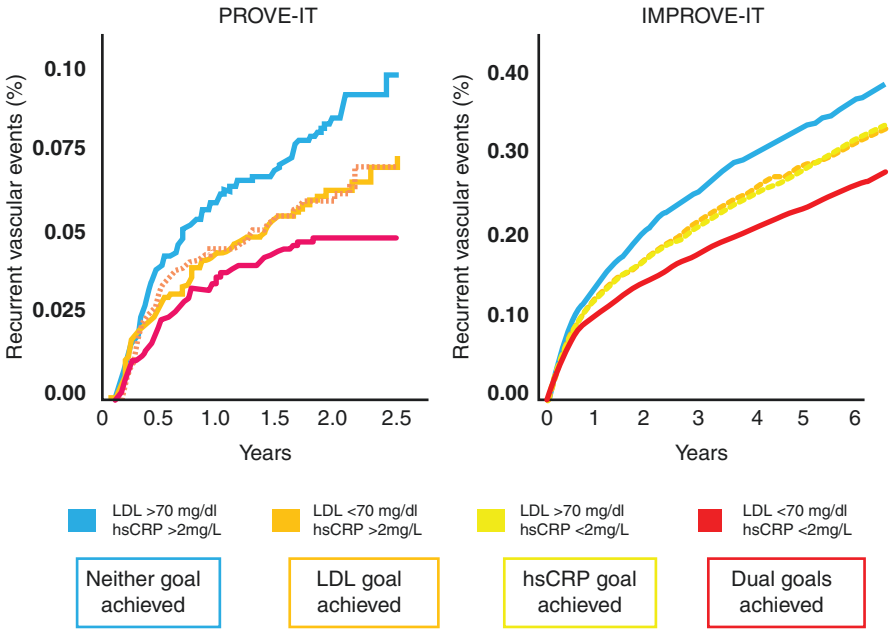

Fig. 13 Recurrent cardiovascular event rates according to whether or not trial participants achieved the "dual goals" of LDL reduction (<70 mg/dL) and hsCRP reduction (<2 mg/L) following initiation of statin therapy (PROVE-IT, left) or the combination of statin therapy and ezetimibe (IMPROVE-IT, right). (Reprinted from Ridker [249]. With permission from Oxford University Press)

once again observed. In AFCAPS/TexCAPS, lovastatin reduced coronary events in participants whose baseline ratio of total cholesterol to HDL-C (TC/HDL-C) exceeded the median irrespective of hsCRP level at baseline [208]. Lovastatin was effective for CV risk reduction in participants with a TC/HDL-C ratio that was lower than the median and a hsCRP level higher than the median. This finding inspired the design of the JUPITER trial. The JUPITER trial demonstrated that hsCRP (>2.0 mg/L) helped to identify a group of patients with "average" LDL-C (<130 mg/dL) who derived considerable benefit for CVD event reduction from statin therapy. An individual level meta-analysis of 160,309 people without a history of CVD by the Emerging Risk Factors Collaboration demonstrated that serum CRP concentrations have a continuous relationship with risk for CAD, ischemic stroke, and cardiovascular mortality [210]. After comprehensive adjustment for risk factor covariates, the hazard ratio per standard deviation increase for CAD was 1.37 (1.27–1.48), 1.27 (1.15–1.40) for ischemic stroke, and 1.55 (1.37–1.76) for CV mortality, and 1.54 (1.40–1.68) for non-CV mortality. In a recent analysis of the Atherosclerosis Risk in Communities Study, among 9748 persons without established ASCVD, hsCRP is associated with incident ASCVD over a median follow-up of 18.4 years independent of atherogenic lipid levels and pooled cohort equation risk equation scores [211]. According to AHA/ACC Multisociety Guideline on the

Management of Blood Cholesterol, an hsCRP >2.0 is a risk enhancing factor and can be used to reclassify risk for developing ASCVD [212].

8.2 Lipoprotein-Associated Phospholipase A_2

Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) is an enzyme carried by lipoproteins such as LDL and HDL particles that hydrolyzes phospholipids to yield a plethora of bioactive, pro-inflammatory lipids. Lp-PLA_2 specifically acts at the sn-2 position of phospholipids to liberate an oxidized fatty acid and a lysophospholipid, both of which are pro-inflammatory. Lipoproteins can serve as a delivery platform of Lp-PLA_2 into the subendothelial space, but Lp-PLA_2 is also secreted by activated macrophages and foam cells and its expression is increased in unstable and rupture-prone atherosclerotic plaques [213, 214]. Oxidized free fatty acids and lysophospholipids boost the inflammatory response by stimulating endothelial cell adhesion molecule expression and local elevations in TNF-α, IL-6, IL-1β, MCP-1, and RANTES [213, 215].

Lp-PLA_2 is a risk marker for CVD independent of other established risk factors. It is considered to be an inflammatory marker specific to atherosclerotic disease. Its validity as an independent risk factor for atherosclerotic disease was established by a number of prospective longitudinal cohorts [216]. In a meta-analysis that included 32 prospective studies and 79,036 participants, Lp-PLA_2 enzyme activity and mass both correlated with risk for coronary heart disease (CHD) and CVD events (Fig. 13). Remarkably, the relative risk elevations incurred by Lp-PLA_2 for these end points were continuous and significant after adjustment for other risk factors and identical to those for non-HDL-C and systolic blood pressure. Use of a combination of hsCRP and Lp-PLA_2 measurements provides greater risk predictivity than when either of these analytes is analyzed alone [217, 218].

Given that Lp-PLA_2 is directly pro-inflammatory by virtue of its capacity to produce two important inflammatory mediators, does its inhibition reduce risk for CVD and its associated events? A variety of studies were performed with darapladib, a substituted pyrimidone that inhibits Lp-PLA_2 [219]. In the Integrated Biomarker and Imaging Study 2, darapladib halted expansion of the necrotic core in human atherosclerotic plaques; in control patients, these continued to expand [220]. Based on this promising finding, other large-scale prospective outcomes trials were performed. Unfortunately, studies in patients with either stable CHD (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) or recent non-ST-segment elevating or ST-segment elevating MI (Stabilization of Plaques using Darapladib – Thrombolysis in Myocardial Infarction 52) both failed to demonstrate any benefit on acute CV events compared to placebo [221, 222]. Thus, although Lp-PLA_2 is a validated marker for CVD risk and causal for atherogenesis, it is not a treatment target. This example highlights the challenge of trying to therapeutically address vascular inflammation, a constellation of pathways with considerable built-in redundancy and feedback between the cells regulating the fire within.

8.3 Myeloperoxidase

Myeloperoxidase (MPO) is a heme peroxidase produced and secreted by monocytes, macrophages, and neutrophils [223]. MPO catalyzes peroxidation, nitration, chlorination, and carbamoylation reactions. MPO modifies LDL particles by converting the tyrosine residues in apoB into 3-chlorotyrosine. These tyrosine residues can also undergo nitration, forming 3-nitrotyrosine. The lysine residues in apoB can be carbamylated (conjugation of a primary amine with isocyanate). MPO can also oxidize and peroxidize the lipid in LDL. All of these alterations render the LDL more prone for scavenging by activated macrophages [224]. MPO modifies HDL particles and leaves them dysfunctional and no longer capable of engaging in reverse cholesterol transport or antagonizing atherogenesis via their anti-inflammatory and antiproliferative effects [225]. The tyrosine residues in apo AI can be nitrosylated or chlorinated, thereby inducing conformational changes in this protein, which inactivates the HDL [226]. Dysfunctional HDL can become pro-inflammatory and promote endothelial cell adhesion molecule expression [227]. MPO also promotes atherogenesis by promoting the following effects: (1) it quenches nitric oxide, leading to vasoconstriction and formation of cytotoxic peroxynitrite ions; (2) endothelial dysfunction and increased apoptosis; (3) activating MMPs and weakening the intercellular matrix and fibrous cap of atherosclerotic plaque, making it less stable and more vulnerable to rupture; (4) increased tissue factor production and risk of thrombosis; (5) releasing hypochlorous acid (bleach; HOCl) which is cytotoxic and inhibits smooth muscle cell migration from the media; and (6) foam cell formation [156, 224] (Fig. 14). MPO is a required cofactor for neutrophil extracellular trap formation [228].

Serum myeloperoxidase levels correlate with risk for CVD and its sequelae. Persons with MPO deficiency states have reduced risk for CVD and CV events [229]. Increased serum levels of MPO correlate with heightened risk for CV independent of other established risk factors [224]. Patients in the highest quartile for MPO compared to the lowest had a 15- to 20-fold higher risk of having a coronary luminal obstruction >50% on angiography, and the association remained significant even after adjusting for hsCRP and Framingham risk scores [230]. Among 1090 patients who sustained an acute coronary syndrome (ACS), those in the highest tertile for MPO compared to the lowest tertile experienced a 2.25-fold higher risk of re-infarcting or dying over 6 months of follow-up from the index event [231]. In addition, among patients sustaining an MI, elevated MPO remains predictive of mortality over a 5-year follow-up period [232]. There are currently no therapeutic means by which to modulate MPO activity in a way that safely modulates risk for ASCVD. MPO is crucial in immune defense as it is bactericidal.

9 Therapeutic Modulation of Systemic Inflammation

As might be anticipated, therapeutic efforts to attenuate inflammation and reduce risk for ASCVD events are challenging. Inflammation is a vital component of host defense. Finding a balance in reducing vascular inflammation without

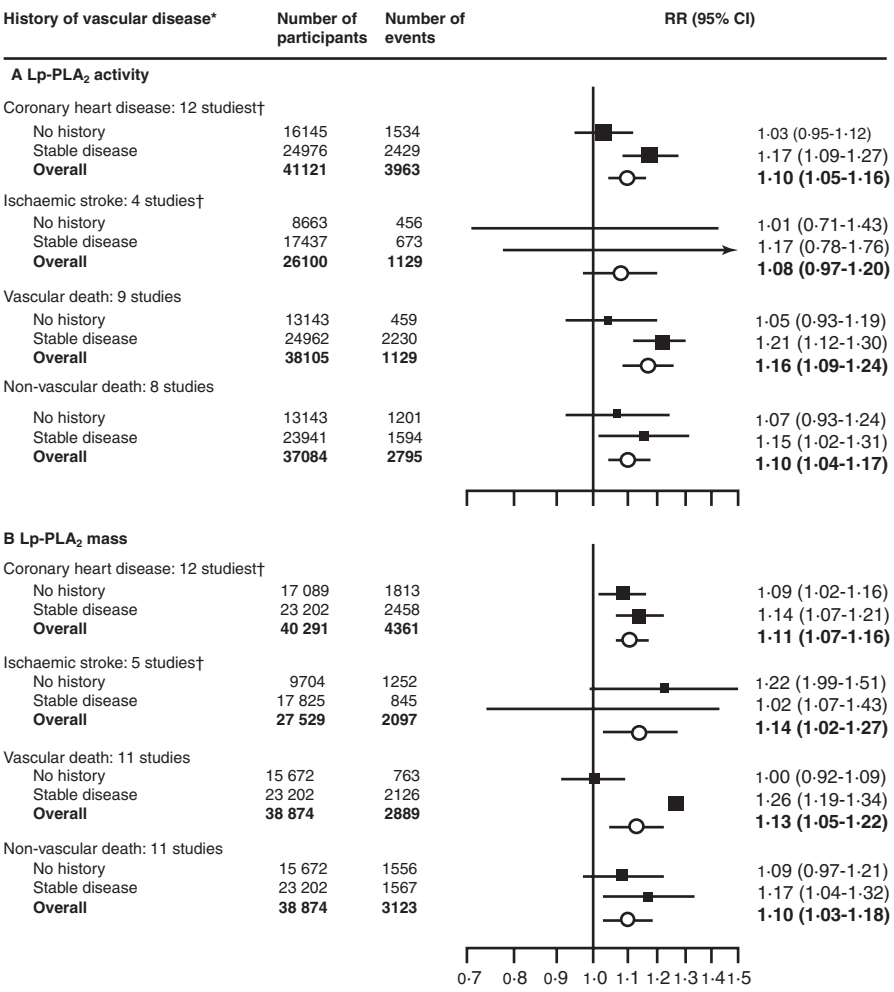

Fig. 14 Risk ratios for CHD, ischemic stroke, and vascular and non-vascular mortality per one standard deviation higher LP-PLA$_2$ activity or mass at baseline, adjusted for other risk factors. (Reprinted from The Lp-PLA2 Studies Collaboration [250]. With permission from Elsevier)

compromising the capacity to fight infection is no simple physiological matter. In the Cardiovascular Inflammation Reduction Trial (CIRT), methotrexate was compared to placebo in 4786 patients with established ASCVD [233]. Methotrexate was a reasonable agent to test since it exerts anti-inflammatory effects in patients with rheumatologic disease. Methotrexate had no impact on serum IL-1, IL-6, or CRP and also provided no benefit for reducing the primary composite end point of CV events, or individual components such as nonfatal MI, nonfatal stroke, need for revascularization, or death. One of the reasons for this may be the fact that

the median hsCRP in CIRT was only 1.6 mg/L, a level that perhaps would not be expected to correlate with significant baseline inflammation.

The Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) randomized 10,060 patients with a prior history of MI and an hsCRP ≥2.0 mg/L to either canakinumab (a monoclonal antibody directed against IL-1β; three doses were used: 50, 150, and 300 mg) or placebo [234]. The 150 mg dose reduced the primary (first occurrence of nonfatal MI, any nonfatal stroke, or cardiovascular death in a time-to-event analysis) and secondary (included the components of the primary end point as well as hospitalization for unstable angina that led to urgent revascularization) end points in a statistically significant manner by 15% and 17%, respectively. Benefit was independent of changes in lipids. hsCRP decreased with canakinumab therapy. For the trial as a whole, there was no mortality benefit with canakinumab therapy, and the rate of neutropenia, infection, and death from sepsis was higher. Mortality from cancer, especially lung cancer, was significantly lower. In an important subgroup analysis of the CANTOS trial, it was shown that for patients whose hsCRP was <2.0 mg/L on treatment with canakinumab, cardiovascular mortality and all-cause mortality were both reduced by 31% compared to the group whose hsCRP still exceeded 2.0 [235].

Colchicine exerts potent anti-inflammatory effects and is commonly used to treat pericarditis and gout. The Colchicine Cardiovascular Outcomes Trial (COLCOT) randomized 4745 patients who had sustained an MI within 30 days to treatment with either low-dose colchicine or placebo [236]. Patients were followed for a median of 22.6 months. The primary (CV mortality, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina leading to coronary revascularization) and secondary (CV mortality, all-cause mortality, MI, stroke, and resuscitated cardiac arrest) end points were significantly reduced by 23% and 15%. CV death, resuscitated cardiac arrest, MI, stroke, and urgent hospitalization for angina leading to revascularization were significantly reduced by 16%, 17%, 9%, 74%, and 50%, respectively. Patients treated with colchicine had a twofold higher risk for pneumonia. Colchicine clearly has promise as a therapeutic agent in the post-MI setting; however, it does not yet have such an FDA-approved indication.

The CANTOS and COLCOT trials provide proof of concept that attenuating inflammation yields reductions in risk for acute cardiovascular events. But there is a trade-off: reducing capacity to mount an inflammatory response results in greater risk of infection. There is urgent need to further balance the risks and benefits associated with the modulation of systemic inflammation, and there are as yet no guideline specified recommendations to inform the use of colchicine in patients who sustain an MI.

10 Intrinsic Resolution of Inflammation

Atherogenesis in the average person once initiated progresses indefinitely because the inflammatory response is perpetuated. Molecular signaling pathways that could resolve the inflammatory response are shut down. Subsequent to acute tissue injury and healing, intrinsic safety mechanisms to resolve inflammation are activated. Much

of this is mediated by specialized pro-resolving mediators (SPMs) of inflammation. The resolution of inflammation is highly conserved and controlled; inflammation resolution is not simply a manifestation of inflammatory inputs shutting down but actively controlled by a diverse array of molecular and cellular machineries.

Leukotrienes and prostaglandins are well characterized products of arachidonic acid (AA) metabolism, and they collectively potentiate inflammation [237, 238]. SPMs (also called immunoresolvents) are formed from American diabetes association (ADA) as well as such omega-3 fatty acids as eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA). These polyunsaturated fatty acids are precursors to the maresins, protectins, resolvins, and lipoxins, all of which participate in inflammation resolution (Fig. 15). The lipoxins are derived from AA and synthesized by three principal enzymes: 5-lipoxygenase, 12′-lipoxygenase, and 15-lipoxygenase. The lipoxins (A4 and B4) are synthesized by both platelets and neutrophils, and these molecules regulate the activity of NF-κB, macrophages, T cells, and neutrophils [239, 240]. The macrophage-derived mediators in resolving inflammation (maresins) are 12′-lipoxygenase-derived metabolites of DHA [241]. The resolvin E and D series of metabolites are derived from EPA and DHA, respectively, via the action of 15-lipoxygenase [242]. The protectins are also produced from DHA [243]. The SPMs bind to highly specific surface receptors on target cells.

Efferocytosis is the receptor-mediated process by which apoptotic cells and apoptotic bodies are removed by phagocytic cells (e.g., macrophages) in a manner that does not activate inflammation [244]. It is a highly efficient process and one that, under normal conditions, involves billions of cells on a daily basis in the human body. Atherosclerotic plaques characterized by expanding necrotic cores have impaired efferocytosis, thereby allowing for cellular debris to continue to accumulate [245]. This is highly pro-inflammatory and contributes to plaque vulnerability and instability. A general theme with the SPMs is that they promote orderly efferocytosis, reduce neutrophil density in plaque, attenuate pro-inflammatory interleukin and cytokine production, and decrease the binding of inflammatory white blood cells to endothelial cells [244]. The SPMs promote macrophage efferocytosis and, in an amplification mechanism, stimulate these cells to produce and secrete still more SPMs [246]. Hence, the macrophage can be converted from a pro-inflammatory cell to a cell that resolves inflammation, demonstrating the enormous versatility of this cell type [247]. The SPMs also promote the production of such inflammation resolving cytokines as annexin-1 as well as IL-10 and IL-13. As shown in Fig. 16, capacity for efficient efferocytosis and SPM production are critical to controlling plaque progression. Plaque progression depends on (1) increased levels of pro-inflammatory mediators and reduced levels of inflammation resolving mediators; (2) the pro-inflammatory environment is pro-oxidative, resulting in more trapped, oxidatively modified lipoprotein particles which promote foam cell formation, which further boosts the inflammatory response; (3) with foam cell lipid loading, there is activation of the inflammasome, release of DAMPs, and necroptosis which all further potentiate inflammation and necrotic core expansion. Plaque stabilization and regression can only occur if (1) the balance between pro- and anti-inflammatory mediators favors the latter; (2) foam cells can off-load excess

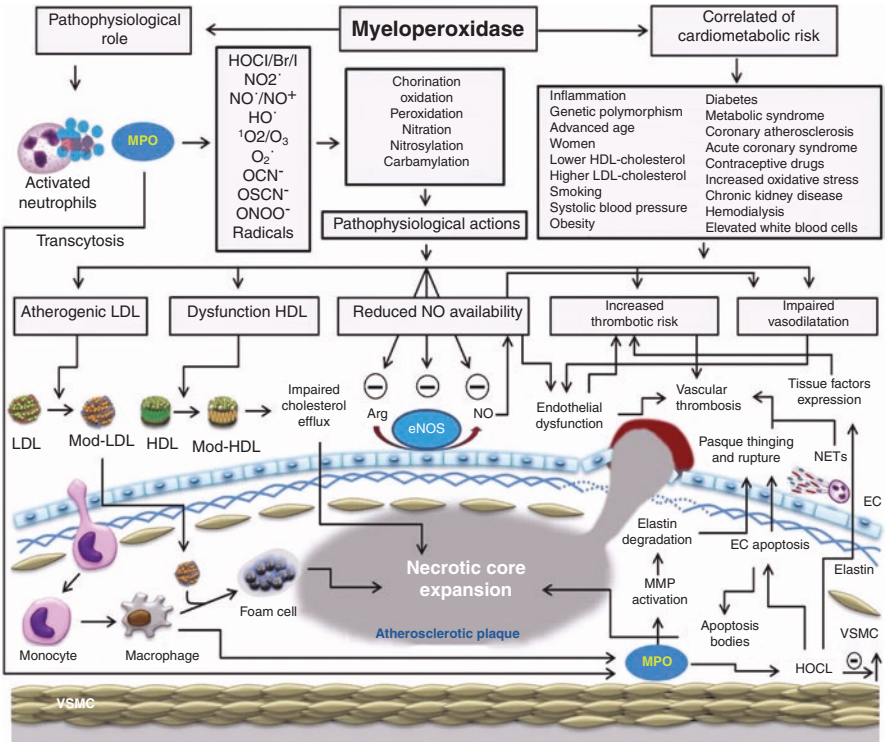

Fig. 15 Putative mechanisms of myeloperoxidase (MPO) participation in cardiovascular disease. Abbreviations: Arg arginine, EC endothelial cells, eNOS endothelial nitric oxide synthase, HDL high-density lipoprotein, HOCl hypochlorous acid, LDL low-density lipoprotein, Mod modified, NO nitric oxide, MMP matrix metalloproteinases, NETs neutrophil extracellular traps, VSMC vascular smooth muscle cells. Negative signs indicate inhibition. (Reprinted from Ndrepepa [224]. With permission from Elsevier)

cholesterol; (3) macrophages and neutrophils can undergo orderly apoptosis which does not induce inflammation; and (4) macrophages can engage in efficient phagocytosis and efferocytosis of apoptotic cells and other debris [245].

11 Conclusions

Atherogenesis is not a process that involves a progressive, passive uptake of lipid into the subendothelial space eventually resulting in the development of obstructive plaque and tissue ischemia. Atherosclerotic cardiovascular disease is a manifestation of chronic inflammation in the arterial wall. Inflammation is a highly orchestrated and synchronized physiological state that is activated when the endothelium becomes dysfunctional in the face of such risk factors as hyperlipidemia, hypertension, insulin resistance, diabetes mellitus, and smoking, among others. Endothelial

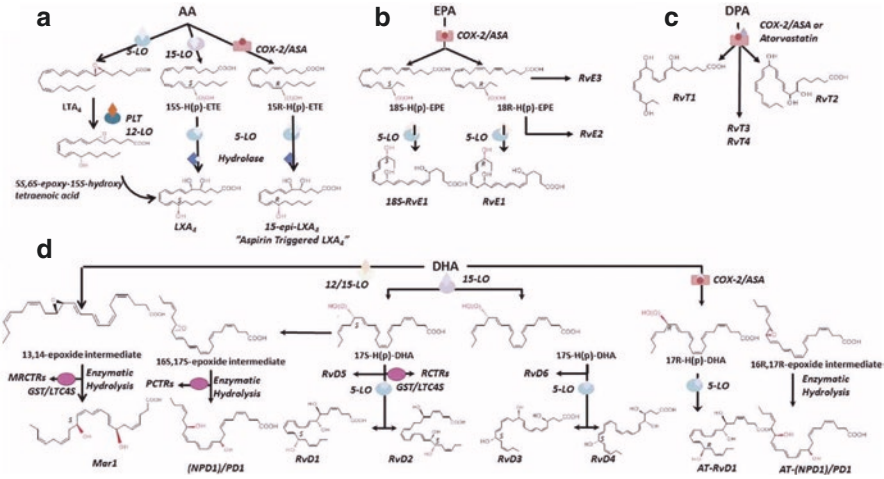

Fig. 16 Biosynthesis and structures of specialized pro-resolving lipid mediators . The biosynthetic pathways leading to lipoxins (**a**), E-series resolvins (**b**), SPM derived from DPA (**c**), D-series resolvins, protectins, and maresins (**d**) are illustrated. Structures and stereochemistries of some members of each SPM family are shown. AA arachidonic acid, EPA eicosapentaenoic acid, DPA docosapentaenoic acid, DHA docosahexaenoic acid, LO lipoxygenase, COX-2 cyclooxygenase 2. MCTRs maresin conjugates in tissue regeneration, RCTRs resolvin conjugates in tissue regeneration, PCTRs protectin conjugates in tissue regeneration. GST/LTC4S glutathione-S-transferase/leukotriene C_4 synthase. (Reprinted from Recchiuti [251]. With permission from Creative Commons License 4.0: https://creativecommons.org/licenses/by/4.0/)

dysfunction results in reduced nitric oxide production and an upregulation of a variety of adhesion molecules which promote the binding, rolling, and transmigration of inflammatory white blood cells into the subendothelial space. The white blood cells include monocytes, neutrophils, mast cells, and T helper cells. Chronic inflammation gives rise to a pro-oxidative, prothrombotic, and pro-growth (clonal expansion) state. Monocytes are converted to resident macrophages which scavenge oxidatively modified lipoprotein particles; with progressive lipid uptake and formation of lipid inclusion bodies, macrophages become macrophage-derived foam cells. Foam cells can coalesce to form fatty streaks. Fatty streaks can become atheromatous plaques as foam cells and necrotic debris accumulate in the setting of impaired efferocytosis. Chronically inflamed atheromatous plaque can undergo architectural changes that predispose to rupture as metalloproteinases thin the fibrous cap, with cholesterol crystal formation, hemorrhage into the base of the plaque from adventitial vasa vasorum, and sudden torsional influences like vasospasm. Ruptured plaques activate platelets and thrombosis secondary to the sudden availability of tissue factor, exposed collagen, calcium, and adenosine-5′-diphosphate (ADP). The thrombus can lead to luminal occlusion and tissue ischemia. Inflammation can be turned on by prostaglandins, leukotrienes, cytokines, chemokines, and interleukins. Inflammation can also be resolved via the activity of such interleukins as interleukin-4 and interleukin-10, as well as lipoxins, maresins, resolvins, and protectins. Atherosclerosis represents a maladaptive physiological response since inflammation is allowed to

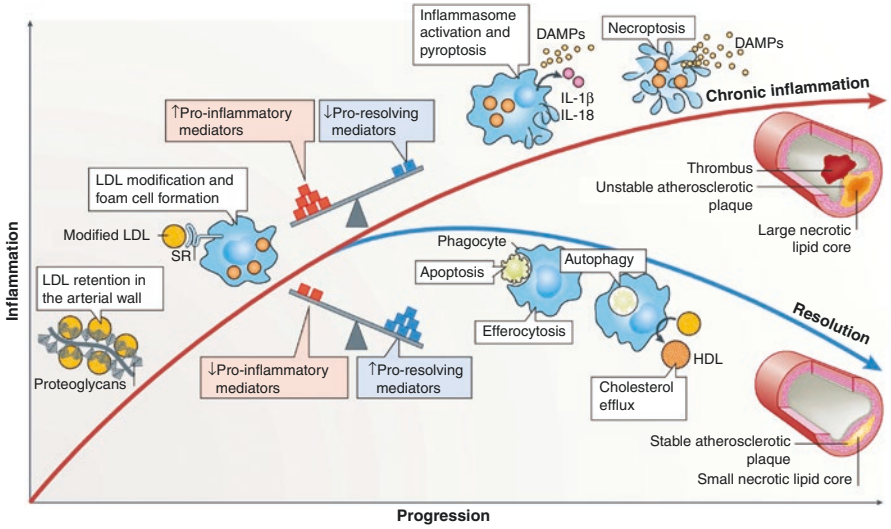

Fig. 17 The balance of pro-inflammatory and anti-inflammatory processes controls the resolution of the lipid-driven inflammation in atherosclerotic lesions. Retention of LDL particles by arterial wall proteoglycans and subsequent modification of the retained LDL induce inflammation in the arterial wall. Macrophages ingest the modified LDL particles via scavenger receptor (SR)-mediated endocytosis and become foam cells. If the balance between pro-inflammatory and pro-resolving mediators is tilted toward inflammation, the resolving mechanisms fail. Under these conditions, pyroptosis (mediated by inflammasome activation) or necroptosis can ensue. These pro-inflammatory forms of cell death further promote inflammation and generation of a large necrotic lipid core. These unstable atherosclerotic plaques might ultimately lead to plaque rupture and a local occluding arterial thrombus. Conversely, if the balance between the mediators is tilted toward pro-resolving mediators, apoptosis and autophagy-associated cell death and cholesterol efflux from the lesions are favored, and efferocytosis of the dead cells can lead to resolution of inflammation. These processes promote the formation of a stable plaque with a small necrotic lipid core. DAMPs damage-associated molecular patterns. (Reprinted from Bäck et al. [245]. With permission from Springer Nature)

persist, ultimately resulting in acute vascular events within myocardium, the brain, and other tissues (Fig. 17).

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The Role of Genetics in Preventive Cardiology: Utility of Clinically Available Genetic Tests

H. Robert Superko

Summary

- Genetic testing fills an unmet clinical need in preventive cardiology.
- Genetic testing can be utilized in combination with noninvasive imaging.
- Genetic tests can improve standard CAD risk classification.
- Genetic tests have clinical utility in some dysrhythmias.
- Genetic tests can identify specific causes of cardiomyopathies that may be of clinical help to the patient and family members.
- Genetic dyslipidemia tests can provide a more specific diagnosis and risk prediction than the standard lipid profile.
- Financial cost of genetic tests has decreased greatly in the past 10 years.
- Genetic tests enhance personalized medicine.

1 Introduction

Benjamin Franklin is famously believed to have said: "an ounce of prevention is worth a pound of cure." This is even more relevant today in the era of genetic testing which can help identify which individuals require what kind of prevention and help avoid the one diet, or one drug, fits all conundrum prevalent in modern cardiovascular disease prevention. Knowledge of the genetic make-up of patients allows a sophisticated approach to individual management that was unavailable a decade ago. This chapter will address relevant genetic tests that are commercially available and how they may be utilized to provide improved individualized cardiovascular disease (CVD) management.

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This chapter will briefly address history, the unmet clinical needs genetic testing addresses, genetic tests that improve CVD risk prediction, the concept of a family heart disease clinic, tests that are associated with atrial fibrillation, tests available for cardiomyopathy and dysrhythmias, and tests useful in dyslipidemias.

1.1 History

The knowledge that certain physical traits can be transmitted from one generation to another has been known to humans since Neolithic times and utilized for enhancement of desirable traits in livestock animals [1]. Famously, the monk Johann Gregor Mendel, in the 1850s, conducted experiments on the transmission of physical traits in peas which arguably heralded the modern age of genetic understanding. His name is indelibly associated with genetics and the concept of "Mendelian inheritance." Throughout history, cutting edge physicians have recognized the importance of inherited traits, and in the coronary heart disease (CHD) area, Sir William Osler, discussing a patient in 1892, is famously quoted as saying, "**Entire families** sometimes show this tendency to early arteriosclerosis. A tendency which cannot be explained in any other way than that in the make-up of the machine **bad material** was used for the tubing" [2].

In the past few decades, knowledge of the complexity and molecular basis of genetics and CHD has greatly expanded to include the genetics of complex diseases such as atherosclerosis and type 2 diabetes mellitus [3]. While the promise of clinically useful genetic tests has been around for decades, a few relatively recent scientific breakthroughs allow the promise to become a reality. While DNA was isolated by Miescher in 1869, and Watson and Crick received the Nobel prize for elucidating the double helix in 1954, it was the discovery of the polymerase chain reaction by Kary Mullis in 1985, for which he received the Nobel prize in 1993, that provided the tool to advance genetic research in humans in any large way. In 2001, a draft sequence of the human genome was presented by both Venter and Collins which provided the road map for future research plans and discoveries [4, 5]. This was a Herculean effort by numerous individuals and institutions aided by a new strategy for genome sequencing in 1996 [6].

Much of this relatively recent human research involved the use of a laboratory method known as a DNA microarray and also referred to as "gene chips." These chips could determine a specific single-nucleotide polymorphism (SNP) identified by a specific reference sequence number (RS). Through laboratory method advancements, in the early 1980s, these gene chips could at first measure only a few SNPs, but then in rapid sequence, they could determine 100,000, then 500,000, then one million, or more SNPs on each subject [7]. This laboratory method allowed the development of the genome-wide association study (GWAS) approach to the discovery of a plethora of SNPs statistically associated with cardiovascular issues. Through this approach, some genetic differences associated with disease risk have been identified that provide a risk estimate based on the presence of specific SNP

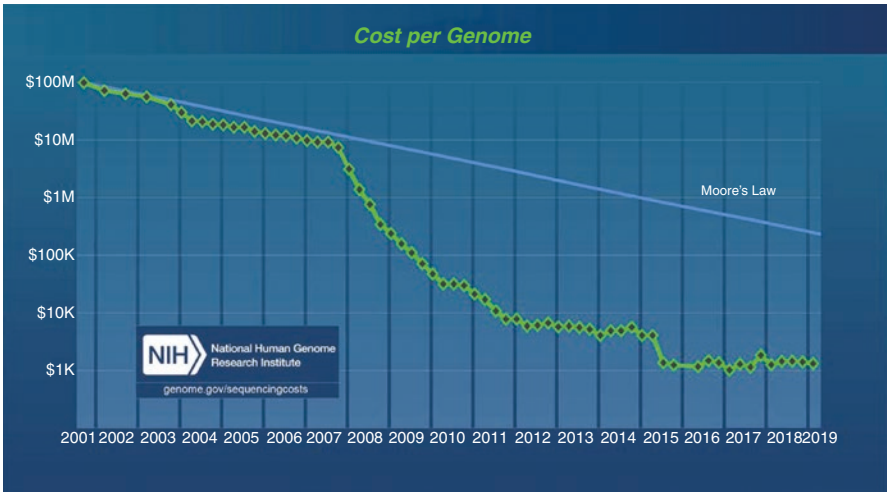

Fig. 1 Typical cost of sequencing a human-sized genome on a logarithmic scale. Note the drastic trend faster than *Moore's law* beginning in January 2008 as *post-Sanger sequencing* came online at sequencing centers (*Wetterstrand, Kris (21 May 2012). "DNA Sequencing Costs: Data from the NHGRI Large-Scale Genome Sequencing Program". Large-Scale Genome Sequencing Program. National Human Genome Research Institute. Retrieved 24 May 2012*). (Reprinted from Wikipedia. Retrieved from: https://commons.wikimedia.org/w/index.php?curid=30648381. with permission from Creative Commons License 1.0: https://creativecommons.org/publicdomain/zero/1.0/deed.en)

differences in populations with and without the disorder of interest. Due to the very large number of data points, analysis of the results of gene chip experiments requires advanced statistical methods for valid analysis and often requires a p value of $<10^{-8}$ to be considered statistically significant [8].

In a similarly rapid pace, the financial cost of genetic testing has fallen dramatically. It was estimated that the cost of sequencing the first human genome by Celera was approximately $100,000,000, but now commercially available gene sequencing can be obtained for well under $1000 (Fig. 1). In 2018, Dante Labs and Veritas Genetics offered whole-genome sequencing (WGS) for $200 [9, 10]. However, the sophisticated bioinformatics part of the full interpretation is generally not included with these low prices.

The explosion of scientific knowledge in this area has led to new uses in the cardiovascular medical field to improve risk classification and guide treatments. This chapter will address the practical utility of some commercially available genetic tests that are available to the clinician and patients in 2020. Many of the sophisticated aspects of modern genetics offer great expectations for future diagnosis and treatment but will not be addressed since they are not clinically available or have clear clinical implications at this time.

Clinical utility of inherited cardiovascular risk testing currently exists utilizing both phenotypic and genotypic markers which allows a new battle against coronary heart disease (CHD) [11]. These markers can improve the accuracy of CHD

risk prediction, help in defining a diagnostic etiology, as well as guide the optimal treatment and importantly be informative in family counseling [12, 13]. One major impediment to widespread clinical adoption of this concept involves privacy issues. Privacy issues were addressed in the Federal genetic nondiscrimination bill (Genetic Information Nondiscrimination Act H.R. 493 of 2008) which was passed by both the House of Representatives and the US Senate and on May 22, 2008, signed into law by President Bush [14].

2 Genetic Tests Help to Fill an Unmet Clinical Need

Detection of individuals at high risk for CHD and treatment of CHD has made great advances in the past two decades. Programs designed to identify high-risk individuals have been emphasized at the national and international level [15, 16]. Yet one aspect of CHD risk determination has been scientifically accepted but relatively ignored in the clinical community, namely, incorporation of information gained from family history and DNA blood test results into routine clinical care [17]. With advances in our understanding of genetic influences on CHD risk, the time has come to apply this knowledge in routine clinical practice in order to address unmet clinical needs. Indeed, 30 years ago, Karl Berg wrote:

> Knowledge of genetic factors in the etiology of coronary heart disease has not so far been adequately utilized in attempts to combat premature CHD. The time has now come to utilize genetic information in a setting of family-oriented preventive medicine. This approach would greatly improve the efficiency of preventive efforts, utilizing predictive genetic testing and targeting counseling on those who need it most." [18]

It is accepted that family history of heart disease is one of the most powerful determinants of CHD risk and is independent of the common CHD risk factors including smoking, hypertension, diabetes, and some lipids [19, 20]. The link between CHD and inheritance is indisputable and the evidence strong and consistent. Modern genetic testing can help to fill the unmet clinical need of improved CHD risk prediction particularly in families with a history of cardiovascular disease. Numerous retrospective family studies have been conducted indicating that the risk of CHD in siblings of victims of premature CHD is approximately 50% for males and less for females [21, 22]. Risk in females may be, in part, age dependent since it has been reported that the relative risk is high in first-degree female relatives who were mostly mothers of cases [23]. In siblings of premature CHD patients studied in Finland, the risk of dying from CHD was 5.2 times higher than a control population without such a family history. This risk can be compared to the two- to threefold CHD risk associated with cigarette smoking [24].

Numerous prospective studies of the risk for CHD in first-degree relatives have been conducted [25–31]. In the Nurses' Health Study, in 117,156 middle-aged women, the risk for nonfatal myocardial infarction (MI) was 5.0 if they had a family history of fatal CHD prior to age 60 years and 2.6 with a family history after

60 years of age. Thus, while the presence of CHD at an age <60 years indicated a very high risk, a history in a family member >60 years of age was still very substantial and clinically relevant. These prospective investigations indicate that the risk of MI is at least twofold greater if a family history of CHD is present and that there is a major familial component linking family history and CHD risk that is independent of the classic CHD risk factors.

Studies in twins also provide powerful evidence of the importance of family history and genetics in heart disease. A total of 21,004 Swedish twins have been followed for 26 years and provide evidence that premature death from CHD is strongly influenced by genetic factors [32]. In women, the relative hazard of death from CHD when the twin died from CHD prior to the age of 65 years was 15.0 for monozygotic twins and 2.6 for dizygotic twins, and in men, when the twin died before the age of 55 years, the relative hazard of death from CHD was 8.1 for monozygotic twins and 3.8 for dizygotic twins. These relative hazards were reported to be little influenced by other CHD risk factors. and the effects appear to decrease with increasing age.

Determination of high CHD risk phenotypes/genotypes in adult family members of patients with established CHD can have five important results that may benefit the patient. First, it can serve to alert family members of their personal risk potential when compared to the family member with established CHD; second, it can alert the family member to important gene environment interactions that may affect their heart health; third, it helps to select the most appropriate screening blood tests for family members and avoid overutilization of laboratory services; fourth, it helps to identify family members who may benefit from noninvasive imaging; and fifth, it can assist in treatment decisions.

2.1 Noninvasive Imaging and Genetics

The use of noninvasive imaging has contributed to our understanding of the importance of family history in predicting CHD risk. The historic finding that the risk for CHD is approximately 50% in siblings of premature CHD patients has been reproduced utilizing noninvasive imaging [21]. In 1619 asymptomatic males who underwent coronary artery calcium (CAC) testing, a family history of CHD, in a first- or second-degree relative, was reported to be highly predictive of a positive CAC score with odds ratios approaching 1.50 [33]. In a similar study of 8549 asymptomatic individuals, a family history of CHD in a parent increased the odds ratio to 1.3 in men and women, and a family history of CHD in a sibling increased the odds ratio to 2.3 [34]. The association of a family history of a positive CAC score is particularly powerful in siblings. Seventy-eight percent of individuals reporting a sibling with known CHD had a positive CAC score. Noninvasive imaging screening in families with known CHD may be informative, particularly in family members with a phenotypic or genotypic expression of CHD risk, similar to the family member with known CHD. Combining genetic testing with noninvasive imaging has been

presented as a reasonable clinical tool by the Society for Heart Attack Prevention and Eradication (SHAPE) [35].

3 Specific Genetic Tests and Unmet Clinical Need

3.1 Cholesterol Unmet Clinical Need

Cardiovascular disease risk is associated with elevations in low-density lipoprotein cholesterol (LDL-C). However, many myocardial infarction patients have an LDL-C blood value that would be considered normal in a primary prevention population. Approximately 75% of patients admitted to hospital with a coronary heart disease (CHD) event exhibited a relatively normal LDL-C less than 130 mg/dl, and 23% had an LDL-C <70 mg/dl [36]. Thus, many patients remain at risk for a CHD event even when LDL-C is in an acceptable range and a new strategy to prevent heart attacks is required [37].

Despite significant reduction in LDL-C, a large reservoir of cardiovascular disease risk remains (Fig. 2). The often quoted 25% relative risk reduction, attributed to LDL-C reduction, is actually only a 3.4% absolute risk reduction [37]. For example, in the JUPITER trial, rosuvastatin achieved a 50% reduction in LDL-C [38]. There were 251 events in the placebo group, yet 142 subjects experienced a primary end point in the treatment group despite a 50% reduction in LDL-C. In the Fourier investigation, PCSK9 inhibition, in addition to statin therapy, reduced LDL-C to a mean of 30 mg/dl compared to 92 mg/dl in the statin only group [39]. There were 1563 primary end points in the control group, yet 1344 subjects in the PCSK9 + statin group also experienced a primary end point. Thus, LDL-C reduction alone reduces risk in some patients, but a large group continues to experience a cardiovascular event, and there is a need to expand accurate risk classification utilizing modern genetic tools.

3.2 **9p21** *Primary Prevention Risk Reclassification*

Prediction of the risk for a cardiovascular event in large population groups is represented by several risk calculation algorithms including the Framingham Risk Score and the Atherosclerosis Risk in Communities risk score [40, 41], all of which are developed for large group risk prediction but actually utilized by clinicians for individual patient risk classification. This approach leaves some patients classified as low risk who actually go on to experience a CV event and some patients classified as high risk who never experience a CV event. This has been recognized by leaders in the CV prevention field.

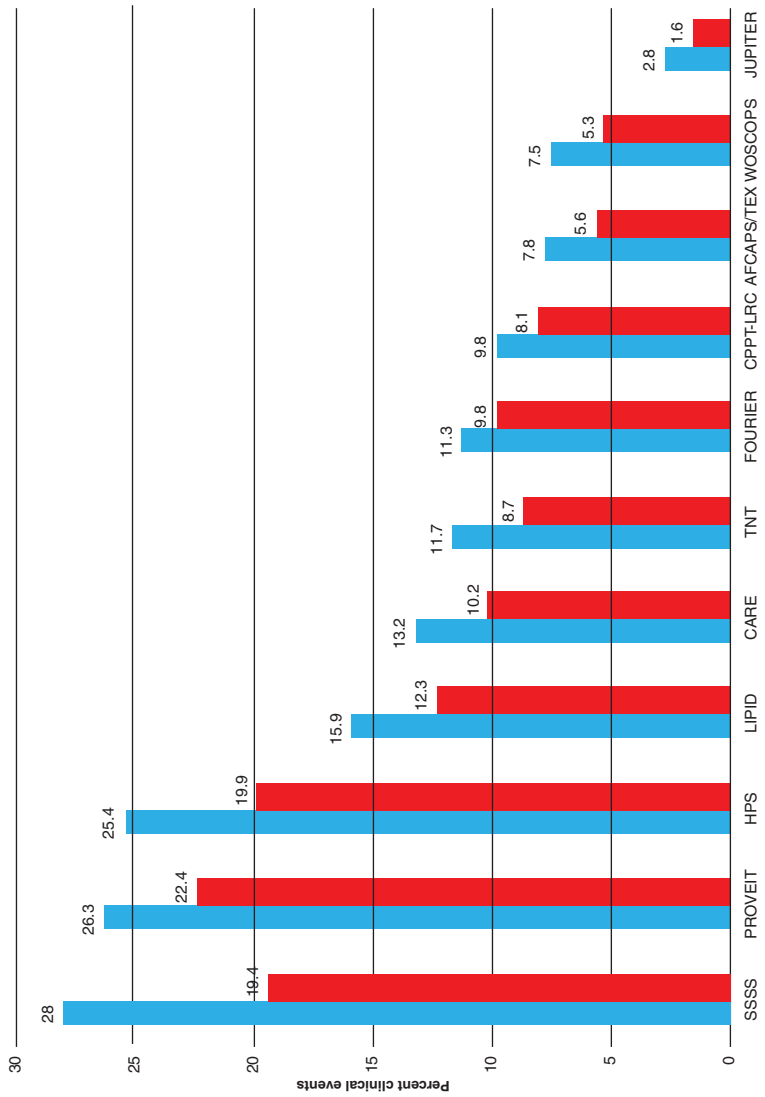

Fig. 2 The residual risk for future CV events is exemplified by the % of individuals who experienced a CV event in the treatment group (red) compared to the placebo group (blue) in a sample of blood cholesterol-lowering clinical trials. The red bars reflect the large group of patients achieving reduced LDL-C yet continuing to suffer from a CV event. This illustrates the clinical need to go beyond standard risk classification and consider genetic testing. (Based on data from Ref. [37])

A majority of middle-aged patients who experienced a first myocardial infarction (MI) had a traditional risk factor profile which would not have qualified them for preventive medical therapy. [42]

Although current risk estimates work very effectively in populations, variation of estimated risk leads to misclassification of true risk in individual patients. [43]

Even risk algorithms based on established risk factors are limited in predictive power for individuals. More effective prediction tools are needed. [44]

3.3 9p21

In 2007, the first common gene that increases risk for coronary artery disease was identified [45]. This polymorphism is located on the short arm (p) of chromosome 9 in the band region 2.1, and so it is referred to as *9p21*. The initial mapping of *9p21* was in an Ottawa population in a genome-wide association study (GWAS) which was subsequently confirmed in independent populations from Dallas, Houston, and Denmark for a total of 23,000 Caucasians. *9p21* is very common, occurring in 75% of the Caucasian population with 50% inheriting a single copy (heterozygous) and 25% two copies (homozygous). Individuals having two copies of *9p21* have increased relative risk for CAD of about 40% and 20% for those with a single copy. *9p21* risk is independent of all known risk factors, namely, cholesterol, hypertension, diabetes, and obesity. This implies a previously unknown risk factor which points to a new pathway for the genesis of atherosclerosis. The region does not contain a protein coding gene but rather an anti-sense non-coding RNA (ANRIL), and subsequent research revealed that the *9p21* polymorphism impacts the activity of ANRIL involved in the inflammatory process [46].

Multiple studies confirmed *9p21* to be a common risk factor for CAD in Caucasians [47–50]. Studies have confirmed that the *9p21*/CAD relationship is not limited to Caucasians. *9p21* has a similar frequency and increased risk for CAD in the Chinese, Koreans/Japanese, and East Indians [51, 52]. The *9p21* locus has been confirmed as a risk factor for abdominal aortic aneurysms/intracranial aneurysms, ischemic stroke, and myocardial infarction [47, 53, 54].

The presence of the *9p21* risk allele has been shown to improve standard risk prediction models. The Atherosclerosis Risk in Communities (ARIC) risk equation can be used to estimate an individual's risk potential and includes a family history of heart disease [41]. The addition of *9p21* information to the ARIC risk score reclassifies 32.9% of individuals in the mid-risk range into more accurate risk categories, and the reclassification index was improved in 45.1% in all risk groups [55] (Table 1).

In 2010, Dondona and colleagues reported that there was a strong direct association between the proportion of early-onset three-vessel coronary artery disease and the gene dose of *9p21* (rs1333049) [56]. The authors concluded that given *9p21*'s ability to predict risk within a CAD population, genotyping *9p21* may be useful not only in determining risk for development of disease but also for risk stratification among patients with documented CAD. This relationship between the *9p21*

Table 1 CVD event risk prediction reclassification in the Atherosclerosis Risk in Communities study when 9p21 risk characterization is added to the standard risk classification [55]. Nine hundred ninety-eight ARIC subjects with 14.6 years of follow-up. Ten-year risk for a CV event is listed on the X and Y axes with the percent accurately reclassified noted in the far right column. Bolded numbers indicate the percent of subjects in which 9p21 genotyping did not change risk classification

	Total				
10-year risk	0–5%	5–10%	10–20% ≥ 20%	Reclassified	
0–5%	**97.8%**	2.2%	0	0	87 (2.2%)
5–10%	7.9%	**82.9%**	9.2%	0	319 (17.1%)
10–20%	0	7.0	**84.2%**	8.8%	382 (15.8%)
>20%	0	0	10%	**90%**	185 (10.0%)
N	3936	1805	2394	1869	

homozygote condition and arteriographic severity suggests that noninvasive imaging of the coronary arteries may be most productive in *9p21* homozygote subjects who comprise approximately 25% of the general population. The presence of the *9p21* polymorphism does not guarantee the presence of CAD but represents an independent risk predictor that helps identify a group at higher risk than previously thought based on traditional risk factor assessment. This creates the opportunity to use genetic tests to identify individuals who are more likely to benefit from noninvasive imaging and helps improve the risk/benefit of CT scanning.

This approach to more accurate risk prediction has taken another step forward by utilizing a panel of SNP tests that capture a wider range of genetic variation [57]. Davies and colleagues have reported that a collection of 12 SNPs including *9p21* improves CAD prediction over and above traditional risk factors [58]. The use of a multiple 27 SNP test appears to have additional benefit. Mega and colleagues reported on a 27 SNP panel, and when primary and secondary prevention subjects were divided into low (quintile 1), intermediate (quintiles 2–4), and high (quintile 5) genetic risk categories, a significant gradient in risk for incident or recurrent coronary heart disease was revealed ($p < 0.0001$) [59]. LDL-C and high-density lipoprotein cholesterol (HDL-C) values were similar across genetic risk score categories. Compared with the low genetic risk category, the multivariable-adjusted hazard ratio for coronary heart disease for the intermediate genetic risk category was 1.34 ($p < 0.0001$) and that for the high genetic risk category was 1.72 ($p < 0.0001$).

A genetic risk score can provide the clinician with an additional tool to characterize cardiovascular risk in their patients. Khera and colleagues have reported that in a large cohort or 55,685 subjects, those with a high genetic risk score had a 91% higher risk of an incident coronary event [60]. However, their analysis also revealed that in those subjects with a high genetic risk score, who adhered to a favorable lifestyle, there was a 50% lower relative risk of CAD compared to those with an unfavorable lifestyle. Despite high genetic risk, a favorable lifestyle still had risk reduction benefit.

The clinical utility of such a multi-SNP test is not limited to risk reclassification in the primary prevention population but has additional utility in helping to identify

who obtains the greatest, and the least, clinical event reduction benefit with statin therapy. LDL-C reduction with statin therapy has become a standard of care in the past few decades. However, there is wide variation regarding individual clinical event reduction benefit. The analysis of the JUPITER trial, ASCOT trial, CARE trial, and PROVE IT-TIMI 22 trial, by Mega and colleagues, revealed that this 27 SNP genetic variant test can determine which patients derived the largest relative and absolute clinical benefit from statin therapy [59] (Fig. 3). Relative risk reduction was 13% in the low-risk group, 29% in the intermediate-risk group, and 48% in the high-risk group ($p = 0.03$). The number needed to treat (NNT) in the primary prevention trials was 66 in the low-risk group, 42 in the intermediate-risk group, and 25 in the high-risk group. A regression coefficient for absolute risk reduction indicated that for each 1% absolute risk reduction achieved with statin therapy in the intermediate genetic risk group, a 1.71% absolute risk reduction would be expected in the high genetic risk group and a 0.29% absolute risk reduction in the low genetic risk group. Thus, this multi-SNP test can increase a health-care provider's ability to accurately determine CAD risk independent of standard risk factors and identifies groups of patients that obtain the greatest and least CVD event reduction benefit from statin therapy.

3.4 Primary Prevention: The Aspirin (ASA) Conundrum

Some genetic tests that identify a high-risk group have a low population frequency but potential clinical utility in the majority of the population that do not carry the polymorphism. One clinical question that continues to create difficulty for primary care physicians is the potential risk/benefit of daily aspirin use to reduce CVD risk. Investigations have indicated that in the secondary prevention population, the benefit of daily ASA and heart disease risk reduction outweighs the potential harm associated with daily ASA use. However, in the primary prevention population, the answer is less clear, and the US Preventive Task Force provided some guidance in 2009 by recommending cut points based on the Framingham Risk Score (FRS) to identify patients who are more or less likely to derive heart disease prevention benefit from daily ASA treatment [61]. The risk/benefit cut point was defined by age and gender and was established as the FRS level at which the number of heart attacks prevented equaled the number of serious gastrointestinal (GI) bleeds caused by daily ASA treatment. This conundrum continues to be addressed in the medical community [62].

The *LPA* intron 25 genotype (rs10455872) test can have clinical utility in determining which primary prevention patients derive the most CVD risk reduction benefit from daily aspirin and assist in balancing the aspirin associated increased risk of a serious GI bleed balanced against the CVD event risk reduction. *LPA* is a polymorphism in the protease-like region of the [a] protein and has been shown to provide useful information to help balance the risk/benefit ratio of daily aspirin use intended to reduce CHD risk. In the Women's Health Study, 25,815 middle aged women were randomized to aspirin (100 mg every other day) or placebo [63]. After 10 years of follow-up, it was reported that women with the *LPA* polymorphism in the placebo

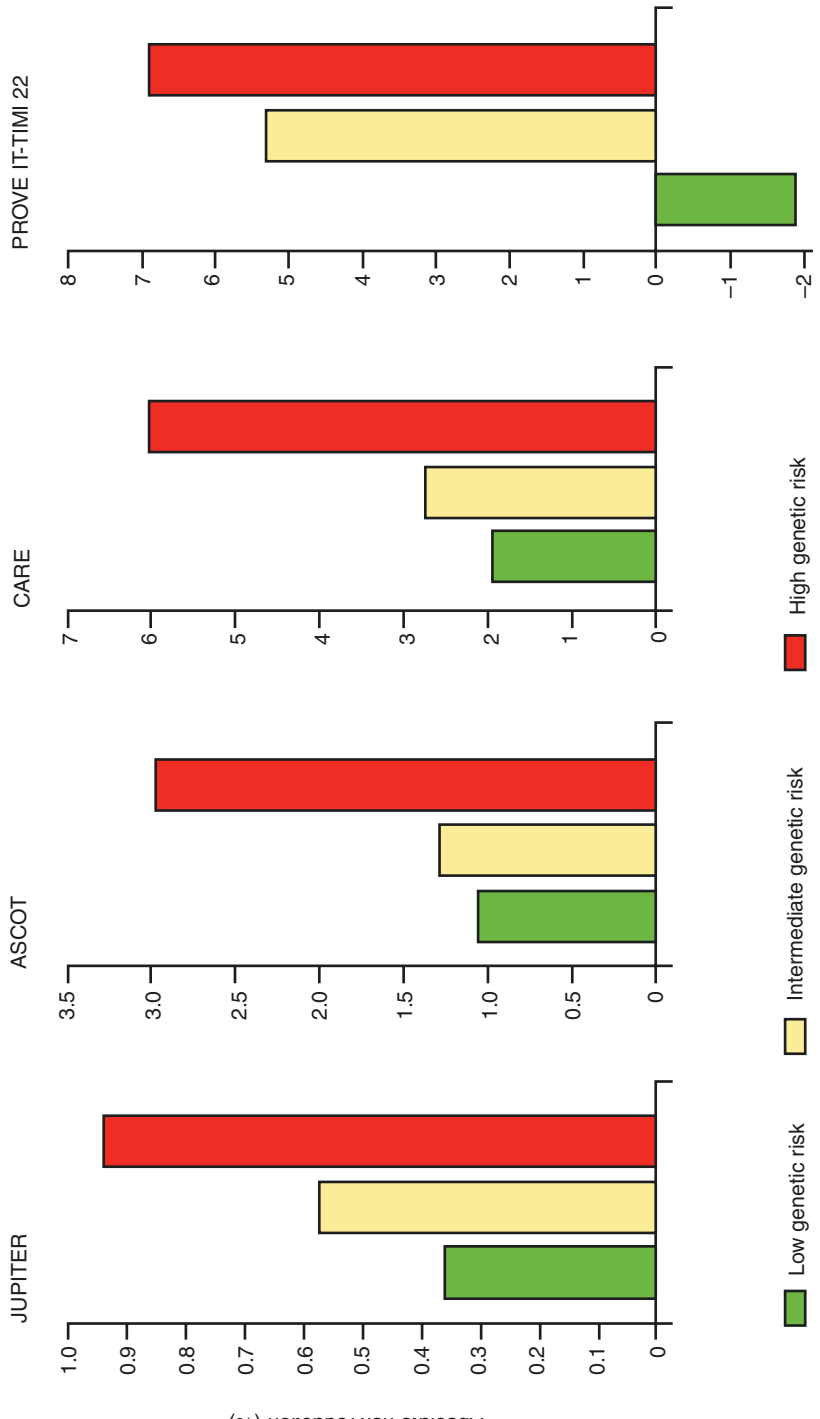

Fig. 3 Absolute risk reductions of coronary heart disease events with statin therapy across genetic risk score categories. In PROVE IT-TIMI 22, the control group is moderate-intensity statin therapy (pravastatin 40 mg), and the statin group is high-intensity statin therapy (atorvastatin 80 mg). (Reprinted from Mega et al. [59]. With permission from Elsevier)

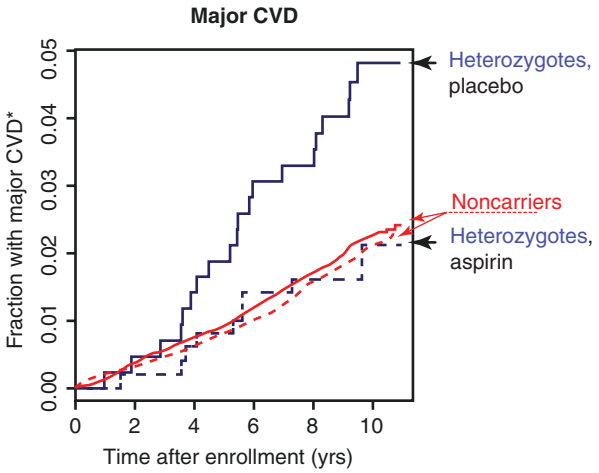

Fig. 4 Kaplan-Meier estimates of the cumulative fraction composite end point of Caucasian women with a first ever major CVD event (myocardial infarction, ischemic stroke, or cardiovascular death) according to rs3798220 carrier status and treatment group. (Reprinted from Chasman et al. [63]. With permission from Elsevier)

group experienced significantly more CV events compared to those non-carriers of the risk allele in the placebo group ($p < 0.0008$). But, if women with the *LPA* polymorphism were randomized to aspirin, their CV event rate was equal to the non-LPA carriers in both the placebo and aspirin groups (Fig. 4). Aspirin therapy had no effect on reducing CV events in the women without the *LPA* polymorphism. This polymorphism is found in approximately 4% of the population, making it relatively uncommon. However, the clinical utility is in giving daily aspirin therapy advice to the 96% of people who are not carriers of the *LPA* allele, thus reducing the risk of potential gastrointestinal bleeding complications of long-term aspirin use. The number needed to treat (NNT) to prevent one CV event in the Women's Health Study with aspirin was 625 in *LPA* non-carriers but only 37 in the women who carried the *LPA* risk allele. These results were replicated in the Atherosclerosis Risk in Communities (ARIC) study when daily aspirin users were compared to nonusers [64].

There is a relationship between *LPA* genotype and Lp(a) blood concentration. In non-carriers, the mean Lp(a) is ~10 mg/dl; in patients with one affected allele, the mean Lp(a) is ~70 mg/dl; and in patients with two affected alleles, the mean Lp(a) is 154 mg/dl. However, many patients with one affected allele have Lp(a) blood levels that would not be considered elevated [63]. Genetic variations at the *LPA* locus have also been associated with CHD events during statin therapy independent of the extent of low-density lipoprotein cholesterol lowering [65].

3.5 Secondary Prevention: Lp(a) Phenotype

Phenotypic expression of a genetic trait is a way to incorporate genetic information in CVD prevention without the need for DNA tests. Lp(a) is a well-established example [66]. Apoprotein [a], when attached to apoprotein B and LDL, is termed lipoprotein(a), or Lp(a) for short. Lipoprotein(a) is a low-density lipoprotein

(LDL)-like particle with apolipoprotein B covalently linked to apolipoprotein (a) by a single disulfide bond. The importance of this lipoprotein lies in its strong association with CHD and carotid atherosclerosis and its transmission within families in a dominant fashion [67]. This disorder is relatively common, and elevated levels may be present in as many as 20–40% of individuals with CHD. The gene is located on chromosome number 6 and inherited in a dominant fashion, which indicates that ~50% of first-degree relatives of patients with elevated Lp(a) will express elevated Lp(a) levels as well. This finding may help to explain why some patients with relatively normal blood LDL-C and HDL-C values still suffer from atherosclerosis.

Since its initial description by Berg in 1963 as a variant of LDL, the Lp(a) molecule has generated interest regarding its potential proatherogenic or prothrombotic role in human disease [68]. Circulating concentrations of Lp(a) differ widely across individuals and ethnic subgroups, mediated predominantly by genetic variation at the *LPA* gene locus. Individuals contain highly polymorphic copy numbers of the Kringle IV-type 2 domain, with lower numbers relating to smaller apolipoprotein (a) size and increased plasma Lp(a) concentrations [69]. Robust associations between Lp(a) and cardiovascular disease (CVD) outcomes have been noted in studies conducted in general populations [70, 71]. Mendelian randomization studies have linked genetic variations at the *LPA* locus to both circulating plasma concentrations and the risk of CVD, supporting a causal role of Lp(a) in CVD pathogenesis. In the JUPTER trial, even with significant statin-induced LDL-C reduction, participants with low LDL cholesterol and elevated high-sensitivity C-reactive protein, the Lp(a) concentration was not altered with statin treatment and remained a significant determinant of residual risk [72].

Guidance on the clinical utility of Lp(a) phenotype testing has been provided by international groups. In 2010, Nordestgaard and colleagues presented the European Atherosclerosis Society Consensus Panel on Lp(a) [73]. They concluded that the robust and specific association between elevated Lp(a) blood levels and increased cardiovascular disease (CVD)/coronary heart disease (CHD) risk, together with recent genetic findings, indicates that elevated Lp(a), like elevated LDL cholesterol, is causally related to premature CVD/CHD. The association is continuous without a threshold or dependence on LDL- or non-HDL-cholesterol levels. They recommended as a secondary priority to define a desirable Lp(a) level of <80th percentile (<~50 mg/dl). Treatment was primarily niacin and/or LDL apheresis. Recommendation was made on whom to screen and included: (1) patients with premature CVD, (2) patients with familial hypercholesterolemia, (3) patients with a family history of premature CVD and/or elevated Lp(a), (4) patients with recurrent CVD despite statin treatment, and (5) patients with elevated CVD risk as defined by either the European guidelines or the US guidelines. During cascade testing for familial hypercholesterolemia, testing for Lp(a) is effective in identifying relatives with high Lp(a) and heightened risk of CVD [74].

Not only is elevated Lp(a) independently associated with increased CVD risk, but a clear link to increased risk of aortic stenosis and the rate of progression of aortic stenosis has recently been documented [75]. Recent studies have shown that of >2.5 million single-nucleotide polymorphisms (SNPs) analyzed, the *LPA* SNP

rs10455872, which is associated with markedly elevated Lp(a) levels, was the only monogenetic risk factor for aortic valve calcification in multiple racial groups [76–79]. This issue has increased in clinical relevance with the development of a new antisense oligonucleotide treatment that has a significant effect on Lp(a) concentration with reduction of up to 80% reported in a clinical trial [80].

3.6 Arrhythmia

The clinical use of genetic testing in dysrhythmias is an expanding field. Some genetic tests have clinical utility for specific dysrhythmias.

3.7 Atrial Fibrillation (AF)

The *4q25* gene locus is on chromosome 4 and is adjacent to the *PITX2* gene, which is a transcription factor required for cardiac development and left-right asymmetry of the heart and for normal sinus node formation. A *4q25* genotype test determines the genotype of two genetic variants on chromosome 4q25 (rs2200733 and rs10033464) [81]. These two genetic variants have been shown to be associated with atrial fibrillation in genome-wide association studies of large case-control and population-based studies [82–84]. It is especially apparent in subjects over the age of 60 years. These two genetic variants are also associated with stroke and found to be strongly associated with the cardioembolic (CE) stroke subtype [85, 86]. Approximately a third of ischemic stroke cases are classified as cryptogenic stroke, and the choice of an anti-thrombotic treatment (anticoagulant vs anti-platelet), appropriate for the CE stroke subtype, greatly reduces the recurrence rate of CE stroke [87]. The odds ratio for AF for individuals carrying each copy of the minor allele of rs2200733 is 1.7 ($p = 3 \times 10^{-41}$), while that for each minor allele of rs1003464 is 1.3 ($p = 7 \times 10^{-11}$) [82]. The odds ratio for having CE stroke for individuals carrying each minor allele of rs2200733 is 1.5 ($p = 6 \times 10^{-12}$) and for each minor allele of rs1003464 is 1.3 ($p = 6 \times 10^{-4}$) [85]. Thus, the *4q25* genotype test, together with assessment of clinical information, could help stroke subtype diagnosis as well as treatment selection for prevention of stroke in patients having a cryptogenic stroke.

A medical unmet clinical need exists in the increasing prevalence of AF but also as a complication of coronary artery bypass surgery and catheter-based ablation therapy. Atrial fibrillation is prevalent in about 4% of those over 60 years old and 9% of those over 80 [88]. AF increases the risk of stroke by about five-fold [89]. This increased stroke risk can be substantially reduced with appropriate anticoagulant treatment [90]. However, AF can be paroxysmal and asymptomatic and thus is often undiagnosed [91]. Greater awareness and cardiac monitoring can help to detect occult AF [92]. Even for diagnosed AF patients, anticoagulant (warfarin) therapy has been underused because of the bleeding risk and the need to monitor the

patients' international normalized ratio (INR) [93]. Newer anticoagulants are now available which are easier to use and have lower bleeding risk [94–96]. Detecting undiagnosed atrial fibrillation (AF) is a major opportunity to improve AF treatment and stroke prevention in the population [97]. The presence of the *4q25* risk allele allows identification of a population at enhanced AF and stroke risk.

There is also clinical utility in coronary artery bypass graft (CABG) patients and those considering ablation therapy. Postoperative AF occurs in about a third of the CABG procedures. These two genetic variants have been shown to be associated with about a twofold increase in CABG postoperative AF [95, 96]. This genetic test information could assist the selection of perioperative monitoring and therapies to manage the complications due to postoperative AF. In AF patients, considered for catheter ablation treatment, positive *4q25* risk allele test results are associated with a twofold increase in early (7 days) recurrence or a threefold increase in late (up to 6 months) recurrence which could inform risk assessment prior to ablation therapy and post-ablation management and treatment decisions [98].

3.8 Sudden Cardiac Death (SCD) and Pathogenic Arrhythmias

One use of genetic testing involves the concern regarding sudden cardiac death (SCD) in a first-degree relative, particularly if it is premature. Approximately 40% of cardiac arrests are unexplained and may involve genetic issues of importance to family members. Identification of inherited conditions associated with sudden cardiovascular death in first-degree relatives of an SCD victim may impact future life decisions [99].

Genetic tests are available for specific arrhythmias including arrhythmogenic right ventricular cardiomyopathy (ARVC), Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), long QT syndrome (LQST), and short QT syndrome (SQTS) [100]. Approximately 50 genes can be assessed in a typical commercial arrhythmia panel. These tests have clinical utility in confirming the clinical diagnosis, in assessment of first-degree relatives, and future risk reclassification.

ARVC is a relatively rare inherited cardiac muscle disorder but is the most common cause of life-threatening arrhythmias and sudden cardiac death (SCD) in young adults and athletes. It is estimated to account for 10–20% of sudden cardiac death in young athletes. At least five mutated genes are related to ARVC: *PKP2*, *DSP*, *DSG2*, *DSC2*, and *JUP* [101]. It is present in one in 1000 to one in 5000 individuals (~0.1–0.02%). ARVC involves a protein complex that helps to maintain attachments between cells. ARVC replacement of normal cardiac cells with fibrous tissue can result in increased risk of ventricular tachyarrhythmia and sudden cardiac death [102, 103].

BrS is estimated to affect one in 2000 (0.05%) individuals and appears to be most frequent in people of Asian ancestry and is more common in men compared to women. BrS is caused by abnormal ion channel function and is associated with

increased risk for syncope, ventricular tachyarrhythmia, and sudden cardiac death [104–106].

CPVT is associated with cardiac calcium channel dysfunction and can be precipitated by stress-induced release of catecholamines and present as light-headedness, dizziness, and syncope and generally appear in childhood [107]. It is estimated to be present in one in 10,000 (~0.01%) individuals.

LQTS is reflected in prolongation of the QT interval and associated with increased risk for syncope, ventricular arrhythmia, and sudden cardiac death even in patients with normal heart structure [108]. Sixteen genes have been linked to LQTS [109]. There are 17 different subtypes of LQTS associated with monogenic mutations of 15 autosomal dominant genes [110]. Importantly, this diagnosis identifies treatment that can reduce life-threatening arrhythmias and include non-selective beta-blockers such as nadolol [111].

SQTS is characterized by shortening of the QT interval and paroxysmal atrial and ventricular tachyarrhythmias and is associated with an increased risk of atrial fibrillation and sudden cardiac death [112]. It is very rare with approximately 70 cases identified worldwide [113]. It is associated with mutations in at least eight genes and may have some overlap with Brugada syndrome [114]. Standard cardiovascular medications have a variable effect on electrocardiogram (EKG) characteristics. Hydroquinidine (HQ) prolongs the QT interval in SQTS patients, although whether it reduces cardiac events is currently unknown [115]. The utility of genetic arrhythmia testing should be guided by clinical assessment with forethought as to how the diagnosis would affect patient management.

3.9 Cardiomyopathy

Cardiomyopathy and heart muscle dysfunction have multiple etiologies, some of which have a genetic linkage. Cardiomyopathy genetics is complex with epigenetic and environmental factors playing a complicated and interactive role. Incomplete penetrance and variable expressivity are common. A phenotype-genotype based classification, and expert consensus statement, was proposed for cardiomyopathies and channelopathies in 2011 and supported by the World Heart Federation in 2013 [116]. By obtaining a genetic diagnosis, the clinical diagnosis can be confirmed, prognostication and risk stratification can be improved, and there may be useful knowledge in regard to treatment selection [117, 118]. For the preventive healthcare provider, an important benefit of genetic testing for cardiomyopathy polymorphisms in the proband is the ability to address risk status in first-degree relatives by cascade testing which can only occur when a causative genetic variant is detected in the proband. Genetic cardiomyopathy panels are available to the clinician and include approximately 100 or more genetic variants. Practical aspects of genetic testing for cardiomyopathies and channelopathies are an ongoing focus in cardiovascular research [119]. Five of these variants are the most common, and clinical guidance has been developed as an expert consensus statement by the Heart Rhythm Society and the European Heart Rhythm Association [120].

Hypertrophic cardiomyopathy (HCM) is characterized by myocardial hypertrophy and myocyte disarray [121]. When found in families, it is termed familial HCM. Patients with HCM are often symptom-free, but it can cause life-threatening heart rhythms. It is inherited in an autosomal dominant pattern and estimated to affect one in 500 individuals (0.2%). Dilated cardiomyopathy (DCM) is a thinning of a heart chamber wall. DCM usually, but not always, presents with heart failure. It is inherited in an autosomal dominant fashion in 90% of cases, and it is estimated that 50% of the 750,000 dilated cardiomyopathy cases in the USA are familial in nature [120]. Left ventricular non-compaction (LVNC) is characterized by abnormal left ventricular structure that results in a thick and spongy left ventricle [122]. It is a rare condition and estimated to affect ten in one million (0.0001%) individuals. Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVC) is a subtle disorder that affects a cardiac protein complex that maintains cell-to-cell connections [123]. It can involve weakening of the cardiac wall and increases the risk of sudden death particularly during exercise. ARVC is characterized by cardiac muscle cell death and replacement by fat and fibrous tissue in the right ventricle. It is estimated to occur in one in 1000 subjects (0.1%). It can be inherited in an autosomal dominant fashion and tends to run in families [124]. Noonan syndrome (NS) is a relatively uncommon multisystem disorder with clinical features such as facial dysmorphism, congenital heart defects, short stature, skeletal malformations, motor delay, learning disabilities, and impaired coagulation [125]. It is caused by mutations in the *PTPN11* gene, the *SOS1* gene, and the *RAF1* gene and inherited in an autosomal dominant fashion. Its prevalence is estimated to be one in 1000 (0.1%) or one in 2500 (0.04%).

3.10 Dyslipidemia

Plasma lipid levels are highly heritable traits. More than 50% of interindividual variation in LDL-C levels is attributed to genetic factors [126]. A seminal paper, published in 1992, reported that 77% of premature CHD patients expressed an inherited dyslipidemia and 54% of the first- and second-degree relatives expressed the same dyslipidemia [127]. Many genetic contributors to plasma lipid levels have been revealed by studies of Mendelian lipid disorders in families and association studies of lipid levels in the general population. Mendelian lipid disorders result from mutations of severe functional consequence in single genes, whereas variation in lipid levels in the general population appears to be the result of weak-to-moderate genetic variants in multiple genes in combination with environmental factors [128].

3.11 Hypercholesterolemia

Markedly elevated blood LDL-C is a prime example of the clinical utility for genetic testing. DNA sequencing studies have revealed the limitations of specific LDL-C cut points for the identification of patients with pathogenic familial

hypercholesterolemia (FH) variants. Indeed, LDL-C levels are elevated in patients with FH genetic variants, but there is a wide range of LDL-C levels, and individual patients may have a variant and only moderately elevated LDL-C [129, 130]. The combination of an FH variant and elevated LDL-C increases risk dramatically. In patients without an FH variant and LDL-C ≥190 mg/dl, the CAD risk increases sixfold, but in subjects with LDL-C ≥190 mg/dl and a pathogenic variant, a 22-fold increased risk has been noted. Thus, the presence of a pathogenic variant in addition to elevated LDL-C identifies an extremely high-risk group of patients.

In the clinical presentation of markedly elevated blood LDL-C, four genes are generally sequenced in many commercial laboratories: the apoprotein E (*APOE*) gene, the low-density lipoprotein receptor gene (*LDLR*), the apolipoprotein B or ApoB gene (*APOB*), and the proprotein convertase subtilisin/kexin type 9 gene (*PCSK9*). However, patients can have clinical FH without a known variant being identified. The lack of a pathogenic variant on genetic testing does not exclude the diagnosis of FH. Familial heterozygous hypercholesterolemia (FH) has been historically defined based on family history and LDL-C values. In order to make a clinical diagnosis of FH, an eight-point diagnosis system has been utilized that assigns points to characteristics of FH with possible FH defined as 3–5 points, probable FH as 6–8 points, and definite FH as >8 points [131]. However, FH is a monogenic disorder, and the presence of a causative mutation in the *LFLR*, *APOB*, or *PCSK9* genes provides 8 points just by itself. This becomes relevant when medical insurance reimbursement for some treatments becomes a clinical issue. Many commercial companies offer gene sequencing for causative mutations for FH, which generally costs $350–$500. The prevalence of autosomal dominant familial hypercholesterolemia is approximately one in 200–400 (0.5–0.25%) individuals but may be more frequent in some populations such as French Canadians, Lebanese, and Ashkenazi Jews. The American College of Cardiology published the FH recommendation of a Scientific Expert Panel in 2018 [132].

3.12 ApoE Genotype

The most common gene affecting blood LDL cholesterol levels is apo E, located on chromosome 19, which has three major genotypes, designated as E2, E3, and E4 [133]. The most common allele, E3, has a frequency of approximately 0.78, while E4 has a frequency of 0.15, and E2 has a frequency of 0.07. While these are the most common genotypes, analysis of amino acid substitution has revealed at least 25 mutations in apoprotein E. The plasma lipoprotein profile that results from genotype differences relates to poor binding to cell wall receptors in individuals with the apoE2 genotype compared to those with the common apoE3 [134]. Conversely, enhanced binding to LDL cell surface receptors in individuals with the apoE4 genotype enhances clearance of apoE4-containing lipoproteins and suppression of LDL receptors, resulting in increased plasma LDL-C. In patients with elevated LDL-C, the apoE4 genotype is a common contributor to hypercholesterolemia and can be

found in approximately 25% of patients with elevated LDL-C [135]. The clinical utility lies in the finding that subjects with the E4 genotype can respond to low-fat diets with significantly greater LDL-C reduction than subjects with the normal E3/3 genotype [136]. The disease, type III hyperlipoproteinemia, is a genetic example of an interaction of the apoE2 homozygous state with another genetic or environmental factor leading to marked accumulation of triglyceride-rich lipoprotein remnants and accelerated atherosclerosis. Over 90% of individuals with type III hyperlipoproteinemia are apoE2 homozygotes; however, the disease is caused by interaction of the apoE2/E2 state with another genetic or environmental factor because while about 1% of the population express the *E2/2* genotype, only 2% of these develop type III hyperlipidemia, and most individuals with *E2/E2* do not exhibit the abnormal lipid profile.

3.13 LDLR Genotype

It is estimated that approximately 60–80% of FH cases have a variant in the *LDLR* gene and >90% of FH-causing variants are in the *LDLR* [137, 138]. The impact on cardiovascular risk is profound. If left untreated, patients with these variants and elevated LDL-C are approximately 20 times more likely to experience a CV event compared to those without the variant. Unfortunately, those with two variants have a high likelihood of experiencing a cardiovascular event before the age of 20 years. It has been estimated that approximately 1000 *LDLR* variants may be pathogenic [139]. Thus, a single SNP analysis may miss the presence of many variants, and gene sequencing of the *LDLR* is necessary to detect such a large group of possible pathogenic variants.

3.14 APOB Genotype

It is estimated that approximately 6–10% of FH clinical cases have a variant in the *APOB* gene [140]. The phenotypic condition known as familial defective ApoB (FDB) has been diagnosed when LDL-C elevation is less severe than seen with the LDLR variant but still markedly elevated. It was first described in 1987, and while markedly elevated LDL-C is present, classic FH clinical findings, such as tendon xanthoma, are less frequent than in patients with an *LDLR* variant [141]. It results in a glutamine substitution for arginine and noted as rs5742904, and more recently, a second mutation has been identified as rs144467873. While generally thought to be much less common than the *LDLR* variants, a study in the Swiss population reflected a prevalence of one in 230 (0.4%) concentrated in a specific geographic Swiss locale. The prevalence has been reported to be low as one in 5800 (0.02%) in the Latino population. Treatment of elevated LDL-C due to the *APOB* variant is similar to that of patients with an *LDLR* variant.

3.15 Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Genotype

It is estimated that <3% of FH cases have a variant in the *PCSK9* genotype which is a gain-of-function variant that results in fewer LDL receptors on the cell surface and markedly elevated blood LDL-C concentrations [142]. *PCSK9* regulates LDLR degradation, and increased (gain of function) *PCSK9* activity reduces LDLR levels with resulted elevations in LDL-C [143]. This relatively recent discovery has led to the development of *PCSK9* inhibition therapy. In patients with a gain-of-function mutation in *PCSK9*, treatment with a *PCSK9* inhibitor (alirocumab) reduced LDL-C by 73% [144]. In patients already treated with statin therapy and with a baseline mean LDL-C of 92 mg/dl, the FOURIER trial reported that the addition of *PCSK9* inhibition resulted in a 59% reduction in LDL-C and a mean LDL-C of 30 mg/dl [39]. The diagnosis of a *PCSK9* variant allows the opportunity to make a genetic pathophysiologic diagnosis and initiate family cascade testing for the same variant. Genetic risk scores appear to have utility in the identification of a patient subgroup who derive the most benefit from *PCSK9* inhibition. A FOURIER substudy revealed that patients without multiple clinical risk factors or high genetic risk had a low event rate and did not appear to derive benefit from evolocumab over 2.3 years. Conversely, patients with multiple clinical risk factors but without high genetic risk had intermediate risk and intermediate risk reduction. Patients with a high genetic risk, regardless of clinical risk, had a high event rate and derived the greatest relative and absolute benefit from evolocumab [145].

3.16 Sitosterolemia

A relatively rare autosomal recessive genetic disorder of plant sterol metabolism can result in markedly elevated LDL-C, clinical findings, and premature CHD as seen with FH. Sitosterolemia has been described as "pseudo-familial hypercholesterolemia." This condition is characterized by increased absorption and decreased biliary excretion of plant sterols and cholesterol, resulting in significantly elevated serum concentrations of plant sterols, such as sitosterol and campesterol [146]. Sitosterolemia is caused by loss of function and missense mutations in either ATP-binding cassette (ABC) subfamily G member 5 or member 8 (*ABCG5* and *ABCG8*) [147]. It is estimated that its prevalence is one in 200,000 (0.0005%) individuals. In patients with this condition, ezetimibe can dramatically reduce LDL-C levels.

3.17 Polygenic Lipid Disorder Testing

High blood cholesterol from accumulation of many small-effect SNPs can be indistinguishable clinically from a single gene rare variant cause [148]. In approximately one-third of clinical FH cases, large-effect mutation may not be identified, but a

high polygenic score may be appreciated. This has also been noted in patients with extreme HDL-C values [149]. Large SNP panels, comprised of tens to millions of SNPs that have been reported to have some relationship to a lipid disorder or concentration, have been developed that can provide diagnostic information on an individual patient basis for specific SNPs or gene sequencing [150]. When the results of SNP testing with these panels are entered into a scoring scheme, it results in a score that reflects the genetic contribution to the clinical dyslipidemia. In general, the higher the score, the more severe the dyslipidemia. Many of these polymorphism effects can be influenced by gender, ethnicity, age, and lifestyle issues [149, 151]. A genetic score for non–high-density lipoprotein cholesterol based on 345 SNPs has been reported to be significantly associated with the extent of coronary atherosclerosis, as determined by coronary angiography or coronary calcium scanning in Icelandic adults [152]. The association persists even after accounting for LDL-C values.

The therapeutic implications of these polygenic dyslipidemia tests and scores have received less research activity when compared to the LDL-C affecting variants. Declining test costs make it possible to consider genetic testing in individual dyslipidemic patients or their first-degree relatives. For polygenic lipid disorder testing, the specific clinical utility of a score based on these tests has not yet been clearly established, and there are currently no clinical guidelines for such genetic testing in dyslipidemia [153]. The implications of specific SNPs often are affected by gender, ethnicity, and lifestyle factors. One example is the lipoprotein lipase gene and SNP rs326 which showed in the CARDIA study significant relationships to plasma triglycerides and HDL-C and change over time [154]. Interpretation of these results can be challenging, and clinical utility remains an incomplete science. Further, while over 50 genetic risk scores have been suggested, there is as yet no consensus on the composition of a specific risk score for specific patient conditions that has been well validated in regard to its clinical utility [155]. At the present time, the decision on how and when to use genetic risk scores is left up to the individual health-care provider.

4 Conclusions

Preventive cardiology has a long history, and in the last 50 years, the field has appropriately focused on disorders that can be diagnosed with available laboratory test methods. Hypercholesterolemia and dyslipidemia are among the most prominent examples. However, despite progress in the recognition of high-CAD-risk individuals and effective blood lipid treatment, a large reservoir of CAD risk remains. This is the unmet clinical need that genetics can help to fill.

During this time period, it was well known that a family history of CAD was one of the most powerful, if not the most powerful, characteristics in a patient's personal medical history that reflected increased CAD risk. However, until relatively recently, the clinical medical profession lacked available, and affordable, genetic laboratory tools that would permit practical and common application of knowledge

gained through research studies to patient management. This has all changed in the past decade, in part due to increased knowledge regarding genetic differences and CAD risk and the dramatic cost reduction in clinical genetic testing.

Multiple clinical laboratories now make available a plethora of genetic tests to the health-care provider interested in preventive cardiology. These tests may cost ~$50 for some SNP tests and ~$400 for gene sequencing specific to a disorder. Unlike clinical lipid testing that may occur three to four times per year, these genetic tests are once in a lifetime tests and need not be repeated. It also makes affordable cascade testing available to first-degree relatives and makes the concept of a "Family Heart Clinic" a reality [17].

Thirty years ahead of his time, Karl Berg wrote:

> Knowledge of genetic factors in the etiology of coronary heart disease has not so far been adequately utilized in attempts to combat premature CHD. The time has now come to utilize genetic information in a setting of family-oriented preventive medicine. This approach would greatly improve the efficiency of preventive efforts, utilizing predictive genetic testing and targeting counseling on those who need it most." [18]

It is time to incorporate appropriate genetic testing in the preventive cardiology setting and help to fill the unmet need of residual CAD risk.

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Exercise Electrocardiographic Stress Testing

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Summary

- EECG provides essential information for diagnosis, prognosis, and management of patients with cardiovascular disease by a safe, relatively inexpensive method that does not use ionizing radiation.
- EECG can provide objective evidence of myocardial ischemia and thereby of CAD, the leading cause of mortality in our society.
- Large studies correlating exercise-induced ST-segment deviation with angiographically diagnosed CAD indicate that sensitivity for CAD is 60–70% and specificity is closer to 80%.
- Comparisons of the diagnostic utility of EECG to noninvasive imaging tests have been based exclusively on the ST-segment response to exercise, thereby excluding vital prognostic information gained from exercise testing.

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- The traditional formula for peak HR (target HR = 220 minus age) is based on convention rather than scientifically derived. Therefore, this HR should not be an indication to terminate an exercise test if the patient has no abnormal signs of symptoms.
- Exercise-induced ischemic ST depression does not localize the area of myocardial ischemia or the diseased coronary artery. If this information is desired, a cardiac stress imaging test should be performed.
- Transient exercise-induced ST-segment elevation during EECG in leads without a pathologic Q wave is usually related to severe spasm of a "normal" or atherosclerotic coronary artery. It reflects transmural myocardial ischemia and localizes the area of ischemia and involved artery.
- In low-intermediate-risk women and men evaluated for chest pain, EECG is usually considered the first cardiac test for symptom evaluation. The sensitivity and specificity for detection of CAD are comparable in men and women ≥10 years post-menopause.
- The most important predictors of prognosis from EECG are non-ECG variables such as functional capacity (METs) and heart rate recovery.
- It may be reasonable to consider EECG in selected asymptomatic individuals with a high coronary risk profile and a family history of premature CAD or in sedentary middle-aged or elderly persons prior to engaging in an exercise program.

1 Introduction

After its introduction almost a century ago, formal exercise testing has evolved into one of the most widely employed noninvasive methods for assessment of the clinical and physiologic status of the heart and circulatory system. This evolution has been documented by a number of excellent reviews during the past several decades [1–4]. The extensive and vital information obtained during standard exercise electrocardiography (EECG) includes symptoms, functional capacity (FC) and the responses of heart rate (HR), blood pressure (BP), and electrocardiogram (ECG), as well as unique non-ECG features (functional capacity [FC], heart rate recovery [HRR]) of significance for diagnosis, prognosis, and management of cardiovascular disease (CVD).

Master and Oppenheimer introduced clinical exercise testing in 1929 to assess "circulatory efficiency" [5]; an ECG was not included in the procedure, and the treadmill was not yet applied. In 1942, Master and colleagues published their first paper on EECG [6]. These seminal studies presaged what were to become major contemporary goals of exercise testing: (1) exercise-induced ECG evidence of myocardial ischemia and thereby coronary artery disease (CAD) and (2) recognition of the clinical importance of functional capacity (FC) and other non-ECG exercise variables. The twentieth century epidemic of ischemic heart disease aroused concern for

early detection of CAD, which EECG offered by noninvasive provocation of ischemic ECG alterations. Subsequently, the non-ECG information afforded by EECG has assumed increasing attention for its unique diagnostic and prognostic utility [2, 4, 7–10]. Exercise tests with imaging are now the most frequently performed of all noninvasive cardiac stress modalities in patients younger than 65 years, but EECG has maintained a steady rate as reflected by a recent report of over 2 million referrals for all noninvasive cardiac stress tests during a 4-year period [11]. Single-photon emission computed tomography (SPECT) was the most frequent test and EECG was second. Recent publications have suggested that EECG is underused in patients with a high exercise capacity, in many of whom it can obviate the need for costlier stress imaging tests, some of which use ionizing radiation [7–10].

The goal of this chapter is to consolidate current knowledge and extend it with a focus on further advances in exercise electrocardiographic testing (EECG).

2 Exercise Physiology and the Cardiac Response

EECG is based on increased intensity of dynamic exercise which requires an increased supply of oxygen and substrate to the working muscles, i.e., the lower extremity muscle groups during treadmill or other methods of dynamic lower extremity exertion, e.g., cycle ergometry. Increased work is accomplished by a rise in HR and cardiac output, and regional dilation of resistance vessels augments oxygen supply and its extraction from perfusing blood. The increase in cardiac function is reflected by elevation of major determinants of myocardial oxygen consumption (HR, BP, myocardial contractility) [12] (Table 1). HR and systolic BP are readily measured during EECG, and their double product (HR X systolic BP) closely correlates with relative myocardial oxygen demand [12] (Table 2). Thus, increase in the exercise double product yields an approximation of the relative increase in myocardial oxygen consumption and thereby of coronary blood flow. In individuals with normally patent coronary arteries, coronary blood flow can increase fivefold or more to support augmentation of total body and cardiac work. The former can be directly measured as total body oxygen consumption (VO_2) as performed during cardiopulmonary exercise testing [16]. The latter is not usually measured during standard EECG, but nomograms have been developed to estimate VO_2 in terms of METs (Table 2) based on the external work performed during a standard exercise test [13]. Figure 1 is a nomogram of the relationship between exercise capacity and

Table 1 Determinants of myocardial oxygen demand

Major	Minor
Heart rate	External work (load x shortening)
Left ventricular systolic pressure (afterload)	Activation energy
Left ventricular volume (preload)	Basal energy
Myocardial contractility	

Table 2 Terms used to describe performance and interpretation of exercise test and performance

These equations (and nomograms, Fig. 1) provide standards for comparing individuals' exercise performance with reference data for age and sex	
Maximum age-predicted heart rate	Men: 208 – (0.70 × Age) Women: 206 – (0.88 × Age)
METs: Exercise capacity is frequently expressed in terms of METs which provide an estimate of total body work in terms of total oxygen consumption (VO_2). One MET = basal oxygen consumption (3.5 cc/kg/min); five METs reflect a light workload; ten METs indicate high exercise capacity	
Average peak METs based on age and sex	Predicted METs = 16.2 – 0.11 (age)
Predicted METs for age and sex	Men: 18.0 – (0.15 × Age) Women: 14.7 – (0.13 × Age)
Term	*Definition*
True positive (TP)	Abnormal result associated with disease
False positive (FP)	Abnormal result associated with no disease
True negative (TN)	Normal result associated with no disease
False negative (FN)	Normal result associated with disease
Sensitivity	Percent of TP/number of subjects with disease × 100
Specificity	Percent of TN/number of subjects without disease × 100
Positive predictive value (PPV)	TP/TP + FP × 100
Negative predictive value (NPV)	TN/TN + FN × 100
Total predictive accuracy of a test	TP + TN divided by total number of tests
Double product (DP)	HR x systolic blood pressure
This parameter is closely related to myocardial oxygen demand and coronary blood flow, and symptoms of myocardial ischemia (e.g., angina) are precipitated at the same DP in a given individual under the same ambient conditions	
Duke treadmill score (Bruce protocol): Min of exercise *minus* 5 × mm ST-segment depression *minus* 4 × degree of chest pain (0 = no chest pain, 1 = mild, 2 = strong enough to stop exercise)	

Based on data from Refs. [1, 4, 14, 15]

age in sedentary and physically active males. Similar nomograms have been published for women [17].

In the presence of obstructive CAD, coronary blood flow reserve is limited, which may preclude an adequate increase in regional myocardial perfusion at augmented

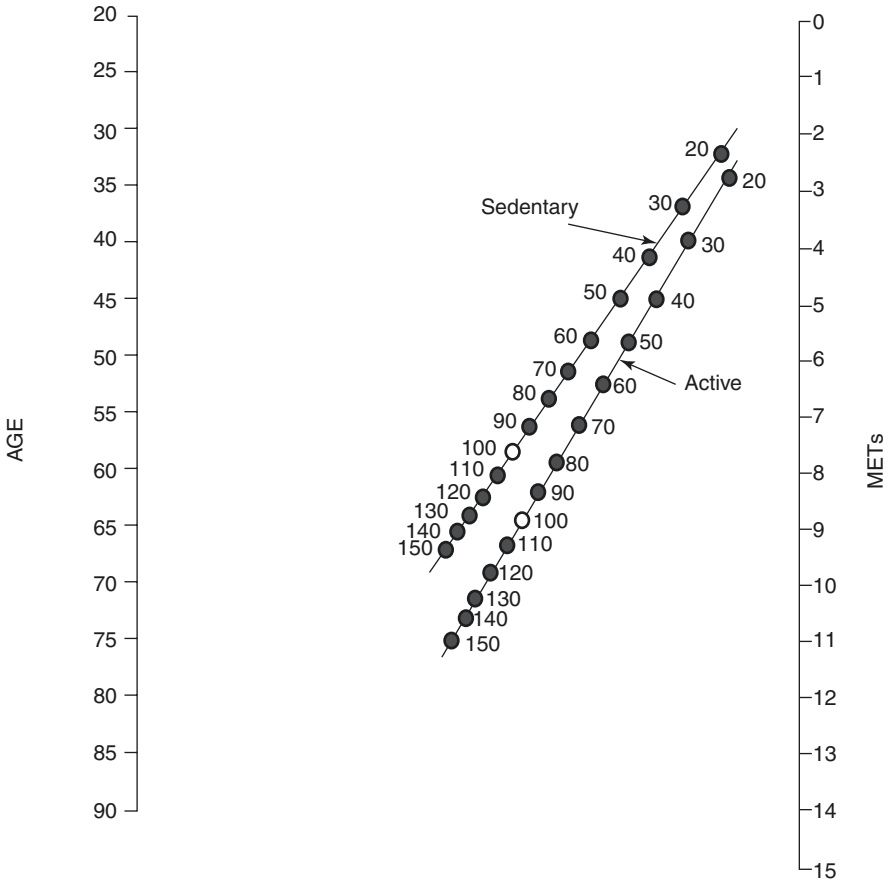

Fig. 1 Nomogram of percent predicted functional capacity (METs) for age in sedentary and active men referred for exercise testing. (Reprinted from Morris et al. [13]. With permission from Elsevier)

cardiac work, thereby resulting in a disparity between myocardial oxygen demand and supply, which can produce myocardial ischemia. This disparity generally occurs when coronary lumen diameter is reduced by ≥70%; the more severe the coronary stenosis, the greater the limitation of coronary flow reserve [18] (Fig. 2). These relationships are the basis for unmasking of myocardial ischemia, detected by characteristic ECG alterations, in the controlled setting of the exercise testing laboratory. Ischemia and myocardial dysfunction may be detected by characteristic symptoms, specific ECG alterations, and abnormalities of non-ECG variables.

A frequently used testing method is the Bruce protocol (Fig. 3), in which the increased exercise intensity of successive stages may be excessive for patients with limited capacity. In these instances, a protocol with less intensive stress, such as the modified Bruce test, is commonly used (Fig. 3). Age-predicted maximum HR

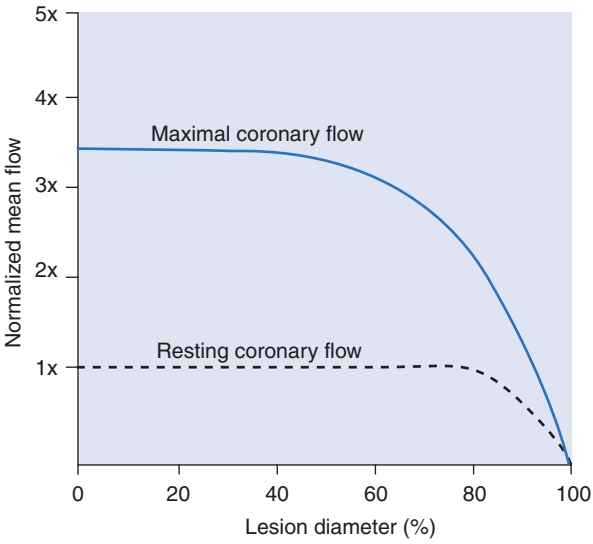

Fig. 2 These curves from an experimental study depict the response of coronary blood flow reserve (upper curve) and resting coronary blood flow to graded coronary artery narrowing. Resting flow does not decline until coronary lumen diameter is reduced by approximately 80%, whereas coronary flow reserve starts to decrease with approximately 50% narrowing of coronary lumen diameter. (Reprinted from Gould [18]. With permission from Elsevier)

is the rationale for selecting target HR which presumably provides an adequate level of intensity to determine if ischemia can be induced. Age-predicted maximum HR is generally estimated by the following equation: 220 - age = maximum HR. It has been widely accepted that an HR at least 85% of age-predicted maximum is required to consider a stress test adequate for detection of ECG evidence of myocardial ischemia. If this exercise intensity is reached, the EECG can be interpreted as sufficient for unmasking ischemic ECG abnormalities (positive test) or documenting absence of ischemic ECG alterations (negative test). If the ECG remains normal but peak HR during the test is <85% of age-predicted maximum, the test is considered nondiagnostic because of failure to reach "target" HR.

This approach to age-predicted maximum HR is based on convention rather than scientific study and persists in the current era. It is reasonable for estimating average age-predicted maximum HR in populations, but the spread around the mean is wide (10–25 beats/min), yielding either an excessive or inadequate target HR for many individuals. More rigorous methods based on large studies report more accurate relationships for age-predicted maximum HR and total work during exercise testing [4, 14, 15, 19–21] (Table 2). However, in a small study performed in our laboratory (n = 164), the positive predictive value of EECG increased at HRs between 65 and 80% and plateaued above 80% [22]. This concept requires further study. In addition, instead of reporting EECG as dichotomously positive or negative, it is more useful to interpret an abnormal exercise test in terms of the risk conveyed or degree of abnormality based on the composite of data from the test, including ECG findings and other information such as functional capacity [1–4]. Terms commonly used in describing the results of exercise testing and performance are described in Table 2.

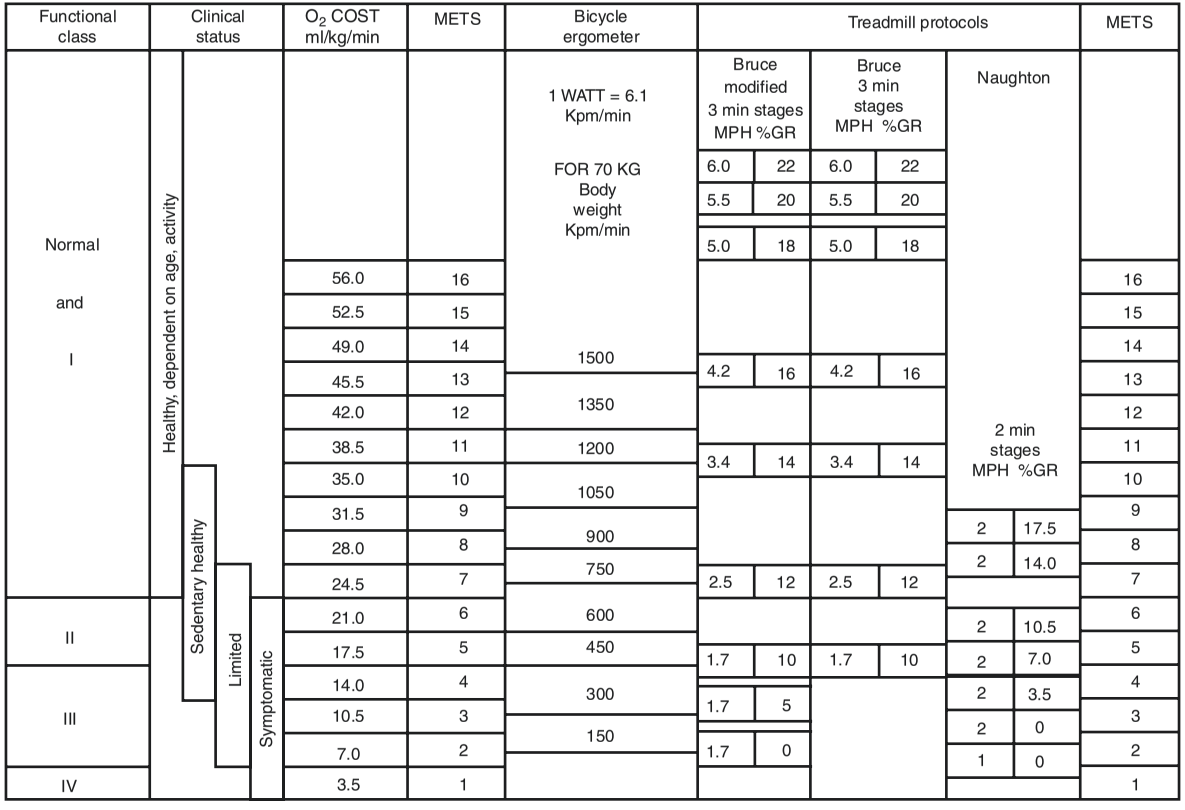

Fig. 3 Protocols of several types of exercise tests. The relationship of exercise workload (total body O_2 cost) and metabolic equivalents (METs) to stages of the tests is shown. Functional class refers to New York Heart Association. (Reprinted from Fletcher et al. [1]. With permission from Wolters Kluwer Health, Inc.)

Several of the relationships in Table 2 warrant brief commentary: (1) The most frequently used terms to describe the diagnostic utility of EECG are sensitivity and specificity. (2) It is helpful to understand sensitivity and specificity as follows: the calculation of sensitivity includes only abnormal descriptors: proportion of positive tests in individuals with the disease in question. The calculation of specificity involves only normal descriptors: proportion of negative tests in individuals without disease. (3) However, to the clinician observing a negative or positive result of an EECG, the negative predictive value (NPV) and positive predictive value (PPV) are of more immediate interest than sensitivity or specificity because they reflect the probability that a given positive or negative test result is correct. (4) The foregoing terms "disease" and "no disease" pertaining to the coronary arteries are defined by the standards set for a specific study. Thus, physiologically significant CAD is commonly defined as ≥70% narrowing of coronary artery lumen diameter determined on coronary angiography. Less than 70% coronary narrowing is broadly considered not to be severe enough to cause ischemia at increased myocardial oxygen demand. The 70% coronary narrowing threshold that defines a significant coronary lesion is an over-simplification which has served reasonably well for clinical purposes. However, it omits important factors that contribute to the physiological significance of a coronary lesion such as its length, lesions in series, vasomotion, response to mediators, and the presence of collateral vessels. The term "specific" is frequently and incorrectly used in cases in which PPV is appropriate. For example, an EECG demonstrating >2.0 mm of ST depression should be described as having a high PPV for ischemia rather than being specific for ischemia.

3 Indications for Exercise Testing

There are numerous indications for EECG, of which the detection of exercise-induced myocardial ischemia, and thereby likelihood of CAD, is the most frequent [1–4, 11]. Symptoms of CVD are wide-ranging and varied, and for many of these, there is a role for EECG in ascertaining clinical impairment and evidence of the underlying condition. Relatively common indications for EECG, in addition to chest pain, include dyspnea, palpitations, fatigue, and syncope. EECG also has an important role in prognosis and management of established CVD. This noninvasive method can unmask symptoms of CVD and their thresholds, estimate extent of disability from estimated functional capacity, provide prognostic data, assess efficacy of medical and interventional therapy, and indicate the basis for an exercise prescription. In patients with established CAD, valvular disease, cardiomyopathy, or congenital heart disease, EECG offers quantitative data to help monitor disease course and the timing of interventional therapy based on both its ECG and non-ECG data.

However, the application of EECG in healthy, asymptomatic individuals has been a continuing concern because of the high rate of false positive tests in this population [1–4, 23]. Therefore, there should be specific indications for EECG in

asymptomatic persons, such as a high coronary risk profile and an early family history of CVD, or for sedentary middle-aged/elderly individuals prior to initiating an exercise program.

4 Administration of Exercise Electrocardiography

Serious complications of exercise treadmill testing are rare: the rate of serious complications is reported as ≤5 per 10,000 tests, and mortality is less than one-tenth the rate of these nonfatal complications [4]. Individuals undergoing EECG should be clinically stable, and a brief history and examination should confirm their capacity for engaging in the demands of the test. EECG is supervised by a physician (or other trained clinician, e.g., physician assistant, nurse practitioner). The ECG extremity leads should be placed on the subject's torso: lower extremity leads on the lower abdomen above the inguinal ligament and upper extremity leads on the infraclavicular areas slightly medial to the shoulders. In addition, EECG requires (1) a normal baseline ECG with isoelectric ST segments, especially if ischemia detection is the indication and (2) the subject's ability to perform an adequate level of exercise, which should be confirmed by a brief history and cardiopulmonary examination. The exercise laboratory should include an ECG workstation on which data can be continuously observed and recorded at the following points: standing rest, each test stage, occurrence of symptoms, or ECG abnormalities, and during the post-exercise period until data have returned to baseline. Communication with the subject during the test is essential in order to be cognizant of the subject's symptoms or need to discontinue the test. BP should be measured at rest and at least once during each stage of the test which should be initiated at a low intensity, "warm-up" level for a brief period (15–20 seconds) to ensure balance and steady gait.

Most EECG protocols comprise 2- or 3-min stages of progressive treadmill speed and grade (Fig. 3). The subject should be checked by brief communication at each stage and notified before the stress level is advanced to the next stage. During the test, subjects may hold the handrails lightly for balance, if necessary. Gripping the rails increases blood pressure and results in a falsely elevated measure of work capacity (METs) (Table 2). The test usually proceeds to volitional fatigue (maximum effort) unless there is need to discontinue it earlier because of symptoms or objective evidence of marked abnormality.

Endpoints include severe chest pain or dyspnea, dizziness, unsteady gait, major ST segment depression (>2.5 mm), sustained ventricular tachyarrhythmia, non-sustained ventricular tachycardia (≥3 consecutive beats, rate ≥100/min), and decrease in systolic BP of ≥10–15 mmHg or to less than the standing BP at rest. Because of its inaccuracy, there is usually little or no reason to use 85% of age-predicted maximum HR as a test endpoint, except in situations such as the early months following myocardial infarction. Subjects should be discharged following the test after HR, BP, and ECG have returned to baseline. Post-exercise BP may be

lower after, than before, the test; this is a normal response if the decrease is modest and the patient is stable.

5 Detection of Exercise-Induced Myocardial Ischemia

Among the multiple reasons for performing EECG, chest pain is the most frequent, typically to aid in the detection or exclusion of CAD by provocation of exercise-induced symptoms and/or signs of ischemia. A variety of exercise protocols are shown in Fig. 1 that are appropriate for differing patients' indications and estimated functional capacity. The initial stress test for evaluation of chest pain in low-risk patients has been EECG without imaging [24, 25] if the baseline ECG is normal, evaluation suggests that the subject can exercise adequately, and estimation of the site and size of an ischemic cardiac defect is not the goal. If the latter data are necessary, a stress imaging study is indicated.

Exercise-induced ST-segment depression in an ECG that is normal at rest has been the hallmark of ECG evidence of myocardial ischemia and thereby of significant CAD. The diagnostic implications of this finding are the same whether ST depression occurs during exercise or only in the post-exercise recovery phase [26]. Figure 4 displays examples of normal and ischemic ST-segment responses to exercise. The latter is defined as ≥0.1 mV ST-segment horizontal or downsloping depression (1.0 mm = 1.0 mV at normal ECG standardization) for a duration of 60–80 msec starting at the J point (1.0 mm = 1.0 mV at normal ECG standardization). With high HRs at which the ST segment joins the initial ascent of the T wave in <80 msec, ST depression for 60 msec is considered sufficient to indicate ischemia. The PPV of ST depression for obstructive CAD increases with greater degrees of exercise-induced abnormalities of the ST response as well as other EECG variables such as HR, BP, and FC. Figure 4 reveals the most obvious ST-segment abnormality (deep, downsloping depression) compared to examples in the figure with less aberration of the ST segment. Thus, it has the highest PPV for CAD, barring any of the multiple factors that can alter the ST segment in the absence of ischemia such as left ventricular hypertrophy, left bundle branch block, drugs, metabolic derangements, and nonspecific changes.

Ischemia is most frequently detected by the lateral precordial leads ($V_{5,6}$), likely related to their position on the chest in relation to the major mass of the left ventricle. Exercise-induced ST depression that is isolated to the inferior leads is associated with a high rate of false positive results that has been attributed to the effects of atrial repolarization on the ST segments in these leads [27, 28]. By contrast, the effect of atrial repolarization on the ST segments of the lateral leads is minimal. Figure 5 displays representative ECG strips at progressive stages of a patient's EECG. Notable findings in these tracings are the normal baseline ECG, ischemic ST depression prior to onset of chest pain, and marked ST depression at maximum exercise with return toward pre-exercise appearance in the posttest phase. The onset of ischemic ECG alterations prior to symptoms of ischemia is common and

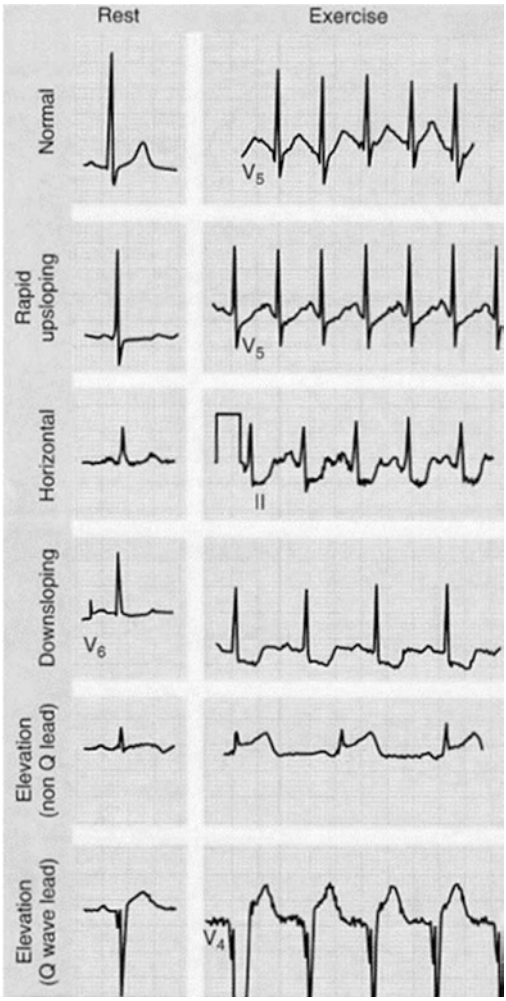

Fig. 4 Examples of ST-segment responses during exercise testing. The top row shows a normal isoelectric ST segment in a resting electrocardiogram; the successive examples, from upper to lower, display increasingly abnormal ST responses during exercise. "Rapid upsloping" ST depression is a common, normal finding if the ST segment is depressed <1.0 mm at 60–80 msec after the J point. "Minor ST depression" shows a noninterpretable ST segment because of the baseline artifact. Ideally, a stable baseline with three consecutive complexes is standard for optimal test interpretation. In the "slow upsloping" example, the ST segment is minimally upsloping and is positive for ischemia with ~2.0 mm ST essentially horizontal depression. "Horizontal" demonstrates >3.0 mm ST depression that is also positive for ischemia, and "Downsloping" reveals J point depression of >2.0 mm with further depression of the ST segment after the J point. The last two examples demonstrate exercise-induced ST elevation in an ECG lead with and without a pathologic Q wave. The first is positive and consistent with coronary spasm occurring during exercise. The last reflects a left ventricular wall motion abnormality without ischemia. Note that the resting examples all show an isoelectric ST segment, allowing meaningful interpretation of ST deviation during exercise. (Reprinted from Chaitman [2]. With permission from Elsevier)

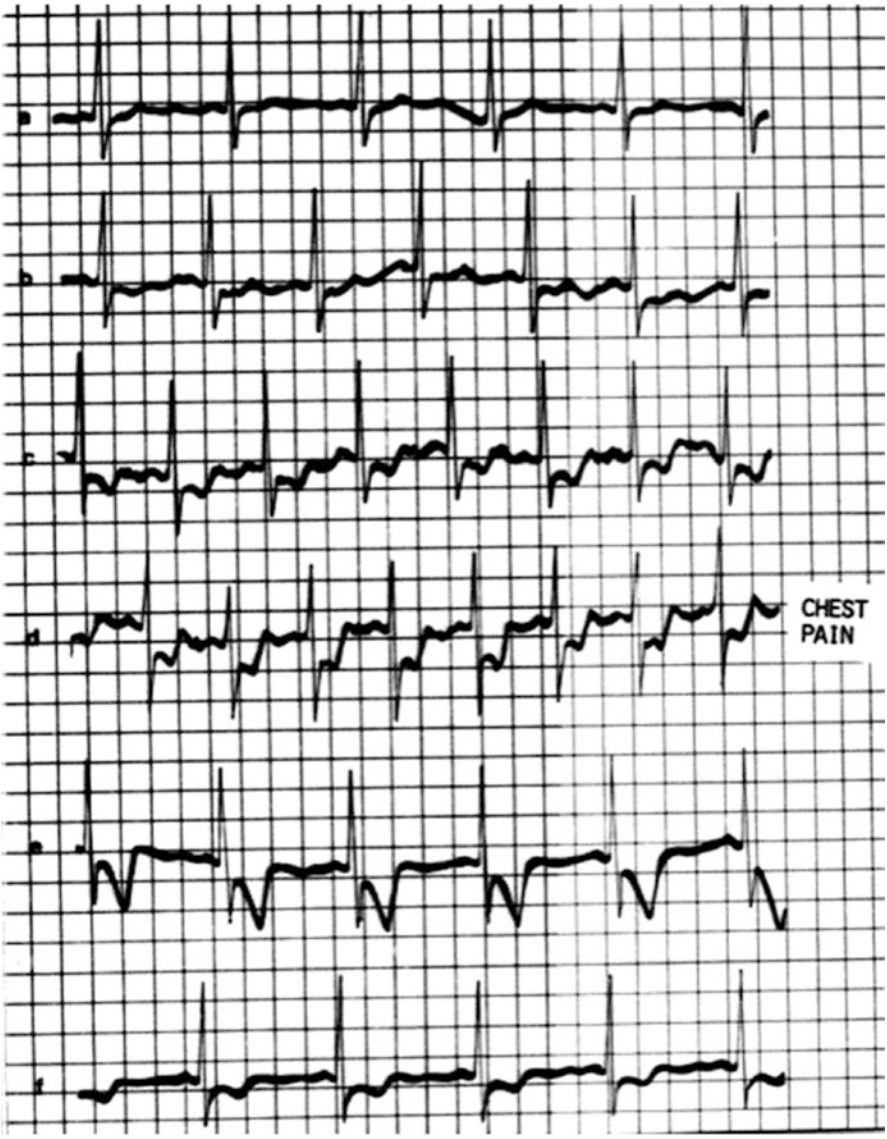

Fig. 5 The electrocardiographic (ECG) record of a progressive exercise test of a middle-aged man. Top line of ECG strip (lead V_5): resting ECG, heart rate (HR) 68/min, isoelectric ST segment. 2nd line: HR has increased to 88/min; ST segment now shows mild depression. 3rd line: HR is 100/min, ST segment shows ischemic depression of 2–3 mm, and the test is positive for ischemia. 4th line: HR 107/min, ST segment depressed 4–5 mm, and chest pain has occurred. 5th line: post-test HR has decreased to 68/min, and there is marked T wave inversion which resolved in 5 minutes. The test shows several key points regarding exercise-induced myocardial ischemia: chest pain occurs later than ECG evidence ischemia, which is initially "silent." The test is markedly positive (4–5 mm ST depression) and accompanied by symptoms, suggesting a high positive predictive value for coronary artery disease or other cause of ischemia. This conclusion is supported by the relatively low HR (100/min) at which the test became positive for ischemia

is an example of "silent myocardial ischemia." It is recognized that in the ischemic cascade, symptoms usually occur after objective evidence of ischemia detected by imaging and ECG findings, suggesting that symptoms are usually less sensitive than ECG or imaging methods for detection of ischemia [29].

The diagnostic accuracy of EECG for detection of CAD based on the standard of coronary angiography in numerous studies has varied widely as reflected by a meta-analysis of 147 reports from over 47,000 patients [30]. The sensitivity of EECG for detection of significant CAD averaged 66% (range, 23–100%), and specificity was 84% (range, 17–100%). These results demonstrated that EECG was associated with relatively high rates of false negatives (about one-third) and lower rates of false positives (about 15%). By contrast, in over 800 patients specifically presenting with angina, all of whom underwent both angiography and EECG, sensitivity for CAD was only 45%, and specificity was maintained at 85%, indicating the effect of decreased referral bias that favors angiography in higher-risk patients [31]. If the ST segments in the baseline ECG are abnormal (depressed or elevated) and the indication for the test is detection of ischemia, it is prudent to choose a stress imaging study because baseline ST-segment deviation precludes reliable interpretation of further exercise-induced alterations. Special criteria for ischemia in ECGs with baseline ST abnormality have been proposed, but their reliability is inadequate for clinical use.

Many factors influence sensitivity and specificity of EECG including pre-test probability of CAD, abnormal baseline ECG, valvular heart disease, left ventricular hypertrophy, cardiac drugs, equivocal ST responses, and "referral bias." The latter refers to preferential angiography in patients with positive exercise tests or a history of a coronary event compared to lesser rates of angiography in low-risk patients. This practice increases sensitivity of EECG for CAD and reduces specificity. Extent of CAD also strongly influences EECG results. In patients with left main and three-vessel CAD, false negative results are unusual in contrast to results in patients with single right or left circumflex CAD, in which a majority of results are false negatives. By contrast, isolated left anterior descending CAD is usually associated with a sensitivity greater than 50%. Of note, many patients with ischemic ST depression on EECG whose functional capacity is $\geq$10 METs have an adequate-excellent prognosis, reflecting the predictive importance of functional capacity, a non-ECG variable of EECG [2, 4, 7–10].

6 Exercise-Induced ST-Segment Elevation

This is a potentially ominous finding that reflects transmyocardial ischemia/injury during exercise testing. It is reported to occur in 0.5–5.0% of exercise tests [32, 33], a variability that is likely attributable to factors such as the definition of ST elevation, inclusion of baseline ECGs with pathologic Q waves, and the number of ECG leads employed during testing. Our experience concurs with the rarity of exercise-induced ST elevation. The presence of pathologic Q waves in the resting ECG may be associated with exercise-induced ST elevation in those leads and usually indicates a left ventricular wall motion abnormality or aneurysm rather

than ischemia. In contrast to exercise-induced ST depression, ST elevation during EECG reliably localizes the ischemic area, which usually also affords identification of the involved coronary vessel. Ventricular arrhythmias and infarction also may occur during exercise-induced ST elevation. The pathophysiology of this finding is analogous to that of Prinzmetal angina, i.e., spasm of an angiographically normal or diseased coronary artery. Figure 6a, b depicts the distinctly rare observation of exercise-induced ST elevation with initial onset in the post-exercise phase of the

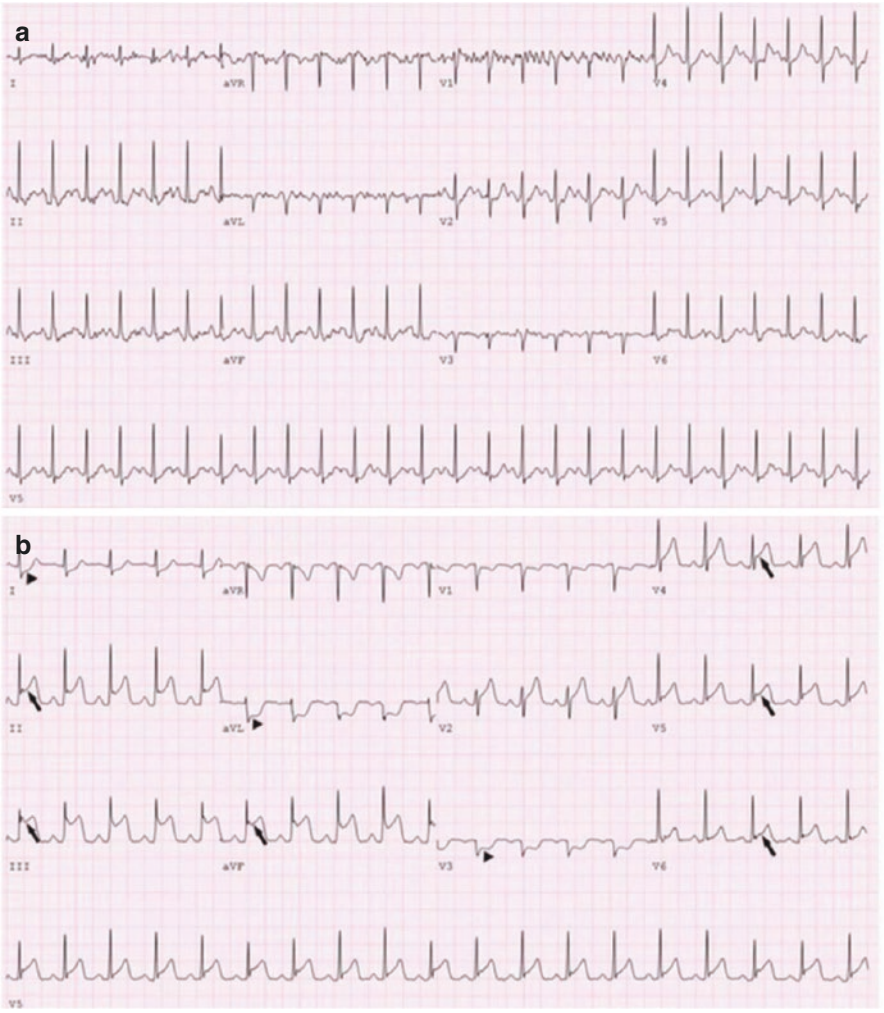

Fig. 6 (**a**). 12-lead exercise electrocardiogram showing sinus tachycardia (maximum heart rate 153/min) and no exercise-induced abnormalities. (**b**). Post-exercise electrocardiogram (1.5 minutes of recovery) showing 3–4 mm ST elevation in leads 2, 3, and aVF (arrows) and 1–2 mm ST elevation in leads V4, V5, and V6 (arrows). There is also ST depression in I, aVL, and V3 (arrowheads). (Reprinted from Takahashi et al. [34]. With permission from Elsevier)

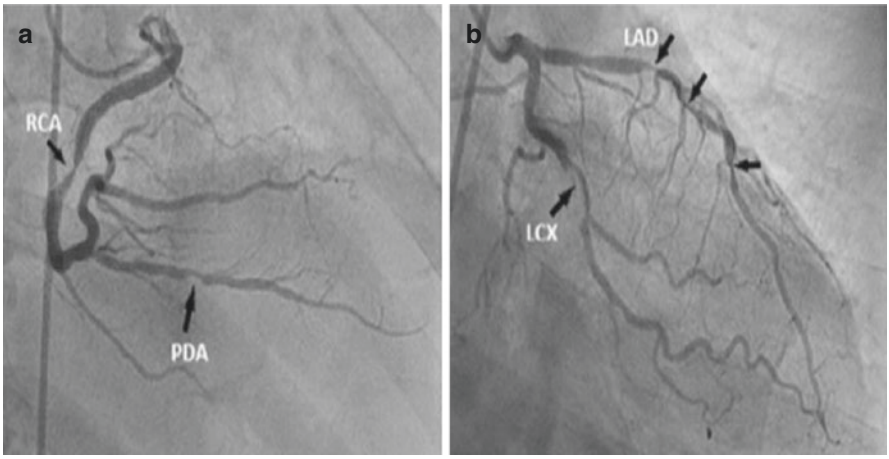

Fig. 7 Coronary angiogram of the patient with the exercise test data shown in Fig. 6a, b. There are multiple coronary artery stenoses (arrows) in the left anterior descending coronary artery (LAD), left circumflex artery (LCX), and right coronary artery (RCA). (Reprinted from Takahashi et al. [34]. With permission from Elsevier)

EECG, which in this patient was associated with severe multi-vessel CAD [34] (Fig. 7). We do not usually perform provocative testing for coronary spasm in these patients because their management is apparent from angiography and testing with a coronary vasoconstrictor conveys unnecessary risk.

7 Pretest Probability of Disease and Bayes' Theorem

Pretest probability of disease has a powerful influence on posttest probability of disease [35], as reflected in Fig. 8. The impact of pretest probability is evident from the magnitude of increase or decrease in posttest probability based on a positive or negative test, respectively. There is minimal alteration of post-EECG probability of disease in association with a negative test and a very low pretest risk of CAD or a positive EECG in a patient with a very high pre-EECG risk of CAD.

The limitations and dilemmas that may result from indiscriminate EECG in asymptomatic, apparently healthy patients have been widely emphasized, as have admonitions concerning the use of EECG as a screening method for CAD in healthy, low-risk populations [9, 23, 35, 37–39]. Bayes' theorem specifies that the accuracy of a test is determined by its sensitivity, specificity, and the pretest probability of disease in the subject tested, or the prevalence of the disease in the population undergoing testing. Bayesian analysis demonstrates the importance of the latter factors on test results, as shown in Fig. 8. Further, if the exercise ECG has a sensitivity of ~60% and a specificity of ~70% for CAD, and the test is applied in a population with very low risk of CAD, the frequency of false positives can actually exceed that

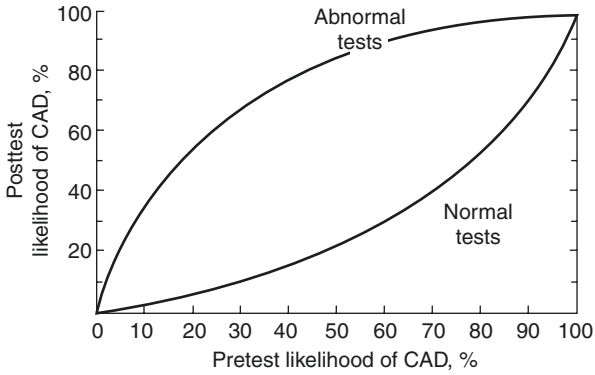

Fig. 8 Graphic representation of the influence of pretest likelihood of CAD (coronary artery disease) (abscissa) on posttest likelihood of disease (ordinate) and its interaction with normal and abnormal tests. (Reprinted from Epstein [36]. With permission from Elsevier)

of true positives. The value of such testing can be counterproductive by resulting in a cascade of further testing, expense, and potential complications. Therefore, asymptomatic patients referred for EECG should usually have at least an intermediate pretest probability of disease and specific reason(s) for EECG.

There is a rationale for stress testing of selected asymptomatic persons such as those with multiple coronary risk factors and a strong family history of premature CAD or those middle-aged or older people who are beginning an exercise training program. Exercise testing provides a quantitative assessment of functional capacity upon which to base a formal exercise prescription or reveals exercise-induced abnormalities of HR, BP, ECG, and symptoms that can preclude vigorous exercise training, at least initially. In the absence of contraindications to exercise training, the exercise test provides a basis for prescribing training intensity, duration, and frequency at levels that can enhance functional capacity and exert a favorable effect on multiple cardiovascular risk factors.

8 Exercise Electrocardiography in Women

Early reports of EECG in women revealed a higher rate of false positive tests for CAD than in men [40]. Based on these findings, it was suggested that stress imaging tests were the most appropriate initial tests in women with chest pain, and this approach is still practiced by many clinicians. These stress imaging studies are costly, and some utilize ionizing radiation. This predicament can be accounted for by several factors. CAD occurs later in women (about 10 years) compared to men, and there was a high rate of premenopausal women in early EECG testing that contributed to the increased false positive rates [41]. With increasing age, the high false positive rate in women declines and is closer to that of men. Thus, as indicated by Bayesian analysis, a high prevalence of normal individuals in the early studies of EECG in women resulted in a high rate of false positive tests, as would occur in any group with an elevated prevalence of individuals without CAD [23]. The 2014 Consensus Statement of the American Heart Association on noninvasive testing of

symptomatic women includes the following recommendations for testing based on risk categories for ischemic heart disease: low-risk patient, no test or evaluation by EECG; low-intermediate or intermediate risk, EECG; and intermediate-high risk, stress imaging study [25]. The Duke treadmill score (DTS) (Table 2), which incorporates treadmill exercise testing, has been generally effective for evaluating diagnosis and prognosis in large cohorts of men and women [42].

Evidence of myocardial ischemia in patients with nonobstructive CAD presents a continuing challenge, and this condition is mainly encountered in women. Although this clinical presentation is not benign [43], a report in 348 women with nonobstructive CAD did not reveal an adverse effect of ischemia on all-cause mortality during a follow-up of 8.5 years [44]. Survival was greater than 95% in patients with and without evidence of ischemia. By contrast, survival was lowest (<85%) in patients with a prior myocardial infarction ($p = 0.05$). This report, therefore, of a limited patient cohort, did not confirm reduced survival on long-term follow-up in women with nonobstructive CAD and evidence of myocardial ischemia in contrast to the adverse effect of prior myocardial infarction. Additionally, we followed a group of 200 low-risk women who presented to the emergency department (ED) with chest pain and were found not to have acute coronary syndrome (ACS) or other serious condition. During a 5-year follow-up (100% of patients), none of these patients experienced ACS [45].

9 Exercise Electrocardiography in Chest Pain Units

EECG has played a major role in the evaluation of low-risk patients presenting to the emergency department (ED) with chest pain, who number more than six million annually in this country [45–51]. Extensive experience has established that an accelerated diagnostic protocol that confirms low risk by documentation of clinical stability, negative resting ECG, and normal cardiac injury markers, including cardiac troponin (sensitive or high sensitivity), provides a firm basis for safe, accurate, early, cost-effective patient discharge [45–51]. Experience with this approach in multiple centers in this country even before the advent of high-sensitivity cardiac troponin revealed no adverse effects of early EECG in more than 2400 patients [50]. We have utilized a symptom-limited, maximal EECG in this setting. Length of stay with this approach has been less than that reported for computed tomography coronary angiography in low-risk chest pain patients presenting to the ED [48]. An NPV of >99% for a cardiac event during 30-day follow-up of low-risk patients presenting to the ED with chest pain is based on numerous studies that have incorporated high-sensitivity cardiac troponin into the protocol, even without EECG [52]. Of considerable interest, we have observed negative EECGs in addition to absence of exercise-induced chest pain on maximal EECG in a large majority of low-risk patients who presented to the ED with the chief complaint of chest pain. All patients underwent EECG on no antianginal agents within an average of 10 hours from presentation.

The evaluation of low-risk patients presenting with chest pain continues to evolve, and the recent availability of high-sensitivity cardiac troponin in the USA,

which affords a more rapid, direct, and accurate means of excluding acute coronary syndrome, has reduced the necessity of advanced cardiac testing (including EECG) in many low-risk chest pain patients presenting to the ED [52].

10 Non-exercise Electrocardiographic Test Variables

The prognostic value of non-ECG exercise data has been recognized for decades [1–4, 53–60], but the interest of clinicians in these findings has not been comparable to that of their concern for exercise-induced ischemia. Non-ECG exercise test variables alone are potent predictors of cardiovascular and other diseases, and they can also be integrated with ECG findings of exercise testing, symptoms, and traditional risk factors to develop scores for refining prognosis, this regard, it is also essential to consider an individual's exercise capacity in the context of vital factors such as age and sex, as demonstrated by nomograms [13, 17] (Fig. 1).

10.1 Heart Rate

This simple exercise factor correlates with prognosis as reflected by an investigation of 58,000 men and women aged 18–96 years [53]. Among multiple clinical and exercise factors assessed, after excluding age and sex, percent of maximum predicted HR achieved was second only to exercise capacity for predicting survival during a decade of follow-up. It was also shown, in a 7.7-year follow-up of almost 1600 men free of coronary heart disease, that chronotropic incompetence, defined as failure to achieve 85% of age-predicted maximum heart rate, was one of several rate-related factors associated with future all-cause mortality, including coronary heart disease and incident coronary heart disease [55]. An important limitation of the predictive capacity of maximum HR is that it is typically dependent on measures such as functional capacity.

10.2 Blood Pressure

The typical response of this variable during EECG is a continuous rise to maximum systolic pressure, which occurs at peak exercise and may exceed 200 mmHg in healthy men with high functional capacity [56]. Diastolic BP remains unchanged or shows a small rise or fall at peak exercise. Peak systolic pressure is typically higher in men than in women. Exercise-induced hypotension, variably defined as a decline of ≥10–15 mmHg or a fall to less than standing BP [61], can indicate serious cardiac disease, onset of complications during the test, or measurement error. In a summary of 11 reports of 6693 exercise tests, the frequency of hypotension (defined

as ≥20 mmHg decrease) was 8.0% [61]. Importantly, almost 50% of patients with exercise-induced hypotension in this study had either left main or three-vessel CAD. However, it is emphasized that the PPV for these outcomes is also highly dependent on the pretest probability of severe disease.

In patients with cardiac valvular disease, functional capacity is a critical factor in determining the timing of valve replacement, and acquisition of this information by history alone may be challenging in some patients. Although previously prescribed in patients with severe aortic stenosis, judicious exercise testing is now recommended in selected patients with this disease to obtain objective evidence of functional capacity and BP response during a progressive exercise test [4]. This approach can document impaired functional capacity and/or inadequate BP response, both of which may be useful in determining the timing of valve replacement. Information of similar value is afforded by EECG in patients with hypertrophic cardiomyopathy [4].

10.3 Double Product

Defined earlier in this chapter as the product of HR and systolic BP, this factor is closely related, in relative terms, to myocardial oxygen demand and thereby to relative changes in coronary blood flow [12]. Unless ambient conditions vary, myocardial ischemia usually occurs at the same double product in a given patient with coronary disease [12, 18]. Froelicher defined an adequate double product as >25,000 [58]. In our middle-aged and elderly patients, this value is rarely achieved, which may be related to age, sex, cardiovascular disease, or impaired physical fitness. More commonly, a double product of >20,000 is considered good-excellent and is attained in a relatively small proportion of cardiac patients. Although the double product affords insight into the balance between myocardial oxygen supply and demand, there are no universally accepted standards or normative values for this informative exercise-derived parameter.

10.4 Functional Capacity

This factor is considered by many as the single most reliable indicator of prognosis obtained from exercise testing in women and men with or without cardiovascular disease, as documented in multiple large, long-term investigations [53–55, 57, 58]. The importance of functional capacity is reflected by the generally favorable prognosis of patients with CAD who have good-excellent functional capacity (>10 METs) and appropriate management of coronary risk factors, as we and others have reported [2, 7, 8, 10]. All-cause mortality and specific cause mortality were independently related to maximal treadmill exercise capacity in an investigation of

over 10,000 men and more than 3000 women during a follow-up of >8 years [53]. Age-adjusted all-cause mortality rates decreased across levels of functional capacity from least-fit to most-fit men (64 to 19 per 10,000 person-years) and declined similarly in women from 40 to 9 per 10,000 person-years. Not inconsequentially, mortality rates for cardiovascular disease and cancer were also lower in those with higher fitness levels. In a study of over 5800 men followed for more than 6 years, nomogram, developed from readily accessible pretest and exercise test variables, demonstrated the following advantages: it was significantly associated with mortality ($p < 0.001$), was able to correctly reclassify multiple patients with intermediate-high-risk Duke treadmill scores to low risk, and accurately predicted 3-year mortality [60]. In a subsequent investigation, a nomogram, developed to predict age-related exercise capacity in women [13], revealed that in both asymptomatic ($n = 5721$, follow-up 8.4 years) and symptomatic women (4471, follow-up 5.3 years), all-cause and cardiac mortalities were twice as high ($p < 0.001$) among those whose exercise capacity was <85% of age-predicted value compared to those whose exercise capacity was ≥85% of age-predicted level. A different perspective than that provided by the foregoing salutary results related to the value of excellent functional capacity has also been reported, indicating that the rate of high-risk CAD was 25% in men with intermediate-high coronary risk profiles and abnormal exercise ECG, despite high functional capacity [62]. However, no follow-up was reported in this retrospective investigation.

10.5 Prognostic Scores

This approach utilizes multivariable analysis by integrating individual data elements that contribute to a numerical score that predicts occurrence of disease or clinical outcomes in symptomatic and asymptomatic individuals. One of the earliest of these methods is the Duke treadmill score (DTS) [63], which utilizes data obtained during exercise testing according to the Bruce protocol (Table 2). Application of the DTS demonstrated that 5-year survival was 72% for patients with a score of less than *minus* 11 (13% of patients) compared to 97% survival in patients with a score of greater than *plus* 5 (34% of patients). The value of this score is its ease of use and its contribution of prognostic information beyond that of standard clinical, anatomic, and ventricular function data. However, the DTS has several limitations: it does not include age, sex, or risk factors; it was developed in relatively young patients (males ≤55 years, females ≤62 years); and it was applied prior to current advances in CVD management. In this regard, we have found favorable survival in many contemporary patients despite a relatively high-risk DTS [7, 10]. Additionally, the DTS has been inconsistent regarding its prognostic utility in elderly patients (age ≥ 75 years), with both support [64] and rejection [65] in subsequent studies. However, in another study, the DTS had similar predictive utility in elderly men as in younger men [66]; but in elderly women, its predictive accuracy was surpassed by both METs and heart rate recovery [67].

10.6 Heart Rate Recovery

Heart rate recovery (HRR) is a potent and independent predictor of risk and is based on the deceleration of cardiac rate following maximum EECG. Post-exercise decline in heart rate reflects vagal prominence associated with cessation of exercise [68]. However, multiple definitions of this parameter have impeded comparison of results from individual studies because methodology differs in the time and other factors related to measurement of post-exercise HRR. These include timing of the measurements (1 or 2 minutes post-exercise), activity state during data acquisition (cool down post-exercise or abrupt cessation), and position (upright or supine). However, the predictive power, consistency, and independence of HRR are consistent and impressive.

Most frequently, impaired HRR is considered a decline of <12 beats/min in the first minute after symptom-limited exercise; <22 beats/min in 2 minutes post-exercise has also been proposed. Impaired HRR is associated with increased risk of cardiac events and decreased survival. In an early study of over 2400 symptomatic persons aged 57 ± 12 years (63% men) followed for 6 years, median 1-minute HRR for the total cohort was 17 beats/min after symptom-limited EECG. In the 26% of patients whose HRR was <12 beats/min, there was a fourfold increase in relative risk of mortality ($p < 0.001$) [69]. Following adjustment for multiple clinical and exercise factors (age, sex, cardiac risk profile, medications, exercise workload, results of myocardial stress scintigraphy), the predictive significance of impaired HRR for mortality persisted (relative risk twofold, $p < 0.001$).

10.7 Combined Predictive Factors

It was subsequently shown that prediction of outcome by Framingham risk scores (FRS) could be enhanced by combination with either functional capacity, HRR, or both of these measures. After adjustment for FRS in over 6100 asymptomatic individuals aged 45 years (46% women) with low functional capacity and low HRR, each of these methods was a significant predictor of 10-year cardiovascular mortality [70]. However, as depicted in Fig. 9, risk was higher when FRS was combined with either the low value for HRR or low functional capacity and highest if FRS was considered together with both of the low functional values.

11 Conclusions

EECG remains one of the most frequently utilized, informative, and safest non-cardiac tests. It provides essential information for diagnosis, prognosis, and management of cardiac disease by unique insight into all three of these areas. EECG

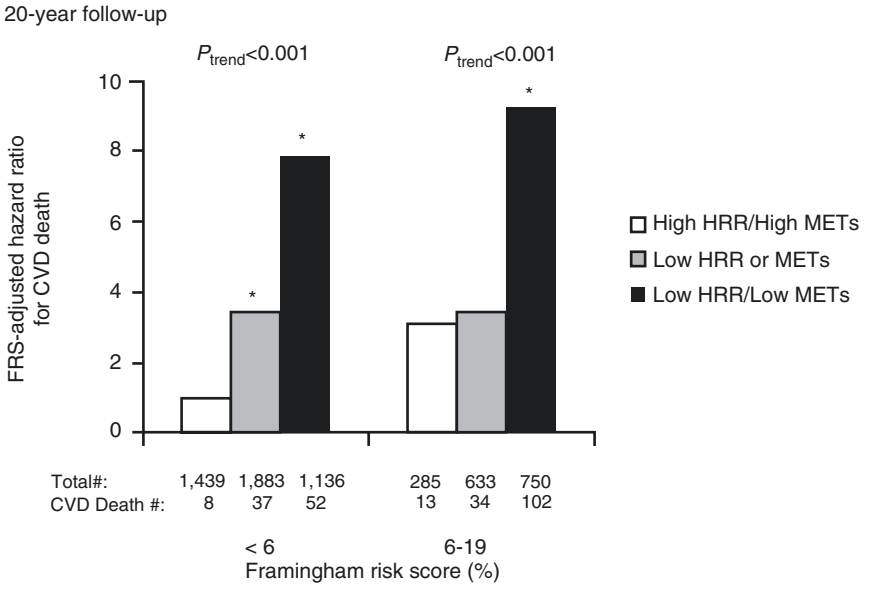

Fig. 9 Enhancement of risk assessment by combining prediction methods. The graph demonstrates Framingham risk score (FRS)-adjusted hazard ratios for cardiovascular death (CVD) at 20 years by adding risk prediction with only one or with both low functional capacity (FC) and heart rate recovery (HRR) measures. Prediction of CVD mortality based on FRS (score of 6 on left, 6–10 on right) was greater when combined with low HRR or low FC and highest when prediction by both was added to FRS. Asterisks indicate significant ($p < 0.001$) increase in CVD. (Reprinted from Mora et al. [70]. With permission from Wolters Kluwer Health, Inc.)

utilizes safe induction of myocardial ischemia to help determine the presence or absence of obstructive CAD. Based on its ECG and non-ECG data, it has furthered understanding of normal and abnormal cardiovascular responses to physical stress and unmasked symptoms and provided objective evidence of myocardial ischemia and the presence of impaired function related to a variety of CVD. The value of the non-ECG variables of EECG, such as functional capacity and heart rate recovery, affords exclusive insights into prognosis. The diagnostic utility of EECG for CAD is comparable in men and women 10 years after menopause, but this test continues to be underutilized in these groups in favor of stress imaging tests, which are costly, some of which use ionizing radiation. Limitations of EECG include inability to localize ischemic myocardial regions and requirement of a normal baseline ECG if the goal of the test is estimation of exercise-induced myocardial ischemia. In addition, it is essential to appreciate that posttest probability of CAD is closely tied to pretest probability of CAD, which is the basis for continuing concerns of using EECG as a screening test for CAD in healthy, asymptomatic persons.

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Ultrasound and MRI Assessment of Cardiovascular Risk

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Summary

- Early detection of the asymptomatic vulnerable patient which has significant subclinical atherosclerosis remains an important goal in patient management.
- Noninvasive imaging techniques including ultrasonography (US) and magnetic resonance imaging (MRI) may help to identify and characterize "vulnerable" plaques and may provide a direct, feasible, and widely available means to refine risk stratification over traditional cardiovascular risk factors.
- Carotid ultrasonography can measure carotid intima-media thickness (CIMT) and detect plaque. Both CIMT and carotid plaque have been shown to be significantly associated with adverse cardiovascular events independent of traditional risk factors.
- The presence of focal plaque appears to perform better than CIMT in cardiovascular risk prediction.
- High-resolution MRI is an important diagnostic tool not only to identify the total plaque burden within the carotid arteries but also to characterize atherosclerotic plaque components.

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- Total plaque burden and specific plaque components including a thin fibrous cap (FC), large fatty or lipid-rich necrotic core (LRNC), and intraplaque hemorrhage (IPH) are validated markers of plaque vulnerability.
- Carotid artery MRI can identify calcification, FC, IPH, and LRNC with moderate to excellent sensitivity and specificity.

1 Introduction

Despite significant advances, atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of morbidity and mortality in the world. Atherosclerosis is a systemic process that begins from a very young age and culminates in the clinical manifestation of ASCVD. Several pathways and risk factors including hypertension, type 2 diabetes mellitus, dyslipidemia, genetic factors, smoking, and inflammation lead to atherosclerosis and plaque formation. Noninvasive imaging of arteries does not discriminate between these pathways but rather reflects the net effect of different pathways on plaque formation (Fig. 1). Atherosclerosis is also a ubiquitous process with presence of plaque in one territory being indicative of the presence or the risk of development of plaque in other vascular territories. Therefore, early imaging-based detection of atherosclerosis has emerged as a useful measure to improve risk stratification algorithms that use traditional risk factors such as the Framingham Risk Score (FRS) and the Pooled Cohort Equation (PCE).

Although data suggest that peripheral arteries such as the iliofemoral arteries are typically the initial locations of plaque development, the carotid artery, given its easy accessibility and size, has emerged as the most common non-coronary artery imaged for cardiovascular risk assessment. In addition to plaque burden, several features such as plaque characteristics and activity that identify a "vulnerable" plaque [1] or the high-risk, rupture-prone plaque which has a higher likelihood of causing an atherothrombotic complication leading to stroke or myocardial infarction [4] have been identified through imaging [2].

Among existing imaging techniques, we focus in this chapter on ultrasonography (US) and carotid magnetic resonance imaging (MRI).

2 Ultrasound

After the initial description of carotid intima-media thickness (CIMT) measurement by Pignoli et al. [3] almost three decades ago, the value of carotid ultrasonography through CIMT measurement and carotid plaque identification, quantification, and characterization for cardiovascular (CV) risk stratification is now well defined. A consensus statement by the American Society of Echocardiography (ASE) and the Society for Vascular Medicine and Biology provided recommendations to guide the

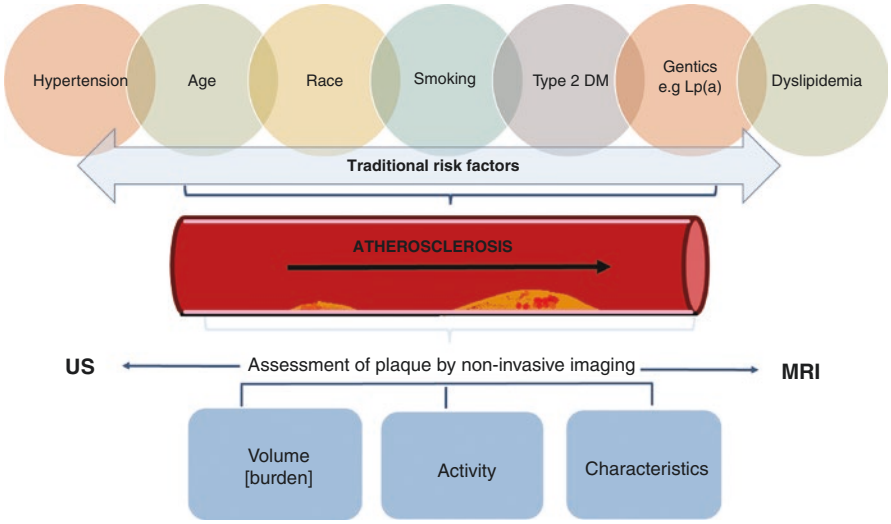

Fig. 1 Atherosclerosis is a multifactorial disease which involves complex interplay of multiple tradition and novel risk factors. Noninvasive imaging of arteries does not discriminate between these pathways but rather reflects the net effect of different pathways on plaque formation. Plaque features include plaque volume (or burden), plaque characteristics (or morphology), and plaque activity, the latter two contributing to plaque vulnerability

use of carotid US in assessing subclinical vascular disease and ASCVD risk [4]. Current recommendations are to use a US system with linear array transducer operating with a frequency of at least 7 MHz with B-mode imaging.

2.1 Definition of CIMT

Imaging of the carotid wall using US produces two echogenic lines, which have been identified by in situ anatomic and in vitro histologic studies to represent the lumen-intima interface and the media-adventitia interface (Fig. 2) [3]. Atherosclerosis is a subintimal process, and ideally, measurement of the intimal thickness would provide a measurement of the burden of atherosclerosis. Overall, the intima contributes anywhere between 1% and 20% in states of health and disease, and hence, it is beyond the resolution of currently available external imaging technology [5]. Therefore, the cumulative thickness of the intimal and medial layers of the carotid artery wall which constitutes the CIMT has been evaluated as a surrogate for atherosclerosis.

There is no single absolute value of CIMT that is considered abnormal as CIMT varies with age, gender, and race [6, 7]. It is recommended, therefore, to use age-, gender-, and race-based thresholds derived from large population-based studies to define abnormal CIMT (typically CIMT >75th percentile [8, 9] or absolute thickness more than 1.0 mm [9]).

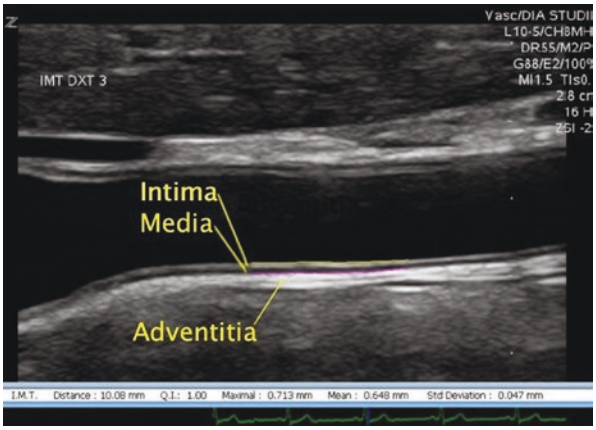

Fig. 2 Two-dimensional ultrasound imaging to assess carotid intima-media thickness (CIMT). Intima-media complex in the CCA. The figure shows the distal 2 centimeters of the CCA. Intima, media, and adventitia are indicated as well as the 1-centimeter area in which CIMT is measured. Abbreviations: CCA common carotid artery, CIMT carotid intima-media thickness. (Reprinted from Gaarder and Seierstad [85]. With permission from Creative Commons License 4.0: https://creativecommons.org/licenses/by/4.0/)

2.2 Definition of Plaque

The Mannheim consensus [10] document is the commonly used definition of plaque, which defined nonobstructive carotid plaque as a focal structure or thickening (1) that is at least 50% greater than the thickness of its surrounding vessel, or (2) encroaches into the arterial lumen by at least 0.5 mm, or (3) demonstrates a CIMT greater than 1.5 mm and is distinct from the adjacent boundary.

2.3 CIMT Imaging and Measurement

The intima-media thickness (IMT) can be measured in different locations, including the common carotid artery (CCA), the bifurcation (bulb), or either of the branch vessels (usually the internal carotid artery). Optimal images for IMT measurement should ensure that there is a clear demonstration of the blood-intima and media-adventitia boundaries on both near and far walls of the carotid artery ("double-line" sign).

CCA IMT is generally preferred as it demonstrates higher yield and reproducibility compared to the internal carotid artery (ICA) and bulb [6, 11] given its perpendicular location to the transducer beam and relatively superficial location allowing easy accessibility. The ASE [4], based on protocols from large epidemiological studies, recommends the use of the distal 1 cm of the far wall, as opposed to the near (closest to the transducer) wall of each CCA. Although measurement reproducibility of the near and

far walls have been reported to be comparable [11], measurement of the near wall is more challenging due to lower yield [12] and accuracy than that of the far wall because of technical considerations. Typically, the CCA should be imaged at three different angles (anterior, lateral, and posterior), and each angle measured three times (total of 18 measurements across both sides) over at least 1 cm segment to improve precision.

2.4 Plaque Imaging

CIMT measurement should be supplemented with a systematic scan of the extracranial carotid arteries for the presence of carotid plaques. The most common location of plaque is within the carotid bifurcation due to more non-laminar flow in the region, followed by the ICA [13], while plaque is much less common in the CCA. A circumferential scan with multiple anterior and posterior angles of the near and far walls of all three (CCA, bulb, and ICA) segments of the carotid artery is required to avoid missing plaque.

2.5 Plaque Quantification

Measures of quantifying plaque have been developed and include:

1. *Plaque score* is the sum of the total number of distinct plaque lesions along the distal 1 cm of the right and left CCA, carotid bulb, or proximal 1 cm of the ICA in any wall (near, far, lateral).
2. *Plaque height/thickness* is the maximum thickness/height in one plane, and its measurement requires demonstration from two different angles in both longitudinal and cross-sectional views.
3. *Plaque area*: Once plaque is identified using a transverse view of the carotid artery, a longitudinal view is used to manually trace the lesion and area calculated using semi-automated or automated software. If multiple plaques (same artery or bilateral) are present, their respective areas are all summed to define total plaque area. Plaque area is more reflective of plaque burden than a single plane measurement, especially in the case of eccentric-shaped plaque.
4. *Plaque volume*: Recent advancements allow three-dimensional (3D) volumetric assessment of carotid plaque volume (Fig. 3), over at least 1 cm, of a specific segment of the artery [14].

2.6 Plaque Characterization

Early standard ultrasound technique had a limited role in characterizing plaque morphology. Initially, plaque was merely characterized as homogenous or heterogeneous, depending on uniformity of plaque echogenicity [15]. However, with recent advances in technology, computer-assisted analysis such as grayscale median

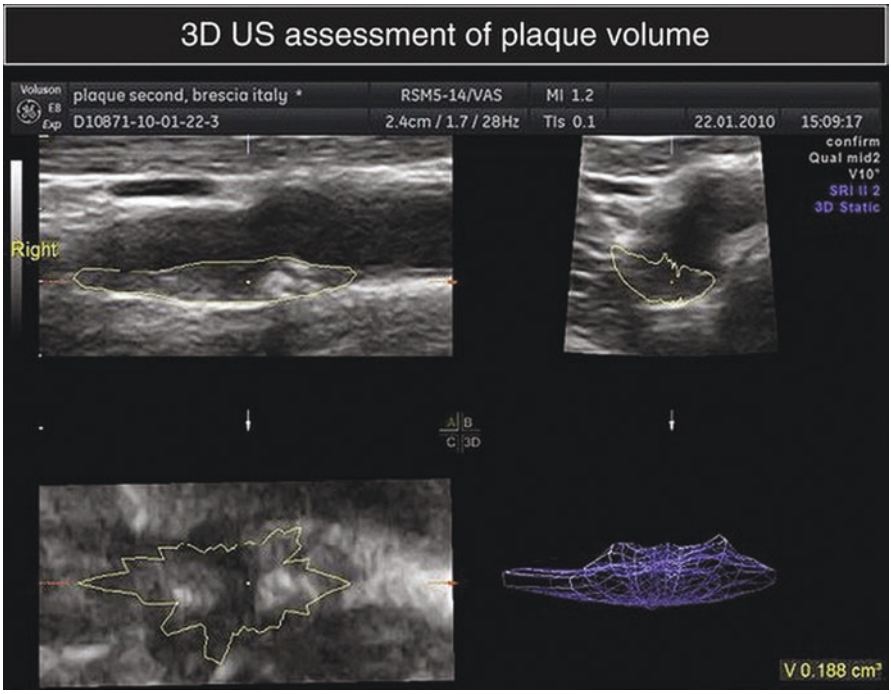

Fig. 3 Three-dimensional (3D) reconstruction of a carotid plaque to assess plaque volume. (Reprinted from Rosei et al. [86]. With permission from Springer Nature)

(GSM) which describes the grey scale pixel intensity is being used to classify the plaque (Figs. 4, 5, and 6). Echolucent carotid plaques (associated with lipid enrichment and hemorrhage into the plaque, lower grey scale median) compared to echogenic plaques (which correlate with fibrous tissue) confer a higher relative risk for ischemic stroke [16]. Furthermore, three-dimensional (3D) US, with its enhanced spatial resolution, allows for more complete visualization of the plaque morphology and surface and can be used to assess for ulceration and surface irregularities, both of which have been shown to be associated with increased risk of stroke and death [17]. Additional tools including plaque mobility [18] and neovascularization using US contrast [19] continue to be developed and evaluated.

2.7 CIMT and Cardiovascular Risk Factors

CIMT is affected by most of the cardiovascular risk factors. In the Framingham Offspring cohort of 3316 subjects, CCA-IMT and ICA-IMT were highly correlated with age, gender, high-density lipoprotein cholesterol, smoking, hypertension, and diabetes [20]. Age was the strongest predictor of both CCA-IMT and ICA IMT.

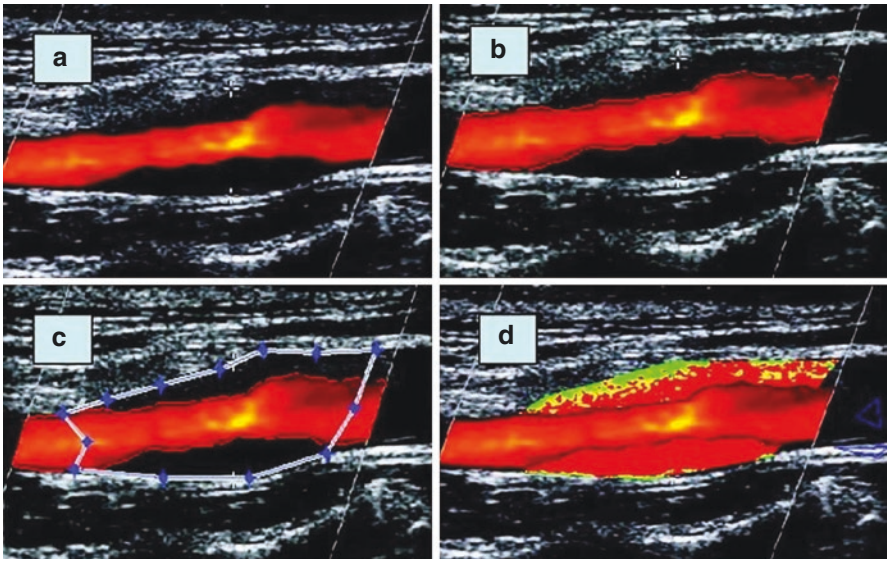

Fig. 4 Ultrasound image of the carotid plaque in an asymptomatic patient. (**a**) Note the different echogenic characteristics of the plaque (anechoic in the far wall and more echogenic in the near wall region). (**b**) The color flow is automatically outlined (see red lines); the limit represents the border zone between the surface of the plaque and the color flow. (**c**) Manual delineation of the adventitia. (**d**) Color mapping of the plaque according to the threshold: <60 (red), 60–90 (yellow), and >90 (green). The surface is delineated automatically between 0 and 0.5 mm, 0 and 1 mm, 0 and 1.5 mm, and 0 and 2 mm. Also note the normalization of the plaque (selection of the darkest and the brightest regions 0–190 with blue triangles). (Reprinted from Sztajzel [87]. With permission from Springer Nature)

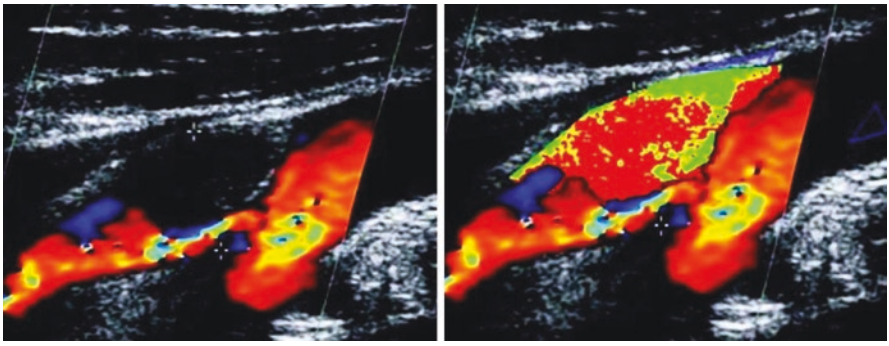

Fig. 5 Plaque image from an 87-year-old patient with an asymptomatic left carotid stenosis of 80%. The proportion of the red color at the surface is of 68% within the 0–0.5 mm, 60% within the 0–1 mm, 57% within the 0–1.5 mm, and 57% within the 0–2 mm regions. The proportion of red color for the whole plaque is of 59%. These findings suggest a plaque with low risk. (Reprinted from Sztajzel [87]. With permission from Springer Nature)

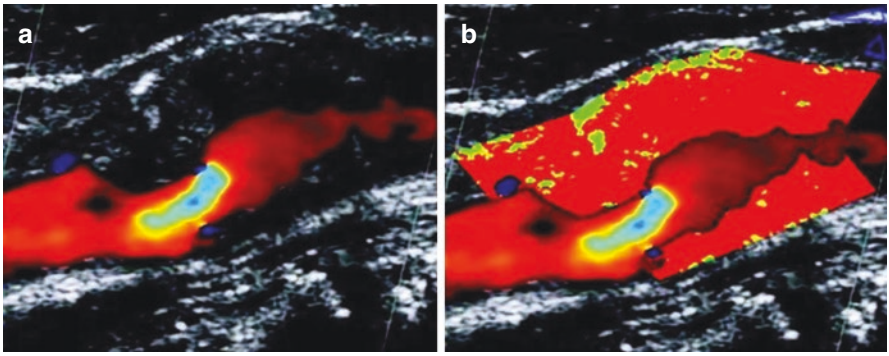

Fig. 6 Plaque image from a 72-year-old man with a symptomatic right carotid stenosis of 70%. The proportion of red color at the surface of the plaque is of 95% within the 0–0.5 mm, 95% within the 0–1 mm, 94% within the 0–1.5 mm, and 93% within the 0–2 mm region. The proportion of red color for the whole plaque is of 89%. These findings suggest a plaque with high risk. (Reprinted from Sztajzel [87]. With permission from Springer Nature)

2.8 CIMT and Cardiovascular Events

Multiple large epidemiological studies including the Atherosclerosis Risk in Communities Study (ARIC) [9, 21], Carotid Atherosclerosis Progression Study (CAPS) [22], Cardiovascular Health Study (CHS) [23], Malmo Diet and Cancer Study (MDCS) [24], and Rotterdam study [25] have consistently demonstrated that CIMT is significantly associated with risk for myocardial infarction (MI), stroke, and death from coronary heart disease (CHD) independent of traditional risk factors (TRF). The CAPS with 2436 individuals younger than 50 years old extended the predictive value of CIMT to younger subjects. It showed that the relative risk associated with increased CIMT was considerably higher in individuals younger than 50 years old [22].

In a systematic review and meta-analysis of eight population studies of 37,197 asymptomatic individuals who underwent one-time CIMT measurement, the age and sex adjusted hazard ratios (HR) for myocardial infarction (MI) and stroke were 1.26 (95% confidence interval (CI) 1.21–1.30) and 1.32 (95% CI, 1.27–1.38) per one standard deviation (SD) CCA IMT increase, respectively [26].

2.9 CIMT and Risk Prediction

Although CIMT correlates well with risk factors and numerous studies have demonstrated that it is strongly associated with cardiovascular events, its additive value over TRF in cardiovascular risk prediction has not been consistently demonstrated. In a meta-analysis, which included 14 population cohorts with a total of 45,828 asymptomatic individuals who underwent one-time CIMT measurement at baseline

(median follow-up 10.8 years), the addition of mean common carotid IMT to the FRS showed a marginal but not clinically meaningful improvement in net reclassification index (NRI) of 0.8% (95% CI: 0.1–1.6%) in the entire study population [27].

In the Framingham Offspring Study Cohort [28] of 2965 subjects followed over 7 years, while the addition of maximum IMT of ICA to TRF resulted in a significant NRI of 7.6% ($p < 0.001$), the mean IMT of CCA did not show a significant improvement in NRI.

The ARIC study, on the other hand, showed promising results in 13,415 subjects without known cardiovascular disease (CVD), where the addition of mean CIMT of all segments to TRF improved reclassification of 7.1% of all subjects and 16.7% of subjects at intermediate risk and modestly increased the area under the curve (AUC) [29]. Similar results were found in the CHS and IMPROVE study. In the CHS study of 4384 CHS participants, addition of CIMT to Framingham Risk Score (FRS) model modestly improved risk discrimination between cases and non-cases of stroke and CVD (NRI = 0.062, $p = 0.015$ and NRI = 0.027, $p < 0.001$, respectively), with no further improvement by adding plaque [30]. In 3703 asymptomatic subjects in the IMPROVE study with at least three CVD risk factors, the addition of mean CIMT demonstrated a significant NRI of 11.3% [31].

On the other hand, in CAPS, which included a cohort of relatively young and low-risk subjects ($n = 5056$), addition of CIMT did not demonstrate improvement in cardiovascular risk prediction when compared to classification based solely on traditional risk scores [32]. However, during a mean follow-up period of 8.5 years (range, 7.1–10.0 years), the event rates (which were ascertained through health insurance data and not follow-up) were low, and hence, whether all events were adequately captured is unclear. In Multi-Ethnic Study of Atherosclerosis (MESA), although addition of CIMT to FRS plus race/ethnicity did show modest improvement in AUC and NRI for prediction of CHD, coronary artery calcium (CAC) provided superior risk discrimination and reclassification compared to CIMT [33].

Moreover, while a single value of CIMT and plaque measurement may be useful, CIMT progression has not been shown to be associated with incident MI, stroke, or vascular death in the population [34], and there may be limited value in performing serial IMT measurements to monitor progression.

The inconsistency demonstrated by CIMT in cardiovascular risk prediction is believed partly due to the heterogeneity in the US and IMT measurement protocols employed and the fact that small measurements are sufficient to increase or decrease an individual's CIMT to >75th percentile or <25th percentile. Hence, if CIMT is used, rigorous protocols are recommended.

3 CIMT in Younger Age and Other Populations

Risk calculators based on TRF which are designed to estimate 10-year cardiovascular risk are not as useful in young adults [35] and women [36] where the 10-year risk tends to be low. An attractive characteristic of CIMT measurement

is that it can be performed at any age and represents the cumulative effect of known and unknown genetic and environmental factors that leads to atherosclerosis. It therefore allows assessment of cardiovascular risk in populations with accelerated atherosclerosis where risk estimation with TRF-based calculators is not accurate, such as populations with inflammatory conditions (e.g., rheumatologic conditions), specific genetic mutations in lipid metabolism (e.g., LCAT and ABCA1 deficiency), smokers, or those with a family history of premature CHD.

CIMT has also proven to be a valuable tool in children with familial hypercholesterolemia (FH) [37]. Guidelines advise starting treatment with cholesterol-lowering medications in children with FH from age 10 years [38]. These recommendations are, for the large part, based on data from CIMT studies which were used to evaluate early subclinical atherosclerosis [39] and the response to statins in FH [40]. Early initiation and long-term statin treatment initiated in patients with FH have been shown not only to slow progression of CIMT but also to reduce risk of cardiovascular events in adulthood [41].

3.1 Carotid Plaque and Cardiovascular Events

Like CIMT, prospective cohorts have also demonstrated the predictive power of the presence of carotid plaque for cardiovascular events [42]. In MESA, carotid artery plaque >25% was associated with both incident stroke and CHD [43].

Plaque burden as assessed by plaque score has been shown to be associated with incident cardiovascular events. In the Three-City Study [44] of 5895 individuals without baseline CVD (aged 65–85 years), the presence of plaque in greater than two sites showed higher risk for CHD compared to single plaque site ($p < 0.001$). In another study by Stork et al. [45], in 367 elderly men (mean age 78 ± 4 years), the risk for MI, cardiovascular mortality, and overall mortality was increased by 52%, 70%, and 45%, respectively, for each increase in the number of plaque-affected arteries ($p < 0.001$) over 4 years. The HR for mortality was 2.9 for a plaque score of 1–2 and 4.5 for a plaque score of 7–12.

In the High Risk Plaque Bioimage study [46], maximum carotid plaque thickness (another measure of plaque burden) was significantly associated with risk of combined CV death, MI, and stroke (HR, 2.0; 95% CI, 0.9–4.3; $P = 0.015$). In a Canadian cohort of 1686 patients [47], the combined 5-year risk of stroke, MI, and vascular death significantly increased with increasing quartile of plaque area after adjusting for baseline characteristics. Similarly, in the Tromso Study of 6584 individuals (aged 25–84 years) with no history of MI, compared to those with no plaque, those in the highest quartile of plaque area had significantly higher risk of MI in both men (HR, 1.6; 95% CI, 1.0–2.4) and women (HR, 4.0; 95% CI, 2.2-7.2) after a 6-year follow-up [48].

Novel 3D ultrasound technology allows for more accurate determination of plaque burden. The BioImage Study of 5808 asymptomatic adults showed that

increasing tertiles of carotid plaque burden (evaluated as sum of plaque areas from both carotid arteries) using 3D US were significantly associated with increased risk for cardiovascular events, compared to those without carotid plaque, after adjustment for TRF [49].

Apart from plaque burden, in the San Daniele study [50], a higher Total Plaque Risk Score (TPRS) (i.e., "high risk" plaque morphology detected by 3D ultrasonography), which included degree of stenosis, plaque surface irregularity, echolucency, and texture, was associated with a higher risk for incident CV events, after adjusting for TRF.

3.2 Carotid Plaque and Risk Prediction

Several studies have established the importance of plaque in risk prediction (Table 1). In the ARIC study, the addition of carotid plaque to TRF significantly improved risk prediction (NRI, 7.7%; 95% CI, 2.3–11.4), especially in women [29]. The addition of both CIMT and plaque information to TRF demonstrated greatest improvement in NRI of 9.9% (95% CI, 3.8–13.5) and AUC. In both the Framingham Offspring Cohort [28] and MESA [43], detection of carotid artery plaque was associated with a significant increase in both the C statistic and NRI.

Quantitative measures of plaque burden such as plaque score, plaque thickness, plaque area, and 3D assessment of plaque show progressive improvement in CV risk prediction over mere assessment of plaque presence. In the Three-City Study [44], addition of carotid plaque score to TRF significantly improved AUC and showed an NRI of 13.7% for prediction of CHD. In the BioImage Study, Baber et al. [49] demonstrated that carotid plaque burden, assessed by 3D US, showed improvement in NRI on the basis of the FRS and PCE that was comparable to CAC [50].

There is growing evidence demonstrating that the presence of focal plaque is superior to CIMT for cardiovascular risk prediction [51]. Besides intimal thickening, CIMT represents smooth muscle hypertrophy and/or hyperplasia which may reflect the presence of cardiovascular risk factors (such as hypertension, or age-related sclerosis), whereas carotid plaque, a subintimal process, is a direct manifestation of atherosclerosis. Both the Tromso Study [48] and the Three-City Study [44] showed that plaque, and not CIMT, provided incremental improvement in risk prediction over TRF. In a meta-analysis of 11 population-based cohorts which included 54,336 patients, carotid plaque, when compared with CIMT, had a significantly higher diagnostic accuracy for the prediction of future MI after adjusting for TRF [51]. In addition, the negative predictive values of carotid plaque compared to CIMT for future events were higher [51]. Hence, while CIMT may still have a role when there is no demonstrable plaque (an example is younger age), there is currently a greater focus on carotid artery plaque measurement when assessing CV risk.

Table 1 Epidemiological studies evaluating the use of CIMT and carotid artery plaque in CHD and CVD risk prediction

	ARIC [29]	CHS [30]	CAPS [31]	Framingham Offspring [28]	MESA [43]	BioImage [49]
Patients, N	13,145	4384	4904	2965	6562	5808
Mean age (sd)	54 (5.8)	72.8 (5.6)	50 (12.9)	58 (10)	61 (10.2)	69 (6.0)
Follow-up, y	15.1	10	8.5	7.2	7.8	2.7
Events	CHD[a]	CVD[b]	Death, MI, or AP	CVD[c]	CHD[d]	MACE[e]
Ultrasound information						
Site for IMT measurement	Mean of all (CCA, bulb, and ICA)	Mean of max CCA or ICA	Mean ICA, mean CCA, mean bif	Mean CCA, max CCA	Mean ICA, max ICA	NR
Area under curve with CIMT/plaque measurements						
TRF only	0.74	NR	0.72	0.75	0.74	–
TRF + CIMT	0.75	NR	0.72	0.75	–	–
TRF + plaque	0.75	NR	NR	0.76	0.75	–
TRF+ CIMT+ plaque	0.76	–	–	–	–	–
TRF + ICA IMT	–	–	0.72	0.76	0.74	–
NRI with CIMT/plaque measurements added to TRF						
TRF + CIMT	7.1	2.7	–	–	–	–
TRF + plaque	7.7	NR	NR	7.3	5	23[f]
TRF+ plaque + CIMT	9.9	–	–	–	–	–
TRF + CCA IMT	–		−2.1	0	–	–
TRF+ ICA IMT	–		0.1	7.6[g]	7.0[g]/6.8[h]	–

Abbreviations: *ARIC* indicated Atherosclerosis Risk in Communities, *AP* angina pectoris, *AUC* area under the curve, *bif* carotid birfucation, *CAPS* Carotid Atherosclerosis Progression Study, *CCA* common carotid artery, *CHS* Cardiovascular Health Study, *CHD* coronary heart disease, *CHF* congestive heart failure, *CIMT* indicates carotid intima-media thickness, *CVD* cardiovascular disease, *ICA* internal carotid artery, *IMT* intima-media thickness, *MACE* major adverse cardiovascular events. *Max* maximum, *MESA* Multi-Ethnic Study of Atherosclerosis, *MI* myocardial infarction, *NR* not reported, *NRI* net reclassification index, *PAD* peripheral arterial disease, *revasc* coronary revascularizations, *TRF* traditional risk factors

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

[b]CVD: MI, fatal CHD, coronary insufficiency, angina, ischemic or hemorrhagic stroke, transient ischemic attack, peripheral arterial disease, heart failure

[c]CHD, HF, or stroke

[d]CHD events, MI, CHD death, resuscitated cardiac arrest, AP, and revasc

[e]CVD death, MI, or ischemic stroke

[f]Carotid plaque burden: sum of plaque areas in both right and left carotid arteries using 3D US

[g]Mean of the maximum IMT measured in ICA

[h]Maximum IMT measured in ICA

Table 2 Comparison of ultrasound and magnetic resonance imaging

Ultrasound	MRI
Advantages: Safe, no ionizing radiation Low cost Image procurement is fast Widely available technology Noninvasive Portable Identification of ulceration, intraplaque hemorrhage 2D and 3D quantification	Excellent soft tissue contrast Unlimited viewing angles Image from aortic arch to distal cervical vessels High resolution High reproducibility Identification of plaque ulceration, intraplaque hemorrhage Avoids ionizing radiation Better reproducibility compared to US
Barriers: Operator dependent Technical challenges (e.g., patient body habitus) CIMT measurement requires exact measurement (dependent on probe positioning and angle) Eccentric plaque can be missed due to changes in probe angle or patient positioning Acoustic shadowing from calcification Vessel tortuosity	Barriers: Low availability High cost Multiple sequences and protocols are time-consuming Not portable Complex training Safety requirements

Abbreviations: *CIMT* carotid intima-media thickness, *US* ultrasound, *2D* two-dimensional, *3D* three-dimensional

3.3 Advantages of Carotid Ultrasound

Carotid ultrasonography offers several advantages for detecting and monitoring atherosclerosis (Table 2). First, it is safe. Second, it can be carried out at relatively low cost. Third, image procurement is fast, which can lead to higher throughput. Furthermore, due to low cost and safety, carotid US can be repeated overtime to monitor plaque progression and can be used as an assessment tool for targeting and evaluating preventative therapy [47], although improvements in reproducibility are needed.

3.4 Limitations of Carotid Ultrasound

Unlike tests such as coronary calcium score, which are automated, US image quality is highly dependent on an operator's ability to scan comprehensively and provide all standardized angles of measurement. Patient body habitus can greatly affect US images relative to other imaging modalities. CIMT requires exact measurements and is highly dependent on angle and probe positioning. Small changes which could occur from minor changes in angle or image location can have a significant impact on the measured value and its clinical implication. Similarly, plaque can be easily

missed, given its eccentric shape, minor changes in angles, or inability to complete a thorough examination with circumferential angles.

4 Role of Carotid Ultrasound in Clinical Practice

The use of CIMT for CHD risk stratification was first recommended by the American Heart Association (AHA) Prevention Conference V in 2000 [52] which concluded carotid US could provide incremental information in asymptomatic patients >45 years old over TRF assessment. It was subsequently endorsed by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III [53]. In 2006, the Screening for Heart Attack Prevention and Education (SHAPE) Task Force promulgated recommendations to screen all healthy and asymptomatic men 45–75 years of age and women 55–75 years of age without CVD for subclinical atherosclerosis using one of two noninvasive imaging modalities, namely, carotid US or coronary artery calcium score (CAC) using computed tomography [8]. A consensus statement from the ASE CIMT task force in 2008 [4] endorsed that an abnormal CIMT could be used to reclassify an individual with multiple CV risk factors to a higher-risk category. Similarly, the 2010 American College of Cardiology (ACC)/AHA guidelines for assessment of cardiovascular risk in asymptomatic adults gave a class IIa indication for the use of CIMT in the initial assessment of cardiovascular risk in individuals at intermediate CHD risk [54]. However, this recommendation was downgraded by both ACC/AHA guidelines in 2013 [55] and 2019 [56] for primary prevention. Neither recommended the use of carotid ultrasonography (either plaque or CIMT) in cardiovascular risk assessment, mainly due to the emergence of strong data supporting CAC score and data as discussed previously that highlighted issues with reproducibility of CIMT and mixed data. The European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines in 2019 [57], however, continue to endorse the use of US in improving risk assessment in individuals at intermediate risk. Our own view is that US does have added value in the estimation of CVD risk, provided high-quality CIMT measurements are obtained and plaque is assessed. Ultrasound could be used to assess both iliofemoral and carotid arteries for the presence and extent of plaque which may offer a systemic view of subclinical atherosclerotic status. Furthermore, plaque in the femoral artery (which can be assessed with US) occurs at a younger age and is more common than in the carotid artery, with studies suggesting that about 30% of subjects have a normal carotid artery but have femoral atherosclerotic lesions [58]. The presence of common femoral plaque, like carotid plaque, has been shown to be independently associated with incident cardiovascular events [59], and cardiovascular risk significantly increased with increasing numbers of plaque-affected arteries [60]. The PESA (Progression of Early Subclinical Atherosclerosis) study demonstrated that in 1779 individuals (50% women, mean age 45 years), without conventional risk factors, about half of the participants had subclinical atherosclerosis detected via

ultrasonography (of femoral and carotid) or coronary calcium imaging [61] who would be otherwise classified as very low risk. This is supported by previous findings of a high prevalence (34%) of carotid plaques in individuals at low FRS and coronary artery calcium score (CACS) of 0 [62]. Furthermore, women are more likely to have zero CAC scores than men [63], whereas intravascular US studies in women have shown that lesions in women have less calcium despite similar plaque burden compared to men [64].

Hence, US may be valuable in identifying plaque at a younger age and in populations which manifest atherosclerosis at a later age, such as women. Additionally, studies have demonstrated improvement in physician adherence to guideline recommendations (e.g., prescription of aspirin, hypertension and lipid-lowering therapy to patients with plaque) [65] and patients' prescribed preventative therapies (such as smoking cessation, diet, and exercise) [66] with the use of imaging-based techniques to detect and quantify carotid plaque. In a large Swedish open-label, randomized controlled trial of 3532 patients without CVD, sharing pictorial representation of personalized carotid US scans showing plaque burden and vascular age to physicians and patients resulted in a significant decrease in cardiovascular risk scores compared to a control group at 1-year follow-up [67].

Hence, ultrasound, given its safety, throughput, and available evidence, still has value in cardiovascular risk assessment although CAC scores have become the principal imaging test in aiding CV risk stratification. With the advent of improved quantification using 3D US and advances in plaque characterization, the value of US in clinical CV risk management will continue to evolve.

5 Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging is an important diagnostic tool not only to identify total plaque burden of the carotid arteries but also to characterize atherosclerotic plaque components in detail. Imaging correlation with surgical specimens suggests that MRI can accurately differentiate plaque features [68]. In addition to total plaque burden, MRI can identify specific plaque components including a thin fibrous cap (FC) [69], large fatty or lipid-rich necrotic core (LRNC) [68], calcification, and intraplaque hemorrhage (IPH) [70] that have been associated with plaque vulnerability and future ischemic events. Hence, the role of MRI in cardiovascular risk stratification has begun to emerge.

5.1 Plaque Characterization

MRI provides tissue contrast and therefore can identify atherosclerotic plaque components and plaque characteristics. This allows for an accurate and noninvasive determination of the specific histological features of carotid plaque.

5.2 *Intraplaque Hemorrhage (IPH)*

IPH has been shown to be associated with ischemic events. In a meta-analysis of eight studies, the presence of IPH in carotid atherosclerotic plaque was strongly associated with incident ischemic cerebrovascular events (HR, 5.7; 95% CI, 3.0–10.9) [71]. The conversion of methemoglobin into hemoglobin results in T1 shortening and leads to a hyperintense (bright) signal on T1-weighted (T1W) MR scans which can be used to detect IPH (Fig. 7). A study by Albuquerque et al. [72] using a T1W sequence demonstrated excellent agreement between the histologic finding of acute or recent hemorrhage and the MRI findings (r = 0.91; 95% CI, 0.81–1.00). IPH can be challenging to distinguish from LRNC as it is often located within the LRNC. Hence, most studies evaluating IPH have used 3D time-of-flight (TOF) sequences which are typically combined with a T1W black blood MRI (BBMRI) scan using a 2D electrocardiographically gated double inversion recovery fast spin echo pulse sequence with fat suppression and an inversion time set to null the blood signal from the carotid lumen. On T1W BBMRI scans, both IPH and

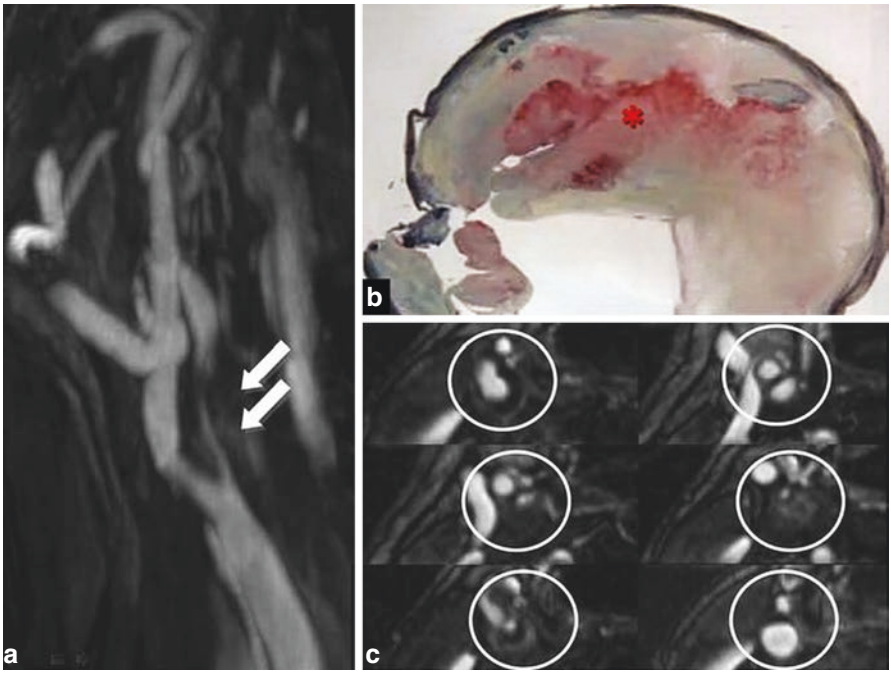

Fig. 7 High-resolution T1-weighted images acquired during the equilibrium phase of gadolinium. (**a**) The presence of a long and eccentric plaque with regular surface but enhancement of the inner plaque component (arrows), compatible with the presence of inflammation and hemorrhage. (**b**) The correspondent histological section confirmed the presence of hemorrhage within the plaque core. (**c**) Axial reformatted images show the localization of enhancement area within the plaque. (Reprinted from Saba [88]. With Springer Nature)

LRNC are hyperintense, whereas on TOF scans, IPH will be hyperintense, while the LRNC will be isointense [68, 70].

5.3 Fibrous Cap

Another key imaging target is the identification of a ruptured fibrous cap or a thin fibrous cap, which is prone to rupture. A significant challenge for MRI is to detect fibrous cap's thickness. These are usually 100–500 μm, which is near the resolution limit of 3T MRI sequences that are typically used. Thicker caps appear as dark bands separating the vessel lumen from the core of the plaque on TOF images (Fig. 8). Thus, the absence of a dark band with a bright gray region directly adjacent to the lumen indicates a thin or ruptured FC. Furthermore, fibrous caps may exhibit gadolinium enhancement which can be visualized as bright bands near the surface of the lumen on post-contrast-enhanced T1-weighted images.

5.4 Lipid-Rich Necrotic Core (LRNC)

LRNC has been shown to be another feature of a "vulnerable" plaque and hence another imaging target to identify high-risk plaques. McDermott et al. [73] showed that the presence of LRNC in the proximal superficial femoral artery (SFA) detected by MRI was associated with significantly increased incidence of amputations and critical limb ischemia, independent of ankle brachial index (ABI). The most common approach for LRNC detection uses T1W sequences [74]. The use of contrast-enhanced T1W imaging allows for improved sensitivity, specificity, and

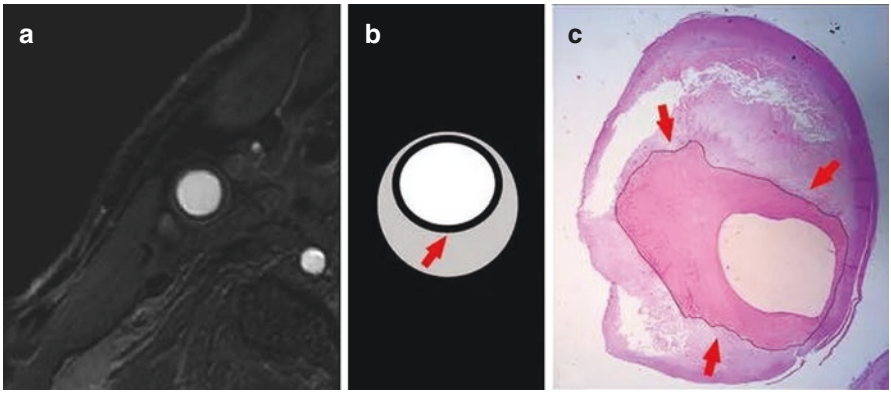

Fig. 8 (**a**) Thick fibrous caps appear as a juxtaluminal band of low signal in time-of-flight (TOF) MR images. (**b**) Schema is demonstrated (red arrow). (**c**) Histological image of a thick fibrous cap (red arrows). (Reprinted from Saba [88]. With Springer Nature)

reproducibility than T2-weighted (T2W) imaging. The accuracy of LRNC detection is further improved if no IPH is present [75] and when LRNC areas are >2 mm^2 [74].

5.5 Calcification

Increased calcification in the coronary arteries has been shown to be a strong predictor of ASCVD events. Calcium in general is considered a marker of plaque stability; however, increased calcification in the arteries also indicates an increased plaque burden and hence may translate into an increased frequency of incident events. Computed tomography has a high sensitivity to detect calcification and is widely accepted as a CV risk prediction tool. MRI can also be used to identify calcification. These can be recognized as dark signal voids, i.e., hypointense areas, within the plaque, on all standard contrast weightings. Saam et al. [74] demonstrated good correlation between MRI and histology for calcification ($r = 0.74$; $P < 0.001$). Bright-blood imaging techniques used in TOF sequences are best to distinguish juxtaluminal calcification from ulcerated plaque.

5.6 Accuracy and Reproducibility of MR Imaging

MRI-identified calcification, FC, IPH, and LRNC demonstrate good correlation with histology. Previous studies that performed a multi-sequence protocol detected IPH with excellent sensitivity (range, 82–96%) and specificity (range, 74–100%) [70, 76]. The detection of LRNC by MRI showed the most variation in specificity (range, 40–100%) and sensitivity (range, 76–98%) [74, 77] depending on the type of sequence (single or multi-sequence, with or without contrast enhancement), size of LRNC, and whether IPH was present or not. Calcification was easily detected on all contrast sequences, with high sensitivity ranging from 76% to 80% and specificity ranging from 86% to 94% [68, 74, 77]. Finally, FC evaluated by MRI also demonstrated good sensitivity ranging from 81% to 100% and specificity ranging from 80 to 96%, as confirmed by histology [68, 75].

Several studies have established good inter-scan reproducibility of plaque morphological measurements by carotid MRI [78] to allow for longitudinal assessment of atherosclerotic plaque.

5.7 MRI, Clinical Outcomes, and Risk Prediction

In a systematic review and meta-analysis of nine studies with 779 subjects, IPH, LRNC, and thin FC detected by MRI were significantly associated with incident ischemic events (stroke or transient ischemic attack) with HR of 4.6 (95% CI,

2.9–7.2), 3.0 (95% CI, 1.5–5.6), and 5.9 (95% CI, 2.7–13.2), respectively [79]. However, there was significant heterogeneity in baseline symptoms (five studies had symptomatic patients) and degree of carotid stenosis (six studies with moderate to high-grade stenosis).

Takaya et al. [80] showed that in a study of 154 asymptomatic patients with relatively high-grade (50–70%) carotid stenosis, thinned or ruptured plaque, IPH, LRNC, and maximum wall thickness were all associated with future cerebrovascular events. However, the study had limited follow-up of 38 months, and more importantly, a small number of events (12 events) occurred.

In a prospective study of 698 subjects without CVD from MESA cohort, Zhang et al. demonstrated that MRI-measured wall thickness demonstrated a more consistent association with incident cardiovascular disease, particularly stroke, than IMT measured using US after adjustment for TRF [81]. In another prospective study of 946 individuals from the MESA cohort [82], MRI-measured remodeling index (defined as wall area divided by the sum of wall area and lumen area), lipid core, and calcium in the internal carotid artery were all significant predictors of subsequent cardiovascular events. The addition of MR remodeling index and lipid core improved the C statistic for event prediction from 0.696 to 0.734, and the NRI was 7.4% and 15.8% for participants with and without cardiovascular events, respectively ($P = 0.02$). Furthermore, in a case-control study, Zhao et al. demonstrated that prolonged intensive lipid-lowering therapy (niacin 2.5 g/d, lovastatin 40 mg/d, and colestipol 20 g/d) was associated with not only reduction in plaque size but also stabilization of plaque due to reduction in lipid composition [84]. Virani et al. evaluated carotid artery MRIs in 1471 participants without CVD of the ARIC carotid MRI sub-study and showed carotid MRI-derived measures of both plaque burden and plaque characteristics may be useful imaging surrogates to identify those at higher risk of future CVD events [83]. Among measures of plaque burden, normalized wall index showed a borderline significant association with incident CVD (HR, 1.23; 95% CI, 1.00–1.52; $p = 0.05$). Among plaque characteristics, lipid core presence (seen in 573 participants) and mean minimum fibrous cap thickness were independently associated with incident CVD (HR, 1.87; 95% CI, 1.13–3.08; $p = 0.014$; HR, 0.67; 95% CI, 0.47–0.95; $p = 0.03$) over a mean follow-up of 3.7 years.

Large-scale studies with longer follow-up and bigger sample size are still needed to determine the improvement in risk prediction afforded by carotid plaque MRI and its impact on patient outcomes.

5.8 Advantages of MRI

Carotid MRI has many advantages over other imaging techniques (Table 2). Unlike conventional imaging techniques, such as US, x-ray, and computed tomography (CT), MRI affords excellent soft tissue contrast and unlimited viewing angles and avoids ionizing radiation. While US is widely available, it is user dependent and has limited spatial, temporal, and contrast resolution, which reduces its accuracy and

reproducibility relative to MRI. Computed Tomography Angiography (CTA) does have a high spatial resolution; however, it involves the use of ionizing radiation. Furthermore, the presence of calcification can affect the ability of CT in the evaluation of plaque burden and composition.

5.9 Limitations of MRI

There are many technical barriers to the implementation of carotid MRI into real-world practice. The initial MRI techniques and protocols used in research for carotid plaque imaging were time-consuming and costly, required specialized equipment, and were only interpretable by a radiologist with highly specialized training. Furthermore, most of the MRI studies have significant heterogeneity in sequences or settings used, which limits general application of MRI. Larger studies investigating comparable sequences and clearly described definitions of these sequences must be performed before a standardized protocol can be applied to real-world practice.

With the wide availability of 3 Tesla field strength MRI systems and newer surface coils, there is sufficient signal-to-noise ratios to acquire high-resolution carotid imaging and make carotid plaque MRI more feasible for routine clinical use. Numerous prospective and retrospective studies have shown these techniques to add unique value in predicting patient outcomes [71, 79]. Plaque assessment by MRI thus stands ready for integration into the clinical workup of patients with suspected carotid atherosclerosis. Availability and cost-effectiveness of MRI will ultimately be important determinants of whether carotid MRI is adopted clinically for cardiovascular risk assessment.

6 Conclusion

In conclusion, both carotid US and MRI can help to detect atherosclerotic disease in early stages and predict the risk of a future stroke or coronary events. Carotid US is reliable, safe, and widely available and allows assessment of CIMT, the presence of plaque, plaque volume, and morphology. CIMT and plaque are correlated with most of the major cardiovascular risk factors as well cardiovascular events. Advances in US and limitations of CIMT have shifted the focus to plaque assessment (burden and characteristics) which will continue to improve and evolve. Carotid MRI, on the other hand, demonstrates good sensitivity and specificity in identifying features associated with plaque vulnerability, including intraplaque hemorrhage, fibrous cap (intact or ruptured), lipid-rich necrotic core, and calcification. At this time, clinical data on the value of MRI in risk prediction are starting to emerge. As the era of precision medicine moves forward, imaging has the ability to play an important role in cardiovascular risk prediction and prevention.

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Role of CT Coronary Calcium Scanning and Angiography in Evaluation of Cardiovascular Risk

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Summary

- Global risk assessment approaches for coronary artery disease such as Framingham risk scores do not accurately assess long-term risks for cardiovascular events.
- Non-contrast computed tomography detection of coronary artery calcium (CAC) improves the ability to accurately predict risk and adds information beyond global risk assessment and identifies patients in need of preventative medical treatment.
- The absence of CAC is associated with a very low risk of cardiovascular death, myocardial infarction and acute coronary syndrome over the next 5 years.
- Current practice guidelines endorse that intermediate-risk individuals are ideal patients for CAC screening.
- CAC scoring improves lifestyle changes and medication adherence.
- Coronary computed tomography angiography (CTA) provides comprehensive information regarding the location, severity, and characteristics of atherosclerotic plaque, especially noncalcified plaque.
- CTA has been shown to have a 99% negative predictive value for ruling out obstructive coronary artery disease.

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1 Introduction

Cardiovascular disease (CVD) is the leading cause of mortality worldwide with coronary artery disease (CAD) accounting for nearly half of all cardiovascular (CV) deaths [1, 2]. Although the mortality rate after the occurrence of myocardial infarction has significantly decreased over the last two decades, the incidence of CAD has remained relatively stable during this period, suggesting that more robust primary prevention efforts are needed [3–5].

In approximately one-half of the individuals, the initial presentation of CAD is either myocardial infarction (MI) or sudden death [6]. Because half of first major coronary events occur in asymptomatic individuals [3, 6], clinicians who want to implement appropriate primary prevention therapy must be able to accurately identify "at risk" individuals.

Clinical decision-making for primary prevention of CAD in asymptomatic individuals is traditionally guided by an initial estimate of the impact of a set of laboratory and physical factors as they relate to the risk of a coronary event. Preventive strategies are then modified and implemented after taking into account economic (personal, insurance provider, national impact) and individual (adherence, side effects) consequences of treatment versus no treatment. Recommendations for diet, weight loss, and exercise offer little or no risk to the patient and yield significant long-term benefits [7]. Most decisions for pharmacologic intervention, specifically those related to lipid lowering, are driven by perception of risk for a given individual that are derived from large studies applied to both heterogeneous and homogeneous populations.

Over the past 25 years, screening for subclinical atherosclerosis using cardiac computed tomography (CT) to screen for coronary artery calcium (CAC) has become well established and now recommended in the guidelines. Use of CAC to identify patients who might benefit from initiation or intensification of risk factor modification efforts is now paramount to prevention efforts. This chapter details the current use of CAC and coronary computed tomography angiography (CTA) for risk stratification and prevention of future adverse CV events.

2 Atherosclerosis and CAD

Autopsy studies have consistently shown that the presence of calcium in coronary arteries indicates the presence of atherosclerosis, and the extent of coronary calcification correlates with the risk of future atherosclerotic cardiovascular disease (ASCVD) events [8]. Detection of CAC is now utilized in current global risk assessment approaches by identifying high-risk individuals who harbor advanced subclinical atherosclerosis.

A minority of patients with CAD do not exhibit traditional risk factors such as hypertension, elevated cholesterol, obesity and smoking. In addition, many patients with such risk factors do not develop CVD. Furthermore, there is substantial variation in the severity of CAD at every level of risk factor exposure. This variation in disease is probably due to a number of factors including genetic susceptibility,

presence of intrinsic biochemical and extrinsic environmental risk factors and duration of exposure to the specific level of risk factors [9].

Most noninvasive methods of evaluating CAD, such as stress testing, generally identify only patients with advanced atherosclerotic disease leading to a flow-limiting coronary stenosis and myocardial ischemia. Quantifying and characterizing atherosclerosis in its preclinical, pre-flow limiting phase so that appropriate preventive strategies can be instituted before an adverse event occurs is necessary. Cardiac CT has evolved rapidly and has been established as a noninvasive method able to visualize the coronary artery lumen and plaque [10].

3 Non-contrast Coronary CT: Assessment of Coronary Artery Calcification

Calcification of the atherosclerotic plaque occurs via an active process of mineralization with deposition of hydroxyapatite crystals and not simple mineral precipitation [11, 12]. It begins in the very early stages of atherosclerosis. Early studies identified CAC by means of electron beam computed tomography (EBCT) as a highly reliable method for identification of arterial calcification with a high sensitivity for detection of significant atherosclerosis. Rumberger and colleagues have demonstrated a strong relationship ($r = 0.90$) between CAC measured by EBCT and direct histologic plaque areas in autopsy hearts [12]. The total atherosclerotic plaque burden was associated strongly with the total calcium burden, but not all plaques were calcified. Moreover, within a given coronary artery, there is a poor correlation and wide variation between the degree of plaque calcification and extent of luminal stenosis on coronary angiography [13]. This may be due, at least in part, to individual variations in coronary artery remodeling, whereby the luminal cross-sectional area and/or external vessel dimensions enlarge in compensation for increasing area of mural plaque. Since research has shown that burden of disease and cardiovascular risk is accounted for by more than focal luminal stenosis, non-contrast cardiac CT is a potentially powerful tool for the identification of patients at risk.

4 Methods of Assessing Coronary Artery Calcium

4.1 Modality for Coronary Artery Calcium Determination

Cardiac CT provides image slices or tomograms of the heart. Multi-detector computed tomography (MDCT) is currently the most frequently used modality to assess the extent and severity of underlying coronary calcification and does not require intravenous contrast [14]. MDCT systems have two principal modes of scanning, which depend on whether the patient on the CT couch is advanced in a stepwise fashion (axial, prospective triggering) or continuously moved at a fixed speed relative to the gantry rotation (helical, retrospective gating).

MDCT with improved spatial resolution allows for rotation speeds 260–350 ms. MDCT has the ability to image every 0.5 mm (submillimeter slices). Resolution of current CT systems uses a matrix of 512 × 512 and 0.35 mm × 0.35 mm × 0.5 mm resolution. The current generation of MDCT systems is capable of acquiring up to 320 sections of the heart simultaneously with electrocardiographic (ECG) gating in either a prospective or retrospective mode. Coronary calcification is determined in axial mode using prospective ECG triggering at predetermined offset from the ECG-detected R wave. Calcified lesions are defined as two or three adjacent pixels with a tomographic density of >130 Hounsfield units (HU) [14].

4.2 Measurement/Scoring of Coronary Artery Calcium Burden

There are currently two CT calcium scoring systems widely used: the original Agatston method [14] and the volume score method [15]. The Agatston score method involves multiplication of the calcium area by a number related to CT density (from 1 to 4 based on HU). With this method, area for all pixels above a threshold of 130 HU is calculated at every 3-mm slice and multiplied by a density factor [14]. The volume score method is less dependent on minor changes in slice thickness and calcium density and is more reproducible [15]. There is an excellent correlation between both scoring methods, and they show similar characterization when applied properly [16]. Both methods provide a total CAC score, which is the sum of the individual calcium scores from the lesions in the four epicardial coronary arteries. An example of significant coronary calcium is shown in Fig. 1.

Standardized categories for the Agatston calcium score have been developed with score of 0 indicating the absence of CAC and scores of 1–100, 101–399, and ≥400 suggesting mild, moderate, and severe CAC, respectively. For a particular age, gender, and race, a web tool https://www.mesa-nhlbi.org/Calcium/input.aspx provides the estimated probability of non-zero CAC and the 25th, 50th, 75th, and 90th percentiles of CAC score distribution. By entering an individual's age, race, and gender information and the observed CAC score, this tool will provide the estimated percentile for the individual by comparing CAC score to others with the same age, race, and gender [17] .

5 Clinical Value of CAC on Assessing Cardiovascular Risk in Asymptomatic Individuals

5.1 Independent Association of CAC with Risk of Future CV Events

There is consensus among studies that CAC is a strong independent predictor for future adverse CV events as well as all-cause mortality even after adjusting for conventional cardiovascular risk factors [18–20].

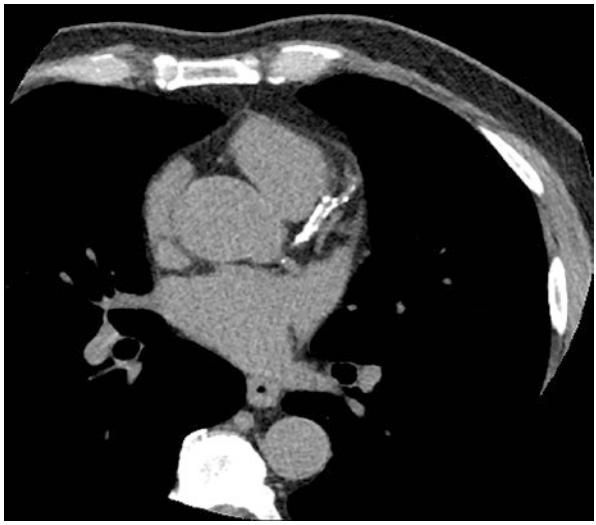

Fig. 1 Example of significant coronary artery calcium (CAC) in the left anterior descending artery from a 256-slice General Electric multi-detector CT scanner

Data from the Multi-Ethnic Study of Atherosclerosis (MESA) on 6722 men and women free of CVD at baseline who were followed for a median of 3.8 years showed that among those with CAC of 1–100, 101–300 and >300, the adjusted hazard ratios (95% confidence interval) for a major coronary event (myocardial infarction or death from CAD) were 3.89 (1.72–8.79), 7.08 (3.05–16.47), and 6.84 (2.93–15.99), respectively, compared to those with a CAC score of 0 [18]. Importantly, this landmark study showed the prediction of CAC for coronary events held not only in Whites but also African-Americans, Hispanics, and Asians. Budoff et al. recently published the 10-year follow-up manuscript from MESA confirming the long-term prognostic importance of CAC in all these ethnic groups, notably showing that a CAC score of >100 was associated with a 10-year risk of ASCVD of >7.5% in each ethnic group [21] which has been deemed the threshold for statin therapy benefit [22]. Malik et al. evaluated the MESA cohort after 11 years follow-up and found the CAC score was independently associated with incident CAD in multivariable analyses in those with diabetes (HR, 1.30; 95% CI, 1.19–1.43), metabolic syndrome (HR, 1.30; 95% CI, 1.20–1.41) and neither condition (HR, 1.37; 95% CI, 1.27–1.47) [19]. Another study from MESA examined the combined association of CAC score and lipid abnormalities with future risk of CVD. They divided the cohort into several categories according to the number of lipid abnormalities (low-density lipoprotein cholesterol (LDL-C) >130 mg/dl, high-density lipoprotein cholesterol (HDL-C) <40 mg/dl for men and <50 mg/dl for women and triglyceride ≥150 mg/dl, one, two, or three lipid abnormalities) and CAC score (0, 1–99, ≥100). Results showed that those with a CAC score of 0 and three lipid abnormalities had an event rate of 5.9 per 1000 person-years compared to 22.7 per 1000 person-years in those with zero lipid abnormality and CAC score ≥100 [20].

The incidence of all-cause mortality in a cohort of 44,052 asymptomatic middle-aged patients without CAD showed all-cause mortality rates for CAC = 0,

CAC 1 to 10 and CAC >10 of 0.87, 1.92, and 7.48/1000 person-years, respectively [23]. The more recent CAC consortium observational cohort study of 66,636 individuals free of established CVD showed that all-cause mortality risk was lowest among individuals with a CAC score of 0. After adjusting for traditional risk factors, individuals with CAC > 10 had a 1.6-fold increased risk of all-cause mortality compared to those with a CAC score of 0 [24]. All these results strengthen the existing evidence that there is a strong independent association between CAC score and future risk of CV events as well as mortality; the higher the CAC score, the higher the risk of future events independent of other risk factors.

5.2 Incremental Value of CAC to Traditional Risk Factors for CV Risk Prediction

Framingham risk score (FRS) has long been widely utilized as the standard risk assessment method to predict future risk of CV events. It incorporates age, gender, smoking history, hypertension, total cholesterol and HDL-C to derive estimated risk of developing a future CV event within 10 years [25]. However, data suggest that the FRS misclassifies a large number of individuals into lower-risk categories when their risk for future events is actually high [26].

In one study, it was shown that within each risk category of FRS, an increasing level of CAC score is associated with a higher risk of nonfatal myocardial infarction or coronary heart disease death [27]. It was also demonstrated that the event rates among those in the high FRS risk group with a lower CAC score were lower than those in the intermediate FRS risk group with a high CAC score.

When CAC with other five novel risk markers for CAD including ankle-brachial index, high-sensitivity C-reactive protein and family history was investigated on the improvements in prediction accuracy in asymptomatic adults with intermediate FRS (estimated 10-year CVD risk of >5 and <20%) who participated in the MESA study, CAC had the strongest association with CAD and incident CVD and showed the highest increment in the area under the curve for incident CAD and incident CVD. CAC also provided the greatest net reclassification improvement (0.659) and the greatest absolute number of correctly reclassified subjects. CAC showed superior accuracy in predicting CVD risk over the FRS in individuals classified as intermediate risk [28].

Even among persons with diabetes mellitus (DM), CAC incorporated with other conventional risk scores resulted in better discriminative ability for incident CAD in patients and was also a better predictor of incident CV events and mortality [29, 30].

5.3 Absence of Coronary Artery Calcification

The absence of CAC appears to be one of the strongest factors to provide reassurance that the risk for future CVD events is significantly lower [23, 31], indicating a "warranty period" protection from CVD events for at least 10 years from the low event rate in patients with a CAC score of 0 being <0.5% [18, 29, 32].

The MESA cohort that examined the distribution of CAC score by risk factor burden reported that a large number of individuals with ≥3 risk factors have a CAC score of 0 (35%) [33]. The rate of hard CAD events in this group (1.4 per 1000 person-years) was similar to those with one risk factor and a CAC score of 0 (1.1 per 1000 person-years). On the other hand, it was observed that the risk is several fold higher among those with an FRS <6% who have a CAC >300 compared to those with FRS >20% but no CAC. When the CAC score was eliminated, risk was about twofold higher among those with ≥3 risk factors compared to those with only one risk factor (1.6 vs. 2.9) in comparison to those with no risk factors [33].

In the elderly population, Mortensen et al. recently compared the ability of 13 different risk markers to downgrade ASCVD risk in elderly individuals. Among the risk markers, CAC = 0 and CAC ≤10 resulted in the greatest changes to post-test risk for CAD and CVD and the greatest improvements in overall risk classification. Event rates were lowest for CAC = 0 (0.9 and 3.2 per 1000 person-years, respectively) and CAC ≤10 (0.9 and 2.8 per 1000 person-years, respectively) [34].

These findings indicate that the absence of CAC reliably predicts low risk for future CVD events in asymptomatic patients and can be used to exclude those who may not benefit from preventive pharmacotherapy.

5.4 Who Should Be Screened with Non-contrast Coronary CT Among Asymptomatic Individuals?

Current guidelines recommend that calcium scanning should be used as a tool to improve risk assessment in patients at borderline or intermediate risk of future CVD events [35–38]. An expert consensus statement from the Society of Cardiovascular Computed Tomography endorses that it is appropriate to perform CAC screening for asymptomatic individuals without clinical ASCVD who are 40–75 years of age in the 5–20% 10-year ASCVD risk group and selectively in the <5% ASCVD group (such as those with a family history of premature CAD) for the assessment of CV risk.

The recent 2019 American College of Cardiology (ACC)/American Heart Association (AHA) prevention guidelines recommend that in intermediate-risk

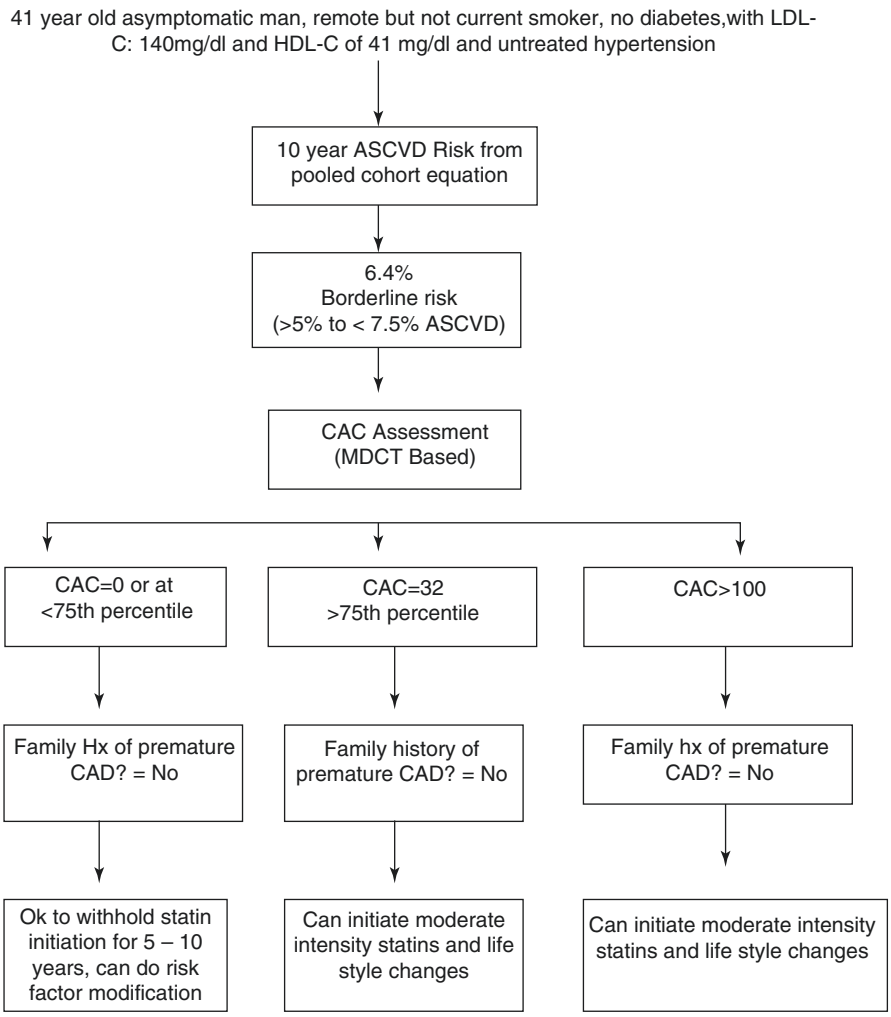

Fig. 2 Incorporation of the CAC score into decision-making for statin initiation in low- to intermediate-risk patients based on current guidelines

adults (≥7.5% to <20% 10-year ASCVD risk) or adults at borderline risk (5% to <7.5% 10-year ASCVD risk), measuring a CAC score is judicious to guide decisions on initiation of statin therapy as CAC score can reclassify risk upward (if CAC score is ≥100 or ≥75th age/sex/race percentile) or downward (if CAC score is 0) [39] (see Fig. 2 for current CV risk assessment algorithm for statin therapy initiation).

The 2018 Multisociety guidelines on treatment of blood cholesterol in adults gave similar recommendations among intermediate-risk or selected borderline-risk adults, with the indication for statin treatment if the CAC score was ≥100 or ≥75th

percentile, and noted statin therapy may be considered in those with lower non-zero CAC scores [38]. This was the first guideline to advocate for considering the withholding of statin therapy in those with a CAC score of 0 (as long as a positive family history, diabetes and cigarette smoking were not present) given such patients were previously not shown to reach the threshold for statin benefit [38, 40].

The guidelines acknowledge that a subgroup among those at low risk may benefit from CAC screening as a large proportion of those considered being at low risk by FRS and having a family history of premature CAD have significant CAC [41, 42]. Because family history is not considered in the FRS, or the ASCVD pooled cohort equation, these risk estimators may misclassify a proportion of individuals into the lower-risk category, despite the fact that they might have increased risk for future CVD events.

5.5 Medication Compliance Following CAC Scanning

Adequate control of risk factors with behavioral modification and medications to control lipids, blood pressure and other risk factors in asymptomatic individuals is the basis of preventive efforts to reduce the occurrence of CV events.

In addition to providing important prognostic information as well as improving risk stratification, knowing one's atherosclerotic disease burden as measured by a non-contrast coronary CT may prompt healthy changes in one's lifestyle as well as improve compliance with preventive pharmacotherapy [43–47].

A retrospective study of 2608 patients (72% men, mean age 58 ± 8 years) who were followed for a mean of 4.1 ± 3.2 years after an initial CAC scan evaluated the motivational effects of CAC score and statin use and weight loss among patients who returned for a follow-up scan. Adherence to statin was lowest (27.4%) among those with CAC score = 0 and gradually increased with higher CAC scores (1–99, 39.2%; 100–399, 53.6%; ≥400, 58.8%; $p < 0.001$). Behavioral modification leading to weight loss was lowest (19.8%) among those with CAC score = 0 and gradually increased with higher CAC scores (1–99, 23.4%; 100–399, 30.8%; ≥400, 33.6%; $p < 0.001$) [46].

A prospective study randomized 2137 volunteers to either CAC scanning or no scanning to evaluate the impact of the addition of CAC to conventional risk factor modification on outcomes of a 4-year change in CAD risk factors and FRS. Compared with the no-scan group, the scan group had significantly greater reduction in systolic blood pressure ($p < 0.02$), serum LDL-C ($p < 0.04$) and waist circumference ($p < 0.01$). Increasing baseline CAC score was associated with a proportionately greater improvement in most CAD risk factors, lower FRS and more weight loss at follow-up [47].

In summary, there is an important role for CAC screening in asymptomatic individuals for both prognostic reasons and risk stratification. Although it identifies individuals at high risk for a future cardiovascular event when it is high, it provides

reassurance to a large group of individuals when it is zero, leading to avoidance of medications and unnecessary diagnostic testing.

6 Coronary Computed Tomography Angiography for Assessing Cardiovascular Risk

Coronary computed tomography angiography (CTA) provides comprehensive information regarding the location, severity, and characteristics of atherosclerotic plaque, thus serving as a robust noninvasive tool for detecting CAD. It is able to differentiate plaques that are calcified, noncalcified, or mixed [48]. In the following section, we describe briefly the image acquisition, diagnostic accuracy of CTA in assessment of obstructive CAD and the prognostic value of plaque subtypes with future cardiovascular risk.

7 Image Acquisition

The development of cardiac CT has been challenging, given rapid cardiac motion, small vessel diameters, tortuous anatomical patterns and overlapping cardiac structures. Current MDCT systems have a faster gantry rotation speed, resulting in better temporal resolution and better z-axis spatial resolution made possible by thin collimations with extensive volumetric acquisitions.

CTA requires the intravenous administration of an iodinated contrast, and approximately 50–100 mL of contrast medium is necessary for adequate coronary artery enhancement. The accurate timing of image acquisition relative to the contrast injection determines overall image quality. A test bolus or bolus tracking technique is used to optimize this timing by determining the amount of time needed for peak contrast enhancement in the aorta.

CTA is performed with electrocardiographic (ECG) gating in a prospective or retrospective mode. ECG gating synchronizes image acquisition with the cardiac cycle. The optimal phase or interval for image analysis is the period during which the heart is the least mobile (usually end-diastole) and the least degraded by motion artifact. Prospective ECG gating entails scan initiation at a defined interval after the R wave, continues for a prespecified duration, and then stops until the same optimal period is reached in the subsequent cardiac cycle, at which time scanning resumes. Retrospective ECG gating employs continuous acquisition of images throughout the cardiac cycle. The images from multiple consecutive heartbeats are then reconstructed at various percentages of the R-R interval (e.g., from 0% to 90% of an R-R cycle at 10% intervals). Gating is the most advantageous at slow heart rates (less than 60 beats/min), where the R-R interval is >1000 msec.

Cardiac motion is minimized with the use of oral and/or intravenous beta-blockers prior to scanning, thereby reducing the heart rate and prolonging the time during the cardiac cycle at which coronary artery velocity is low. Nitroglycerin in sublingual tablets or spray form is used to maximally dilate the coronary vessels in order to obtain high-quality coronary images. Respiratory motion is excluded by performing the scan during a single breath-hold.

8 Image Interpretation

The coronary vasculature on CTA is evaluated through axial images, multi-planar (coronal, sagittal, or oblique) reformations and three-dimensional (3D) volume-rendered datasets constructed from specific phases during the cardiac cycle. Maximum intensity projection (MIP) images allow the evaluation of longer segments of the coronary vessels but can be limited by overlapping structures adjacent to the artery of interest. Curved multi-planar (MPR) reformations are reconstructed on a plane to fit a curve and allow display of the entire vessel in a single image. Three-dimensional (3D) volume-rendered images are useful for selecting images with the least motion artifact and for assessing the relationships among different anatomic structures. Figure 3 shows a volume-rendered image demonstrating severe stenosis of the proximal left anterior descending artery.

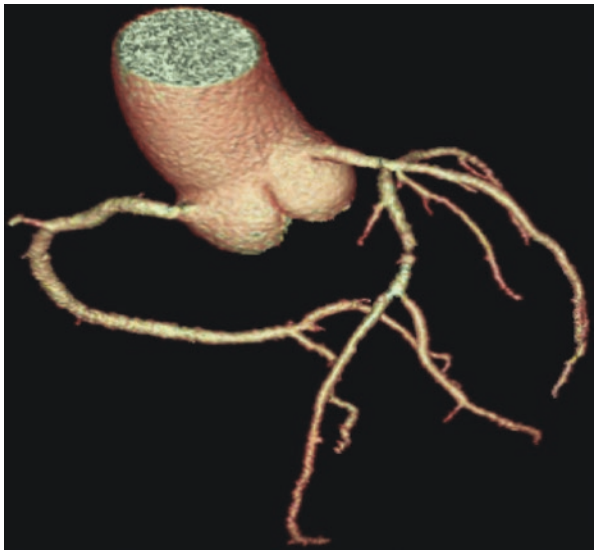

Fig. 3 Volume-rendered image from 64-slice General Electric multi-detector CT scanner showing all coronaries with severe stenosis of the proximal left anterior descending artery

9 Radiation Dose

Advancements in MDCT technology have led to shorter scan times, reduced breath-hold duration, smaller intravenous contrast injections and decreased motion-related artifacts, resulting in lower radiation exposure and improved diagnostic accuracy. The recommendation is that radiation doses for coronary calcium scores are sufficiently low (approximately 1 mSv), which is far below background annual radiation exposures [49]. Also several radiation dose reduction techniques for CTA have been introduced. These include dose modulation (which lowers radiation dose by 30–48%), reduction of kVp to 100 for smaller patients (which lowers radiation dose by 40%), limit top and bottom of scan field (which lowers radiation dose by 20%) [50] and prospective triggering (which lowers radiation dose by 70%) [51]. Collectively, the dose reduction will be approximately 80–90%.

One recent study, without using any other dose reduction technique except for prospective imaging, reported mean patient radiation dose was 77% lower for prospective gating (4.2 mSv) than for retrospective gating (18.1 mSv) ($p < 0.01$), without compromising image quality or diagnostic accuracy [52]. Another study similarly reported that use of prospective triggering reduced radiation exposure by 80% without compromising image quality compared to traditional retrospective acquisition [53].

10 Diagnostic Accuracy of CTA for Detection of Obstructive CAD

Among patients without known disease who get an elective invasive coronary angiogram after noninvasive testing, only slightly more than one-third of them have obstructive CAD [54, 55]. We need better noninvasive testing to improve the assessment of likelihood of obstructive CAD and increase the diagnostic yield of cardiac catheterization.

CTA demonstrates high accuracy for detection of obstructive CAD [56, 57]. Low prevalence of obstructive CAD has been reported in multicenter studies of population of patients with stable chest pain and intermediate risk [54, 55, 57]. A large multicenter study compared the diagnostic accuracy of commonly used noninvasive anatomic and functional imaging in identifying patients with significant CAD defined by invasive catheterization [57]. In this study, 475 patients with stable chest pain and intermediate likelihood of CAD underwent CTA and ≥1 functional test including stress myocardial perfusion imaging by single-photon emission computed tomography or positron emission tomography, stress echocardiography and stress cardiac magnetic resonance. Results showed that CTA had the highest diagnostic accuracy, the area under the receiver operating characteristic curve being 0.91 (95% confidence interval, 0.88–0.94), and sensitivity was 91% and specificity was 92%.

The ACCURACY trial provided the first prospective multicenter data evaluating the diagnostic performance of 64-multidetector-row CTA in individuals without

CAD by evaluating subjects with chest pain at 16 centers that were referred for invasive coronary angiography. A total of 230 subjects underwent both CTA and invasive coronary angiogram. The sensitivity, specificity and positive and negative predictive values to detect ≥50% or ≥70% coronary stenosis were 95%, 83%, 64% and 99%, respectively, and 94%, 83%, 48% and 99%, respectively. The 99% negative predictive value established CTA as an effective noninvasive modality to rule out obstructive CAD [56].

Even among patients with acute chest pain with low to intermediate risk for acute coronary syndrome with normal initial troponin and nonischemic electrocardiogram, Hoffman et al. showed that the 64-slice coronary CTA can be useful for early triage. CCTA had a sensitivity and negative predictive value for acute coronary syndrome of 100% (95% confidence interval, 98–100%) and 100% (95% confidence interval, 89–100%) in patients without CAD [58].

CTA with a high negative predictive value performs better at low prevalence of disease, and therefore, it supports the role of CTA in patients with lower pretest probability of CAD. The recent 2019 European Society of Cardiology Guidelines for diagnosis and management of chronic coronary syndromes recommend CTA to rule out CAD in low-risk patients with chest pain due to its superior accuracy compared to other functional noninvasive testing [59]. The 2016 updated UK National Institute for Health and Care Excellence guidelines also recommend CTA as the first-line noninvasive testing modality for evaluation of patients with typical or atypical anginal chest pain with normal EKG [60].

11 Prognostic Value of CTA in Prediction of CV Outcomes

The burden of angiographic disease detected by CTA provides both independent and prognostic values in predicting all-cause mortality and major adverse cardiovascular events in symptomatic patients independent of conventional risk factors and CAC [61–64]. In patients with chest pain, coronary artery plaque scores obtained from CTA including segment stenosis score, segment involvement score and three-vessel plaque score which assess coronary artery plaque extent, distribution and number of coronary vessels involved were all predictive of higher rates of all-cause mortality independent of other traditional clinical CV risk factors [62]. The absence of coronary artery plaque by CTA, left main artery plaque and proximal left anterior descending artery plaque was associated with high negative predictive value (97.8–99.7%) for all-cause mortality [62]. Hence, the extent of plaque detected by coronary CTA enhances risk assessment in symptomatic individuals. However, in asymptomatic individuals, CTA findings of degree of luminal stenosis and plaque composition add little or no prognostic value for prediction of all-cause mortality beyond traditional risk factors and CAC score [65].

12 Association of CTA-Detected Plaque Subtypes with Traditional Risk Factors

CTA is used to detect and quantify plaque subtypes including calcified, mixed and noncalcified plaque. Figure 4 shows an example of a CTA study demonstrating calcified and noncalcified plaque with severe proximal right coronary artery stenosis.

Rivera et al. studied the relationship between traditional cardiovascular risk factors with the presence and burden of plaque subtypes in more than 1000 asymptomatic Korean individuals who underwent CTA [66]. Increasing age and male gender were overall the strongest predictors for the presence of any plaque as well as for an increased burden of calcified, mixed, or noncalcified plaque. Smoking was strongly associated with the burden of noncalcified plaque. LDL-C levels were associated with the presence and burden of mixed plaque.

Among symptomatic diabetics with intermediate pretest probability risk, it has been shown that they have higher number of coronary segments with mixed plaques compared to nondiabetics even after taking into account traditional risk factors (odds ratio, 2.34; 95% confidence interval, 1.14–4.83) [67]. A prospective case-control study evaluated the prevalence of subclinical coronary atherosclerosis and plaque characteristics in young subjects with type 2 diabetes mellitus (T2DM) while comparing them with an age- and gender-matched nondiabetic population. Compared with nondiabetic patients, the prevalence of CAD and calcified and

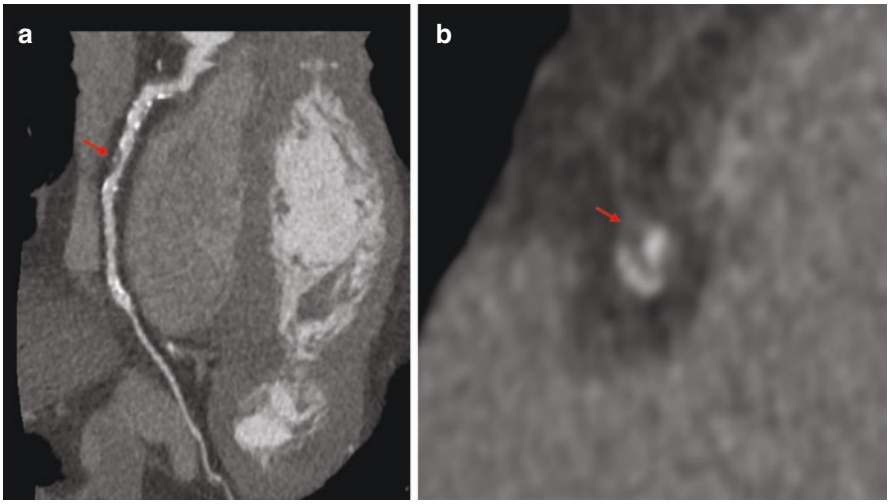

Fig. 4 Coronary CT angiography demonstrates mixed coronary plaque (red arrow) (**a**) Curved multi-planar image showing mixed plaque with noncalcified, soft, lipid-rich plaque and calcified plaque in the proximal right coronary artery (red arrow) with severe stenosis. (**b**) Cross section of axial image showing mixed plaque with noncalcified, soft, lipid-rich plaque surrounding calcified plaque in proximal right coronary artery (red arrow)

noncalcified plaques was higher in patients with T2DM (19% vs. 58%, $p < 0.001$) even after adjustment for traditional risk factors. In patients with a zero CAC score, T2DM had a higher prevalence (46%) of noncalcified plaque ($p < 0.0001$). Fibrous, fibrous fatty, low-attenuation plaque volumes and dense calcium plaque were significantly greater in T2DM even after adjusting for risk factors [68].

Differences in coronary plaque morphology between men and women have been identified [69]. Nasir et al. demonstrated using CTA that women presented with a significantly lower mean number of segments containing calcified plaques (1.43 ± 2.04 vs. 2.25 ± 2.30, $p = 0.004$) as well as mixed plaques (1.67 ± 1.23 vs. 2.25 ± 2.30, $p = 0.05$). Also, in women, the relative proportion of overall plaque burden was more likely to be noncalcified (40% vs. 28%) and less likely to be mixed (22% vs. 28%) or calcified (38% vs. 43%) [69].

13 Prognostic Value of CTA-Detected Plaque Subtypes with Cardiovascular Disease Outcomes

Plaque quantification and composition has incremental value and is valuable in risk stratification strategies. The variety of plaque types assessed on CTA and their association with major adverse cardiac events have extensively been studied. There is currently quantitative computed tomography coronary plaque analysis software (QCT) (see Fig. 5), which allows objective assessment of total plaque burden and burden of individual plaque components: low-attenuation, fibrofatty, fibrous, and calcified plaque that is not possible by visual analysis [70, 71]. Semi- and fully automated QCT analyses have been shown to have excellent performance and strong correlation with intravascular ultrasound in detection of plaque volume, plaque types, and mean plaque burden percentage [71].

Pundziute et al. assessed the relationship of coronary plaque subtypes detected by MDCT and future events of CV death, nonfatal myocardial infarction and unstable angina requiring hospitalization and revascularization [72]. During a mean follow-up of 16 months, among all plaque subtypes, only mixed plaque burden was associated with adverse events (HR, 1.6; 95% confidence interval, 1.6–2.0).

Plaque characteristics such as positive vessel remodeling, napkin-ring sign and low-attenuation plaques (<30 Hounsfield unit) have also been shown to be associated with subsequent development of acute coronary syndrome [73, 74].

Small studies have suggested mixed plaque burden to predict future CV outcomes [75, 76]. Among patients who had cardiac death after a mean follow up of 5 ± 2 years following CTA, Hell et al. in a single center study matched them to controls by age, gender, risk factors and symptoms. Semi-automated software was used to quantify plaque volumes and plaque type on the entire coronary tree, and the results showed that low-density noncalcified plaque, total plaque volume and noncalcified plaque volume were predictors of cardiac death [76].

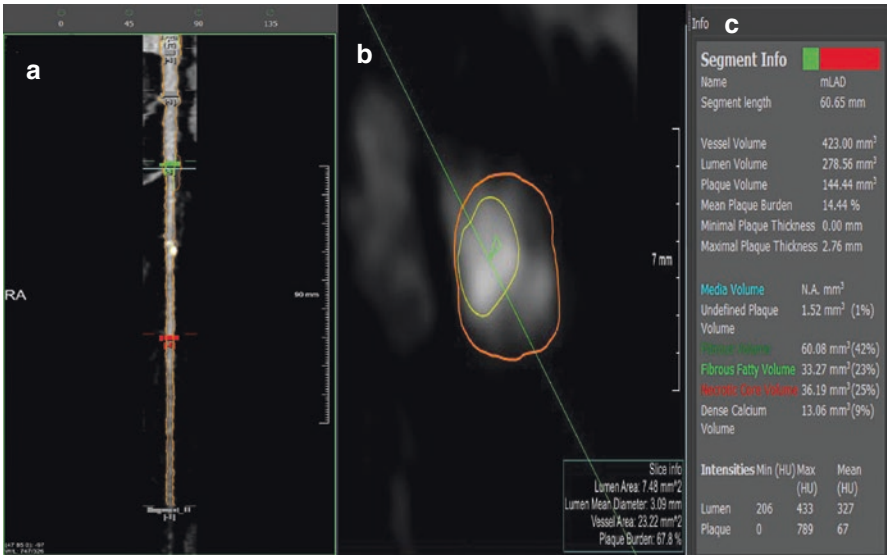

Fig. 5 Example of semi-automated plaque analysis (using QAngio CT research edition Medis Specials Version 3.1.4.1) of left main and left anterior descending arteries, showing longitudinal straightened view. (**a**) Cross-sectional views showing calcified plaque surrounding the vessel lumen (**b**) and plaque analysis results showing total plaque volume (144 mm^3), fibrous fatty volume (33.27 mm^3) and mean plaque burden (14.44%) (**c**)

The pericoronary adipose tissue (PCAT) CT attenuation, which is a promising novel marker for identifying high-risk plaques, is also determined from CTA. PCAT CT attenuation has been able to detect biopsy-proven vascular inflammation among patients undergoing cardiac surgery [77]. Figure 6 shows PCAT CT attenuation analysis, and in the study by Goeller et al., PCAT was shown to be higher around culprit lesions in patients with acute coronary syndrome [78]. This reinforces the additional value of CTA in improving the identification of high-risk patients for adverse CV events and prognostication.

14 Use of Quantitative CT Coronary Plaque Analysis to Study Effects of Therapy on Plaque Progression in Clinical Trials

Currently, quantitative CT coronary plaque analysis (QCT) is used to study the effects of therapy on plaque progression in clinical trials. The effect of 2400 mg per day of aged garlic extract on coronary plaque volume in diabetic patients was evaluated in a randomized controlled trial. Semi-automated coronary plaque analysis

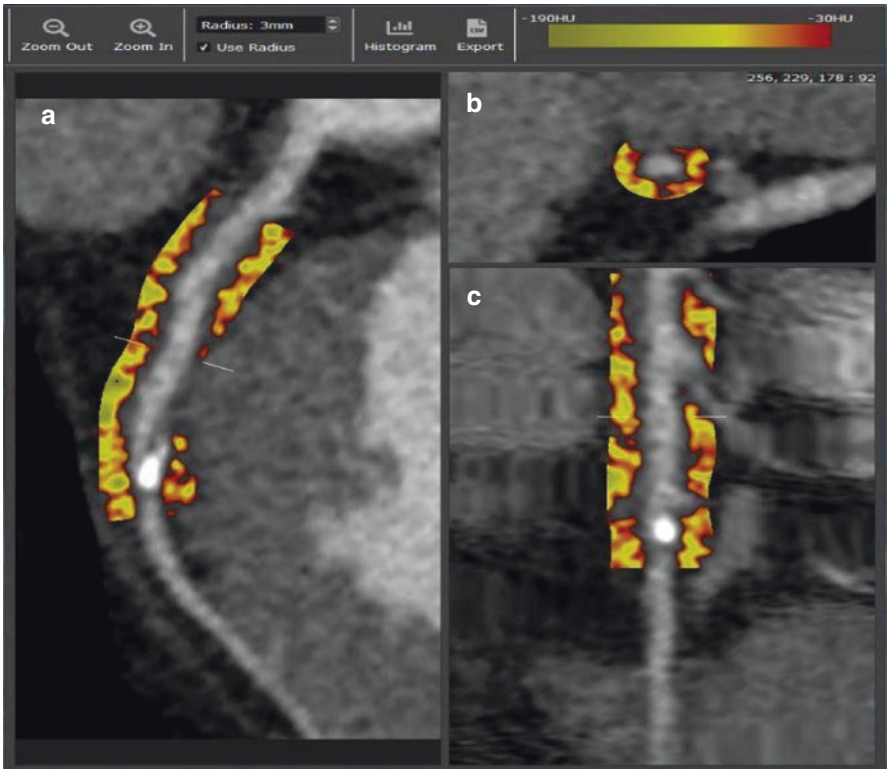

Fig. 6 Quantification of pericoronary adipose tissue (PCAT) CT attenuation (using Autoplaque software) of culprit lesion in the left anterior descending coronary artery in Hounsfield units (HU). PCAT color map ranging from red [−30 HU] to bright yellow [−190 HU]). (**a**) Curved multiplanar view image of PCAT measure. (**b**) Cross-section view of PCAT measure. (**c**) Straightened view of PCAT measure

software (QAngio CT) showed significant regression in low-attenuation plaque by 29% ($p = 0.0415$) after a follow-up period of 12 months among diabetic patients compared to the placebo group [79].

In the Cardiovascular trial, the effect of low-dose testosterone therapy among men aged 65 years or older with hypogonadism on coronary plaque volume was evaluated. Plaque measurement using QAngio CT showed a mean increase in non-calcified plaque volume in the treatment group of 40 mm^3 vs. 4 mm^3 in the placebo group ($p = 0.003$) after 1 year of treatment [80].

In the EVAPORATE trial, 4 g/day of icosapent ethyl: a high-purity prescription eicosapentaenoic acid (EPA) ethyl ester as an adjunct therapy in patients with CAD and on statin was shown to reduce low attenuation plaque volume compared to placebo measured by QAngio CT [81].

15 Conclusion

CAC is independently associated with future risk of CAD and all-cause mortality; the higher the CAC score, the higher the risk. CAC screening improves risk prediction for a future CV event and mortality above and beyond the traditional risk assessment methods such as the FRS and ASCVD pooled cohort equation. Current practice guidelines recommend its use in intermediate-risk asymptomatic individuals where it appears to be the most predictive of future risk. It may also be useful in low-risk asymptomatic individuals with a family history of premature CAD. Among those with symptoms, it may be a useful tool in the low- to intermediate-risk group, where a zero CAC score has a very high negative predictive value for ruling out significant CAD and is prognostic of future CV outcomes. CAC score is also useful in identifying patients who will benefit more from preventive pharmacotherapy like statins.

CTA has incremental value in further quantifying and evaluating other noncalcified or mixed plaque not identifiable by non-contrast CT, which helps to further risk-stratify patients, especially young diabetic patients, with subclinical atherosclerosis in order to initiate preventive therapy. The negative predictive value of CTA in ruling out obstructive CAD is 99%. This makes CTA a reliable method in the emergency department for ruling out obstructive CAD and acute coronary syndrome in patients with low to intermediate risk with acute chest pain, and it has now been recommended by current practice guidelines.

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Cardiovascular Disease Prevention in Women

Anum Saeed and Martha Gulati

Summary

- Cardiovascular disease remains the leading cause of death among women. Primary care physicians, obstetricians, and preventive cardiologists providing care to women remain at the forefront of efforts needed for primordial, primary, and secondary prevention of ASCVD events and minimizing resulting morbidity among women.
- The steps to facilitate coordinated healthcare delivery to high-risk women for prevention of ASCVD revolve around the core principles of utilization of available screening tools, healthy lifestyle promotion for all women, and well-harmonized collaboration between multidisciplinary teams for early intervention and management of risk factors for ASCVD.
- It is important to promote heart healthy dietary habits and lifestyle recommendations for all women. Discussion of lifestyle and behavior modifications should be visited at each clinician-patient interaction.
- Screening for female-specific or female-predominant ASCVD risk factors should be performed at each clinician-patient visit by optimal history-taking skills and use of preexamination surveys.
- The presence of female-specific ASCVD risk factors should prompt the in-depth screening for any other ASCVD traditional risk factors and/or risk enhancers to aid the appropriate calculation of the 10-year ASCVD risk score and risk assessment.

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- Aggressive management of ASCVD risk factors by lifestyle and behavior modifications (in accordance with AHA's Life's Simple 7) and early pharmacological treatment initiation and adherence surveillance should be regularly performed.
- Collaboration and communication between multidisciplinary care teams including primary care clinicians, obstetrics/gynecology or "cardio-obstetrics," cardio-oncology [1], and other disciplines are encouraged when indicated.
- Encourage utilization of Women's Heart Centers, wherever applicable, and continued promotion of research funding in the field of ASCVD prevention for women to further the knowledge into female-specific mechanistic pathways of disease processes and ultimately therapeutic targets and delivery to curtail cardiovascular morbidity and mortality.

1 Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality among women worldwide [2, 3]. In the United States, while cardiovascular mortality overall is the leading cause of death in women, for those under the age of 75 years, cancer mortality predominates [1]. The impact of sex and gender contribute to the difference in the pathophysiology of atherosclerotic cardiovascular disease (ASCVD), in addition to differences in treatment and outcomes [4, 5]. Further, not only does the impact of traditional ASCVD risk factors differ by sex, but also there are certain risk enhancers of ASCVD that are sex specific.

In the recent past, an increase in scientific progress has begun to identify a spectrum of risk factors for ASCVD which may be specific to women. Previously, there was a severe lack of knowledge of sex-specific risk factor assessment in women given low enrollment in clinical trials and analysis [6]. Sex-specific risk factors for women include age of onset of menarche, adverse pregnancy outcomes, the impact of oral contraceptives and hormone replacement therapy, premature ovarian failure, premature menopause, breast cancer, and related treatments. These sex-specific risk factors confer additional threat beyond the traditional risk factors among women. Even now, after two decades worth of progress, the complete understanding of traditional risk factors and sex-specific risk enhancers and awareness of sex-differences is lacking.

In this chapter, we will review the identification of female-specific risk factors for cardiovascular diseases and their utility in risk stratification and discuss primary preventive strategies for women.

2 Perception of Cardiovascular Diseases Among Women

The perception of ASCVD risk among women is traditionally less than that for men. This is true among primary care physicians and cardiologists. In a survey of 1011 American women and 300 physicians (200 primary care physicians [PCPs] and 100

cardiologists), the majority in both groups did not rank cardiovascular disease as a "top concern" for women [7]. Among women responders to the survey, 45% suggested that cancelling or postponing a physician appointment until achieving target weight loss was a common practice [7]. Furthermore, only 22% of PCPs and 42% of cardiologists reported being "extremely well prepared" to provide care for women patients [7].

Women are less likely to receive aggressive lipid management compared to men, even in the modern era [8]. Among 5618 participants of the PALM (Patient and Provider Assessment of Lipid Management) registry (43% females) eligible for statin based on the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) cholesterol guideline for primary and secondary prevention, women were less likely than men to be treated with a statin (67% vs 78%, $P < 0.001$) or to receive a guideline-recommended statin intensity (35% vs 44%, $P < 0.001$). Women were also less likely to believe that statins were safe (47.9% vs. 55.2%%, $p < 0.001$) or effective (67.9% vs. 73.1%, $p < 0.001$) and more likely to report discontinuation of a statin compared to men [6].

3 Cardiovascular Disease Risk Factors

The traditional ASCVD risk factors (including smoking, obesity, diabetes, hyperlipidemia, and hypertension) affect both men and women and increase cardiovascular risk, but there are established sex differences in how these traditional risk factors affect women compared to men. Sex is biologic and dictated by chromosomes (in contrast with gender, which is socially construed). Every cell has a sex, and ultimately, the heart and vascular system respond differently to risk factors based on the expressed biological sex. Some ASCVD risk enhancers occur exclusively in women, known as "female-specific" risk factors, while certain risk factors are prevalent more frequently in women compared to men and are called "female-predominant" risk factors [5, 9] (Fig. 1).

3.1 Traditional Risk Factors

Age: One of the leading risk factors for CVD is age. In women, the cardioprotective effect of estrogen during premenopause years can result in a ~8–10-year lag in the onset of CAD [4, 10]. This effect is diminished as expected in the menopausal ages of women, and after the age of 55 years, the risk for CAD increases similarly in both men and women. However, at all ages, the incidence of CVD remains lower in women than in men [1].

Obesity: According to the latest National Health and Nutrition Examination Survey (NHANES) 2017–2018 data, obesity was prevalent in 42.4% adults without any significant differences between men and women. Among women, the prevalence of obesity continues to increase and is 39.7% in age group 20–39 years, 43.3%

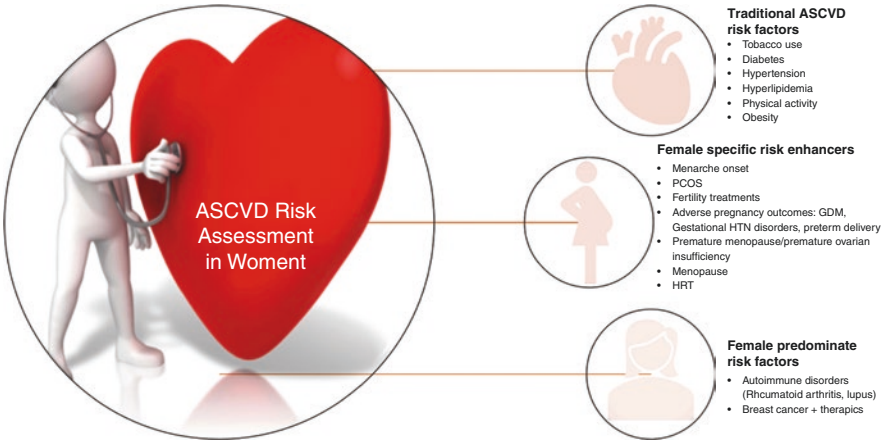

Fig. 1 Atherosclerotic cardiovascular disease risk factors across a woman's life span. Abbreviations: ASCVD atherosclerotic cardiovascular disease, PCOS polycystic ovarian syndrome, GDM gestational diabetes mellitus, HTN hypertension, HRT hormone replacement therapy

among those aged 40–59 years, and 43.3% among those aged 60 years and over [11]. Class III obesity (with a body mass index [BMI] ≥ 40 kg/m^2) increments occur in a linear manner for women, but not men, within the past decade [2]. The impact of obesity on the development of ASCVD seems to be greater in postmenopausal women and is thought to be due to a redistribution of fat around the abdominal area with a predisposition for developing metabolic syndrome. The guidelines on ASCVD prevention in women recommend that women should maintain or lose weight through appropriate physical activity, caloric intake, and formal behavior modification programs with a goal BMI of <25 kg/m^2 or waist size <35 inches [4].

Physical Activity: Low physical activity is associated with higher cardiovascular risk, and women remain less physically active than men at all ages. Both low physical activity and prolonged sitting have been shown to augment ASCVD risk [12]. In a study involving 1.1 million females without ASCVD, with a follow-up time over 9 years, those who reported moderate activity were found to be at lower risk of ASCVD events. However, strenuous physical activity was no more beneficial than moderate exercise [13].

The 2019 ACC/AHA CVD Prevention guidelines [14] emphasize that a comprehensive lifestyle intervention encompasses regular self-monitoring of food intake, physical activity, and weight. Recommended aerobic moderate-intensity physical activity (e.g., brisk walking) is ≥150 minutes/week (equal to ≥30 minutes/day on most days of the week) with higher levels of physical activity (approximately 200–300 minutes/week) to maintain weight loss. The recommended goal for vigorous exercises is 75 minutes per week.

Smoking: Smoking and smokeless tobacco (chewing tobacco and other forms) use are a well-known cause of CVD and all-cause mortality. A recent meta-analysis of 75 cohort studies (~2.4 million individuals) showed a 25% greater coronary heart

disease (CHD) risk in women smokers compared with men smokers (RR, 1.25; 95% CI, 1.12–1.39). As reported in the Heart Disease and Stroke Statistics-2020 Update by the AHA, 59.3% of women in the United States report lifetime exposure to tobacco smoking or products [2] and overall, approximately 12.2% of women over the age of 18 years are current smokers in the United States. Even though this percentage of women smokers is lower than men, the risk conferred by smoking is greater in women [15]. A reduction in smoking has previously shown ~13% decline in the incidence of ASCVD risk [16].

As in men, women should be advised not to smoke and to avoid environmental tobacco smoke. Smoking cessation counseling at each encounter, nicotine replacement therapy, and other pharmacotherapy options as indicated in conjunction with a behavioral program promoting smoking cessation should be initiated. It should be recognized that smoking cessation works differently in women compared with men. Men have more nicotine receptors in their brain, and nicotine replacement appears more effective in men than in women. Varenicline, on the other hand, has been shown to be more effective as a smoking cessation aid in women [17].

Hypertension: Approximately 46% of US adults have hypertension (defined as systolic blood pressure [SBP] ≥130 mm Hg or diastolic blood pressure [DBP] ≥80 mm Hg). The prevalence of hypertension is higher in Blacks than in Whites, Asians, and Hispanic Americans and rises noticeably with older age. Hypertension risk is higher in older women than in older men [18, 19]. Approximately 67% of women aged 60 years and over have hypertension compared to ~59% of men over age 60 years with hypertension (Fig. 2) [20].

In premenopausal women, the endogenous estrogens support vasodilation which results in lower blood pressure, but it is not simply dichotomous. A recent analysis of longitudinal blood pressure patterns in men and women showed steeper increases in women compared with men beginning in the third decade of life with a similar continued trajectory through the life course (likelihood ratio test $\chi 2 = 531$ for SBP; $\chi 2 = 123$ for DBP; $p < 0.001$). In models fully adjusted for CVD risk factors, these sex-based blood pressure trajectory differences are significant (likelihood ratio test $\chi 2 = 314$ for SBP; $\chi 2 = 31$ for DBP; $p < 0.001$) [21].

The issue of whether antihypertensive treatments differentially affect blood pressure responses in women is currently lacking. For women, blood pressure changes during pregnancy, even if transient, can have long-term implications for not just future risk of hypertension but also risk for many forms of cardiovascular disease. This is addressed in a later section.

Dyslipidemia: The prevalence of elevated total cholesterol (TC) ≥200 mg/dL and ≥240 mg/dL occurs in 42% and 13% of women ≥20 years, respectively, in the United States [1]. Similarly, 30% of women over 20 years have a low-density lipoprotein cholesterol (LDL-C) of ≥130 mg/dL, and 10% of these women have high-density lipoprotein cholesterol (HDL-C) <40 mg/dL. Elevated LDL-C, triglycerides, and non-HDL-C and low HDL-C have all been associated with increased risk for CVD in women [22–24]. HDL levels are higher in women [25], and on average, HDL-C is ~10 mg/dL higher in women than in men throughout their lives. HDL is inversely associated with ASCVD events [26]. Nonetheless, HDL as a target of

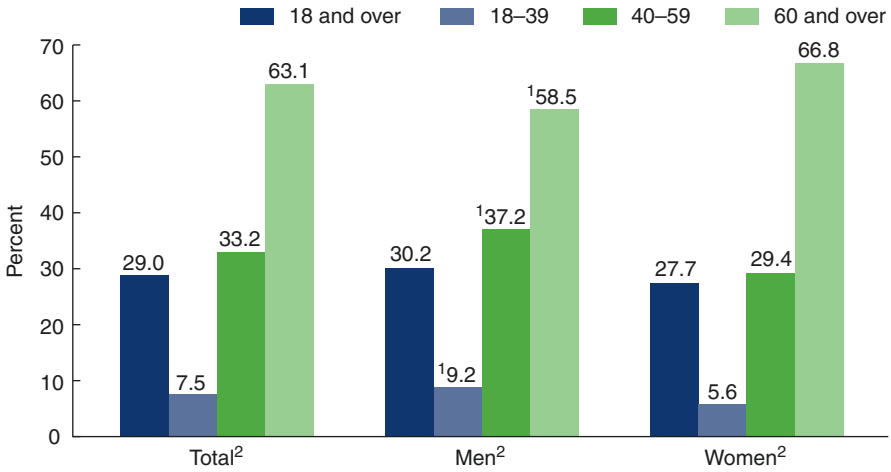

Fig. 2 Prevalence of hypertension among US adults aged 18 years and older, by sex and age (2015–2016). Estimates for age group 18 years and over are age adjusted by the direct method to the 2000 US Census population using age groups 18–39, 40–59, and 60 and over. Crude estimates for age group 18 years and over are 32.1%, total; 31.8%, men; and 32.4%, women. [1] Men significantly different from women in the same age group. [2] Significant increasing trend by age. (Reprinted from Fryar et al. [20].)

therapy has to date never improved outcomes and is not the target of the ASCVD risk assessment.

The 2013 and 2018 ACC/AHA cholesterol guidelines were made sex specific with the inclusion of sex in the pooled cohort formula for ASCVD risk estimation [11, 19]. There is consideration of high-intensity statin therapy for those with 10-year ASCVD risk ≥7.5%, and high-intensity statin therapy is recommended as the first-line therapy in patients aged ≤75 years who have clinical ASCVD. In addition, the 2018 ACC/AHA cholesterol guidelines use "risk-enhancing" factors which favor statin initiation in adults 40–75 years of age without diabetes mellitus and 10-year risk of 5–19.9%. Premature menopause (age < 40 years) and history of preeclampsia are included in the list of risk-enhancing factors.

Data from the Centers for Disease Control and Prevention show that less than half of the 78.1 million statin-eligible individuals were taking the medicines [27] and, interestingly, women are less likely to be prescribed statins than the men with equal risk [28]. This is despite strong evidence that women and men respond with equal efficacy and reduction in ASCVD events on statins [29, 30].

Diabetes Mellitus: Diabetes mellitus remains a major risk factor of ASCVD risk in women as well as men. A large body of evidence showing the aggressive association of elevated hemoglobin A1C, even below the threshold for diagnosis of diabetes mellitus, with adverse cardiovascular outcomes after adjustment for traditional ASCVD risk factors exists [31–34].

Women with diabetes have a significantly higher risk of coronary heart disease and stroke incidence than men with diabetes [35]. A systematic review from 64

cohort studies (inclusive of 858,507 individuals) showed an approximately 44% greater sex-specific relative risk ratio for incident CHD in women with diabetes compared to men (1.44 [95% CI 1.27–1.63]) in fully adjusted risk factor models [35]. The same pooled cohort analysis (inclusive of 775, 285 individuals) also showed a relative risk of 2.28 (95% CI, 1.93–2.69) versus 1.83 (95% CI, 1.60–2.08) for incident stroke in women and men with diabetes, respectively [36].

Women with diabetes mellitus are typically less likely to have an HbA1c <7% and receive less aggressive treatment for many modifiable CVD risk factors than diabetic men [37]. Clinical trial interventions to lower HbA1c have failed to demonstrate ASCVD benefit with intensive versus standard glycemic control [32, 38–40].

The currently applicable guidelines recommend an HbA1c <7%, if achieved without causing significant hypoglycemia, for ASCVD risk reduction [4]. In adults 40–75 years of age with diabetes, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy at least is indicated [5, 41].

3.2 Female-Specific Risk Factors

Onset of Menarche: Age at onset of menarche is associated with ASCVD risk. Early menarche (occurring at or before the age of 12 years) and late onset menarche (>15 years) have been shown to increase risk for adverse cardiovascular outcomes including myocardial infarction, stroke, and heart failure hospitalizations. In a cohort of 648 women from the WISE (Women's Ischemia Syndrome Evaluation) study, history of menarche at age ≤10 years and ≥15 years showed adverse cardiovascular event hazard ratios of 4.53 (95% CI, 2.13–9.63) and 2.58 (95% CI, 1.28–5.21), respectively, compared to women with menarche at age 12 years.

Adverse Pregnancy Outcomes: Pregnancy is a cardiometabolic stressor that may unmask underlying vascular and metabolic abnormalities [42]. Gestational hypertensive disorders (gestational hypertension and preeclampsia) and gestational diabetes affect approximately 3–20% of pregnancies and confer an additional risk for CVD in women [9, 43, 44].

Gestational Hypertensive Disorders: Hypertension affects approximately 10% of pregnancies and is one of the leading causes of maternal and fetal morbidity and mortality [45, 46]. Hypertensive disorders during pregnancy can be classified as preeclampsia, eclampsia, chronic hypertension, and gestational hypertension. Preeclampsia is defined as new-onset hypertension after 20 weeks' gestation, proteinuria (0.3 g/24 h), and/or end organ dysfunction.

Gestational hypertensive disorders have been linked to increased risk of developing hypertension [47] as well as CVD later in life [45, 48–50]. The mechanism of the increased risk of CVD in women with gestational hypertensive disorders is poorly understood. However, women with preeclampsia history have endothelial dysfunction and increased levels of both VCAM-1 (vascular cell adhesion protein 1) and ICAM-1 (intercellular adhesion molecule 1) several years after pregnancy.

Therefore, it is plausible that the unique shared state of endothelial dysfunction, oxidative stress, inflammatory response, and increased expression of procoagulants may be responsible for the increased CVD risk in women with preeclampsia. Preeclampsia and CVD also share similar risk factors including obesity, insulin resistance, and renal disease [35].

A prospective study including 14,403 women, with a median follow-up time of 37 years, showed that preeclampsia was associated with CVD death (HR, 2.14 [1.29–3.57]), and this risk of CVD death was predominantly higher among women with onset of preeclampsia by 34 weeks' gestation (HR, 9.54 [4.50–20.26]) [51].

A recent study published from a longitudinal population-based cohort from the United Kingdom which included 1.3 million women showed that women who had one or more pregnancies with preeclampsia were at significantly higher risk of almost every cardiovascular event, including incident stroke (HR, 1.67 [1.54–2.35]), coronary artery disease events (HR, 1.82 [1.34–2.16]), and cardiac death (HR, 2.12 [1.49–2.99]) when compared to women who did not have hypertensive diseases of pregnancy [52].

The 2018 AHA/ACC multi-societal cholesterol guidelines [41] defined preeclampsia as an independent sex-specific risk enhancer for ASCVD development. The American College of Obstetricians and Gynecologists has recommended yearly assessment of blood pressure, lipids, fasting blood glucose, and BMI following a medical history of preeclampsia [53]. Beyond more aggressive screening, women with a history of hypertensive disorders of pregnancy should be advised to focus on lifestyle modifications including diet, weight, exercise, and smoking cessation.

Hypertensive disorders of pregnancy should be considered when assessing ASCVD risk in any woman.

Gestational Diabetes: Gestational diabetes mellitus (GDM) is defined as new-onset impaired glucose tolerance during the third trimester of pregnancy. Normal glucose metabolism typically returns after pregnancy. However, despite glucose metabolism returning to normal, patients with a history of GDM have an elevated risk for developing diabetes mellitus in the future [54]. Additionally, numerous population cohorts have shown that gestational diabetes increases the risk for ASCVD [55].

The GENetics of Non-Insulin dependent Diabetes (GENNID) Study examined a cross-sectional group of parous women who had first-degree relatives with type 2 DM. Of these, 332 had GDM and 663 did not. Although the incidence of CVD was self-reported, women with prior GDM were more likely to have metabolic syndrome and type 2 DM and had an increased prevalence of CVD (15.5 vs. 12.4%) [56].

A population-based retrospective cohort study from Canada examined the risk of type 2 DM and CVD in women with a history of GDM. From a single province with 351,685 women in which 8191 had GDM, those with GDM had a greater risk of developing type 2 diabetes mellitus when compared to women without GDM (27% vs 3.2%, over a mean follow-up period of 11.5 years). There was also an increased risk of cardiovascular events in those with GDM compared with those without GDM with a hazard ratio of 1.71 (1.08–2.69). Nonetheless, the hazard ratio of cardiovascular events decreased to 1.13 (0.67–1.89) once adjusted for subsequent

diabetes and was no longer significant. The findings suggest there is an increased risk of CVD in patients with GDM, but the development of diabetes mellitus after gestation accounted for most of this increased risk [57].

A retrospective study of women from France between 2007 and 2008 examined this association in 1,518,990 deliveries. In this population, 62,958 had GDM with their pregnancy. After adjusting for age, DM, obesity, and hypertensive disorders in pregnancy, GDM was significantly associated with a higher risk of CVD (adjusted odds ratio, 1.25 [1.09–1.43]) in just 7 years after their delivery. In another retrospective cohort analysis from the United Kingdom, 9118 women diagnosed with GDM were found to have increased incidence rate ratios (IRRs) for ischemic heart disease (2.78 [1.37–5.66]), hypertension (1.85 [1.59–2.16]), and type 2 diabetes (21.96 [18.31–26.34]) in the postpartum period [58] when compared to age- and pregnancy-time-matched controls. The authors also noted that long-term surveillance of CVD risk factors including diabetes and hypertension (HTN) was suboptimal. A recent meta-analysis which included 5,390,591 women from nine studies concluded that young women with GDM had a twofold higher risk of postpartum ASCVD events (RR, 1.98 [1.57–2.50]) compared to women without GDM. Furthermore, the effect size of incident ASCVD events among these women was independent of future incidence of type 2 diabetes [55].

An abnormal glucose challenge test, which is part of routine screening test during pregnancy, has also been associated with adverse lipid profile and ASCVD event risk in postpartum stages [59].

Recent studies have shown that the early increase in CVD risk cannot be exclusively attributable to the subsequent development of diabetes and GDM should be considered an independent risk factor for ASCVD, independent of the presence or absence of diabetes or metabolic syndrome [60]. Abnormal glycemic control during pregnancy is now postulated to be an independent risk factor for future risk of diabetes as well as ASCVD events. The postulated explanations include the presence of underlying genotypic predisposition and a more likely cardiometabolic profile to developing CVD which expresses phenotypically during the stressors of pregnancy. A prospective approach is more enhanced surveillance for ASCVD risk factors and preventive interventions in women with a history of GDM.

Preterm Delivery: Preterm delivery, defined as the delivery of an infant <37 weeks, has been associated with adverse cardiovascular outcomes for women in later years [61, 62]. In an analysis from the Nurses' Health Study, the risk of ASCVD events in 70,182 women with a history of preterm delivery was examined. After adjusting for age, race, parental education, and pre-pregnancy lifestyle and the traditional cardiovascular risk factors, women with preterm delivery in the first pregnancy had an increased risk of ASCVD [1.42 (95% CI, 1.16–1.72)] when compared with women with a term delivery (≥37 weeks) in the first pregnancy [61]. The association of subclinical atherosclerosis has also been linked with a history of preterm delivery in women [63]. In the Pregnancy Outcomes and Community Health Moms (POUCHmoms) study, a total of 605 women underwent B-mode ultrasound to measure the average intima-media thickness (IMT) across the common carotid, bulb, and internal carotid artery segments over a follow-up period of 7–15 years [63].

There were significant differences in maternal vessel remodeling in the carotid bulb (as measured by IMT with average of eight segments) in women with a preterm delivery (0.592 mm) history versus those without (0.575, $p = 0.04$) [63]. In addition, women with a history of preterm delivery have increased risk for developing traditional CVD risk factors (hypertension, type 2 diabetes mellitus, and hypercholesterolemia) in the years after pregnancy [64]. In a meta-analysis of 21 studies with over 338,000 women with previous preterm deliveries, preterm birth was associated with an increased risk of future maternal ASCVD (RR, 1.43 [1.18–1.72]) and cardiovascular disease death (RR, 1.78 [1.42–2.21]) [65]. In addition, the risk for all outcomes in the meta-analyses (i.e., future incident cardiovascular events, cardiovascular death, coronary heart disease events, coronary heart disease death, and stroke) was higher when the preterm delivery occurred prior to 32 weeks (which is the very or extremely preterm as defined by the World Health Organization) compared to 37 weeks [65].

Therefore, it is prudent to elicit aggressive ASCVD prevention interventions in women with a history of preterm delivery.

Premature Menopause and Premature Ovarian Insufficiency: The most common postulation in delayed onset of CAD in women versus men is the role of circulating estrogen and its cardioprotective role. In addition to pregnancy-associated disorders discussed above, premature menopause (before age 40 years) is also a recognized risk-enhancing factor [41]. A recent meta-analysis concluded that women who had menopause at age younger than 45 years were more likely to have an incident coronary heart disease event (RR, 1.50 [1.28–1.76]) compared to women undergoing menopause at age ≥45 years [66].

Premature ovarian insufficiency (POI) is defined as cessation of ovarian function before the age of 40 years and results in a prolonged estrogen insufficiency. Reports have associated POI with an increased risk of cardiovascular disease [67, 68]. A meta-analysis from ten observational studies, including 190,588 women, showed that POI was modestly associated with incidence of coronary heart disease events (HR, 1.69 [1.29–2.21] = 0.0001) but not with stroke [69].

Although the ACC/AHA guidelines recognize premature menopause as a risk enhancer for ASCVD events, evidence promoting hormonal replacement therapy (HRT) is controversial. In the Women's Health Initiative (WHI) study, estrogen-progestin replacement had no cardioprotective effect, and signals of harm were observed with higher risk of coronary heart disease events (HR, 1.29 [1.02–1.63] and stroke (HR, 1.41 [1.07–1.85] [70]. Similar results demonstrating a lack of benefit in a secondary prevention cohort of women were seen in the HERSII follow-up trials (adjusted overall relative hazards for CVD outcomes of 0.97 [95% CI, 0.82–1.14]) [71, 72]. As a consequence of these results, HRT is not recommended as primary or secondary prevention for ASCVD in the current guidelines. Nonetheless, noting the presence of premature ovarian insufficiency and the age of menopause should be part of any woman's ASCVD risk assessment.

Fertility Therapy
The limited data available currently does not support the conclusion that assisted reproductive therapy increases risk for ASCVD. The General Reproductive Assistance and Vascular Illness (GRAVID) Study from Canada is a population-based study used to assess long-term risk of CVD following fertility therapy. Women who gave birth after receiving fertility therapy had about half the risk of cardiovascular disease or death in the subsequent decade compared with women who gave birth without this therapy [HR, 0.55 (0.41–0.74), $p < 0.0001$] [73]. Nonetheless, women who received fertility therapy had an increased risk of pregnancy complications such as maternal metabolic syndrome, including GDM and gestational hypertension, but lower long-term cardiovascular risk [74].

At this time, fertility treatment itself is not considered an independent risk or protective factor for ASCVD beyond noting the adverse pregnancy outcomes that may occur in the short term. However, there is an early signal to suggest that women who have failed fertility therapy have an increased risk for future ASCVD events [74]. In a study examining whether failure of fertility therapy was associated with subsequent adverse cardiovascular outcomes, it was demonstrated that the annual rate of ASCVD events was 19% higher among women who did not give birth after fertility therapy compared to those women who did (adjusted relative rate ratio, 1.21 [95% CI, 1.13–1.30]; $p < 0.001$). It is plausible that fertility therapy failure could be an indicator for future ASCVD risk as it poses a unique cardiometabolic stress test. This hypothesis warrants further investigation.

Hormonal Contraceptive Methods: Approximately 80% of women in the United States have reported use of oral contraceptive methods at least once in their lifetime [75]. Oral contraceptives with estrogen may raise triglyceride levels, and elevations in LDL-C levels have been noted in patients taking hormonal contraceptives containing norgestrel or levonorgestrel. Some observational data suggest that earlier first- and second-generation oral contraceptives were associated with significantly higher risks of incident ASCVD events and thrombosis, particularly when used in smokers [75]. A thorough ASCVD risk assessment includes obtaining optimal history of a woman's type and duration of contraceptive methods to optimally gauge preventive strategies.

3.3 Female-Predominant Risk Factors

Autoimmune Diseases: Systemic autoimmune disorders including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) tend to affect women more often than men [76]. Studies show a robust association between inflammatory diseases (including RA, SLE, and scleroderma) and increased CV mortality in men and women [77].

Individuals with rheumatoid arthritis have a two- to threefold higher risk of myocardial infarction (MI) and a 50% higher risk of stroke [44]. Systemic lupus erythematosus has been reported in case-control studies to increase the risk of myocardial infarction between nine- and 50-fold over the general population [45]. Inflammatory diseases affect the microvasculature, thereby being a cause of progressive CAD.

The 2018 ACC/AHA guidelines include inflammatory diseases as an ASCVD risk enhancer which favor initiation of statin therapy for individuals with borderline ASCVD risk score [41].

Breast Cancer and Breast Cancer Therapy: There is a strong association of breast cancer and associated therapy with increased risk of cardiac mortality and morbidity. There are several shared risk factors for developing breast cancer and ASCVD including dietary habits, obesity, family history, and smoking [78–80]. Women with breast cancer have increased prevalence of cardiovascular risk factors.

Chemotherapeutic drugs, predominantly the anthracycline class and trastuzumab, have been shown to increase the risk of ASCVD and congestive heart failure [81–83]. Radiation for breast cancer treatment, specifically to the left breast, accelerates atherosclerosis. Although the underlying mechanisms of the cardiotoxic effect of radiation therapy remain unclear, myocyte injury, inflammation, increased oxidative stress and fibrosis, as well as downstream microvascular dysfunction may be some of the basis. The typical radiation-based injuries include constrictive pericarditis, myocardial fibrosis, and valvular and/or coronary artery lesions [51]. Women with preexisting cardiac risk factors also have been noted to have a greater absolute increase in risk from radiotherapy. It is to be noted that radiotherapy regimens for breast cancer have evolved over the past few decades and recent single institutional registry data have supported the conclusion that breast radiation therapy-induced ischemic heart disease events may be decreasing [84, 85]. Nevertheless, this remains a strong concern since some women may still have augmented risk for CVD events after radiation therapy.

The cardiotoxic potential of breast cancer itself and its therapies is severalfold. First, there are some shared risk factors which contribute to the development of breast cancer and CVD. Further, breast cancer therapies may result in accelerated atherosclerosis or heart failure (CHF) manifestations in later years post therapy in breast cancer survivors. This period of breast cancer diagnosis and treatment may be an important window to continue implementing CVD risk factor modifications. Further, a long-term posttreatment surveillance strategy needs to be implemented among these for monitoring late cardiotoxicity and/or non-therapy-related CVD event risk.

4 ASCVD Risk Assessment

The Pooled Cohort Equation has been developed to predict ASCVD outcomes (both fatal and nonfatal myocardial infarction and strokes) in both men and women 40–75 years of age by incorporating traditional risk factors such as age, total cholesterol, high-density lipoprotein cholesterol, cigarette smoking, history of

hypertension, diabetes, and blood pressure [4]. The risk scores are used to assess short-term and long-term risks. These equations were derived separately for Caucasian men, African American men, Caucasian women, and African American women allowing sex- and race-specific risk estimation, with the limitation that not all races are represented here. Though the Pooled Cohort Equation was derived from large community-based studies incorporating a spectrum of the US population and validated in various natural history studies, it has limitations when applied to individual patients. These limitations can be partly overcome by accounting for each individual's baseline or acquired characteristics (called *risk enhancers* in the 2018 AHA/ACC multi-society cholesterol guidelines) such as ethnicity and concurrent medical comorbidities that significantly alter the CVD risk. Several conditions specific to women identified as risk enhancers have been described above and should be considered when estimating 10-year ASCVD risks in women.

Given that the 10-year risk ASCVD risk assessment tool [86] still has room for improvement, serum biomarkers and imaging modalities, such as carotid ultrasound and coronary computed tomography scans, are additional modalities to detect subclinical atherosclerosis and improve preventive strategies among women.

Carotid Intima-Media Thickness

Carotid intima-media thickness (CIMT) assessment uses nonionizing-radiation ultrasound to measure the combined thickness of the intima and media of the carotid artery wall [38]. Several studies have shown that CIMT improves risk prediction for CVD and can be used as a surrogate marker for atherosclerosis [71–73]. In the Atherosclerosis Risk in Communities (ARIC) study, the addition of CIMT detected the presence or absence of plaque and improved coronary heart disease (CHD) risk prediction when added to traditional risk factors. The study included 13,145 subjects (7463 women). Approximately 23% of the subjects were reclassified by adding CIMT and plaque formation together or separately. Approximately 61.9% of those in the intermediate-risk group (5–20% estimated 10-year CHD risk) were reclassified to lower risk. In this study, the plaque presence improved risk prediction in women more profoundly compared to men.

It is hypothesized that middle-aged women typically have a low prevalence of atherosclerosis; hence, definite plaque presence may be more useful than CIMT.

Previously, the 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults recommended CIMT for further cardiovascular risk assessment in asymptomatic adults at intermediate risk based on clinical judgment [87]. However, the 2018 ACC/AHA did not recommend routine CIMT testing alone to guide ASCVD risk assessment due principally to more recent studies showing limited prediction beyond risk factors [11]. The presence and type of plaque, however, should be an important consideration when evaluating CIMT scans.

Coronary Artery Calcium Score

Coronary artery calcium (CAC) score, measured by low-radiation-dose computed tomography, is a powerful assessment tool to help improve CVD risk prediction. CAC predicts CVD risks in men and women; however, evidence suggests that the prognostic implications as well as patterns of coronary artery calcium may differ between the two genders. Data from the CAC consortium showed that women

(across age deciles) had a lower prevalence of detectable CAC compared with men. The increase in proportion of women with CAC detection was ~10 years later in women (at age 46 years) than men. Furthermore, across the CAC subgroups (CAC 1–100, 101–399, ≥400), women had fewer calcified lesions, fewer calcified vessels, and lower CAC volume. Among a subgroup with detectable CAC, women had greater lesion size and higher mean plaque density values. Long-term CV mortality was similar for both men and women in whom CAC was undetectable; however, detectable CAC was associated with 1.3 higher hazard ratio for CV death among women when compared with men counterparts ($P < 0001$) [4]. More recent data strongly signify the differences in the sex-specific CAC patterns and increased mortality associated for women with lesion size and number increments [88].

Observational data strongly suggest the high impact of elevated CAC score and patients' preference to continue taking potentially lifesaving preventive therapies [88, 89]. As per the 2018 ACC/AHA Cholesterol Guidelines, CAC score is recommended as a risk assessment refining tool for individuals with intermediate CVD risk (≥7.5% to <20%) by the poooled cohort equation (PCE) and for some of those with borderline (5% to <7.5%) risk. The presence of significant CAC (score ≥100 Agatston units or ≥75th age/sex/race percentile) or absence of CAC (score of 0) can, respectively, upward or downward reclassify risk to guide prevention strategies.

5 Future Directions

In the educational and clinical practice aspects of sex-specific cardiovascular disease prevention, the development and expansion of heart centers for women [80, 81] throughout the United States is an initiative central to the mission of some of the leading cardiovascular organizations in the country. The impact of such focused clinics at academic medical centers and within the community setting will allow sex- and gender-specific clinical training, cultural and diversity training, and emphasis on adherence to evidence-based guidelines and emerging research in this area. Furthermore, continued efforts toward increasing awareness of sex differences in cardiovascular disease of physicians and healthcare providers as well as the general public is a critical step required to improve the cardiovascular health of women.

In the research domain, the introduction of the "omics" tools (genomics, transcriptomics, proteomics, and metabolomics) is a promising pathway to more comprehensive and optimal risk stratification strategies. Recently, Paynter and coworkers identified and validated eight dysregulated metabolites significantly associated with ASCVD in a cohort of postmenopausal women [82]. The ability to concurrently study a large number of metabolites and proteins in the plasma is an opportunity not only to potentially discover unknown pathways of CVD among men and women but also to attain precision of risk stratification.

6 Recommendations

Cardiovascular disease remains the leading cause of death among women. Primary care physicians, obstetricians, and preventive cardiologists providing care to women remain at the forefront of efforts needed for primordial, primary, and secondary prevention of ASCVD events and minimizing resulting morbidity among women.

The steps to facilitate coordinated healthcare delivery to high-risk women for prevention of ASCVD revolve around the core principles of utilization of available screening tools, healthy lifestyle promotion for all women, and well-harmonized collaboration between multidisciplinary teams for early intervention and management of risk factors for ASCVD [5, 90].

The key steps proposed for a comprehensive healthcare delivery model (Fig. 3) will likely include:

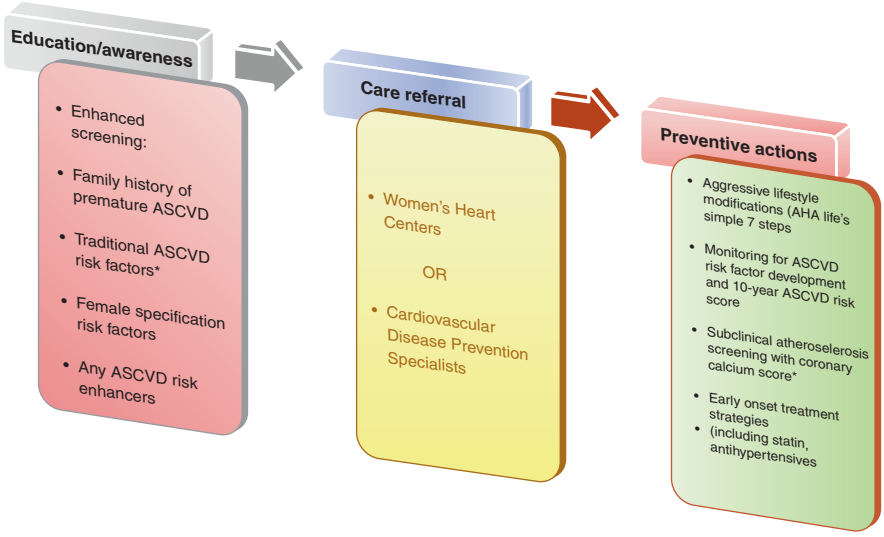

Fig. 3 Cardiovascular disease prevention care flow in women. A projected collaborative approach to cardiovascular disease prevention in women. Initial screening of women is done by primary history taking to elicit the presence of female-specific* (pregnancy-related disorders, history of premature menopause) and female-predominant (breast cancer, breast cancer therapy, autoimmune diseases) traditional ASCVD risk factors (smoking, obesity, metabolic syndrome, hypertension, diabetes, hyperlipidemia, hypertension) and detection of ASCVD risk enhancers. A prompt referral to Women's Heart Center of "high-risk" women for coordinated ASCVD prevention strategy planning and implementation via "Actions." Abbreviation: ASCVD atherosclerotic cardiovascular diseases

1. Promotion of heart healthy dietary habits and lifestyle recommendations for all women. Discussion of lifestyle and behavior modifications should be visited at each clinician-patient interaction.
2. Screening for female-specific or female-predominant ASCVD risk factors should be performed at each clinician-patient visit by optimal history-taking skills and use of preexamination surveys.
3. The presence of female-specific ASCVD risk factors should prompt the in-depth screening for any other ASCVD traditional risk factors and/or risk enhancers to aid the appropriate calculation of the 10-year ASCVD risk score and risk assessment.
4. Aggressive management of ASCVD risk factors by lifestyle and behavior modifications (in accordance with AHA's Life's Simple 7 [91]) and/or early pharmacological interventions when indicated.
5. Treatment adherence surveillance to medical therapies by use of available medical records, telehealth, and in-person visit.
6. Collaboration and communication between multidisciplinary care teams including primary care clinicians, obstetrics/gynecology or "cardio-obstetrics" [9], cardio-oncology [1], and other disciplines when indicated.
7. Utilization of Women's Heart Centers wherever applicable [92] for early screening, detections, and management of ASCVD risk factors (Fig. 1) as well as continued education of women and clinicians through adequate training and community outreach for promotion of cardiovascular health.
8. Finally, continued promotion of research funding in the field of ASCVD prevention for women to further the knowledge into female-specific mechanistic pathways of disease processes and ultimately therapeutic targets and delivery to curtail cardiovascular morbidity and mortality.

7 Conclusions

Cardiovascular disease remains the leading cause of death in women. Despite progress made in this field, mortality from cardiovascular disease is on the rise, along with a continued increase in the prevalence of ASCVD risk factors. Although the majority of cardiovascular disease is preventable, the focus on prevention is often ignored due to lack of awareness of cardiovascular disease risk in women within the medical community and within the population at large. Preventive measures are necessary to reduce mortality and preserve cardiovascular health in women. Understanding the sex-specific differences in ASCVD risk factors can change the approach to the preventive care in women.

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Racial/Ethnic Considerations in the Prevention of Cardiovascular Disease

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Summary

- Racial/ethnic disparities continue to exist in the prevalence, morbidity, and mortality of cardiovascular disease across the USA and worldwide.
- The concepts of race and ethnicity are more useful as classifications to describe population health within social constructs and are less accurately linked to genetic or biological differences.
- Hypertension is the most widely prevalent and attributable risk factor in the development of macro- and microvascular complications of cardiovascular disease, affecting blacks in the USA more than any other population.
- Less than one-fourth of the adult US population adhere to the contemporary guidelines on physical activity, with the highest reported rates of physical inactivity in black and Hispanic women.
- Social determinants of health (i.e. adverse health behaviors, socioeconomic status [SES], and environmental factors) have a predominant effect on all chronic diseases, and systematically contribute to racial/ethnic disparities of cardiovascular disease health care and outcomes.

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- Contemporary multisociety guidelines recommend specific evidence-based treatment of elevated blood cholesterol, high blood pressure, and primary prevention for different racial/ethnic populations.
- Interventions to achieve health equity will require diverse public health programs with an emphasis on population-specific management of the differential risk factor and adverse health behaviors in all populations.

1 Introduction

Contemporary concepts of race and ethnicity recognize these descriptions as categories within a social construct, without true genetic or biological associations. The US federal government of defines race as the self-identification of a person(s) to one or more predefined social groups within the white or Caucasian, Black or African American, American Indian or Alaska Native, Asian, or Native Hawaiian and Pacific Islander populations of the United States [1]. Ethnicity is defined as having relation to either a Hispanic or non-Hispanic origin. Hispanic origin includes people with relation to Spain, Spanish culture, or Latin American descent [2]. The Centers for Disease Control and Prevention (CDC) adopted these racial and ethnic groups from the Directive NO. 15 of the Office of Management and Budget on May 12, 1977 [3]. The recommendation to include these classifications in federal and nonfederal programs has assisted in record-keeping, collection, statistical reporting, and presentation of data on race and ethnicity (see Figs. 1 and 2).

Therefore, utilization of race/ethnicity categories for data reporting remains important for population descriptions, often revealing unique aspects of disease burden and/or disparate outcomes in health care. While racial/ethnic categories are imperfect for determining perceived genetic differences, race/ethnicity descriptions can highlight social similarities and perceived physiological differences, often revealing disparate treatment and outcomes [6]. In the USA, many individuals increasingly identify with one or more races, and share common genotypes from several different racial groups, based on regional ancestry [7]. Moreover, studies have also shown many people of Hispanic origin often do not identify with a separate racial group, further limiting the categorization of the race of people from different ethnic backgrounds into a socially identifiable population [1, 8]. Therefore, the development of prevention strategies using race and ethnicity as separate genetic entities for atherosclerotic cardiovascular disease (ASCVD) is probably less effective than focusing on the prevention of environmental and comorbid risk factors which contribute to ASCVD populations of similar social constructs (see Fig. 2). This chapter will focus on the impact of race/ethnicity (Asian, American Indian/Alaska Native, black or African American, white or Caucasian, and Hispanic ethnicity) on US epidemiology of ASCVD, highlighting the degree of comorbid conditions or risk/behavioral factors involved in each socially defined population, while discussing evidence for preventive measures of each group.

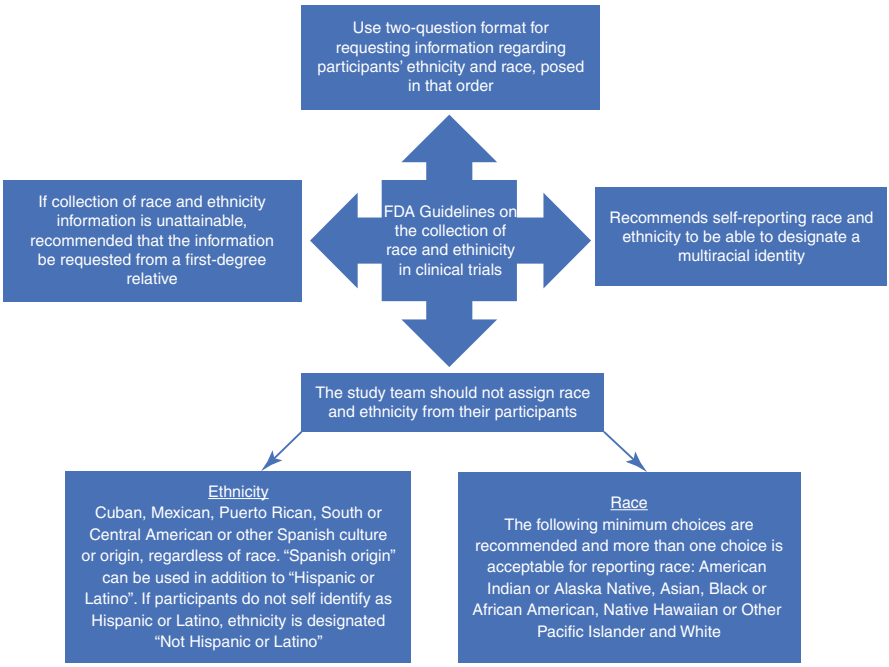

Fig. 1 Federal recommendations of race/ethnicity definitions. Collection of race and ethnicity data in clinical trials: guidance for industry and food and drug administration staff. 2016 Oct. (Available from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/collection-race-and-ethnicity-data-clinical-trials)

Why do racial and ethnic disparities in ASCVD continue to persist?

- *Individual and systemic social determinants of health*
- *Access to healthcare, insurance and preventative medicine*
- *Provider bias*
- *Patients unaware of their condition and their consequences*
- *Atherence to pharmacotherapy*

Hypotheses for the favorable Hispanic ASCVD mortality rates

- *"Healthy migrant effect" – Hispanic immigrants may be selected for overall good Health*
- *"Salmon bias" – U.S. Hispanic residents return to home country to die or when ill*
- *"Cultural effect" – Culturally influenced lifestyle, social networks and family structure may Agree with Salmon be a protective effect against negative effects of low SES*

Fig. 2 Hypotheses of racial/ethnic disparities in atherosclerotic cardiovascular disease. (Based on data from: Nelson et al. [4]. (Comparative Effectiveness Review, No. 222.) Evidence Summary. Available from: https://www.ncbi.nlm.nih.gov/books/NBK550964/, Kochanek et al. [5])

2 Social Determinants of Health and ASCVD Risk

An essential and potentially potent first step in reducing ASCVD racial/ethnic disparities should address the social determinants of health (SDH) that continue to systematically and disproportionately affect minority populations in the USA. Defined as "the circumstances in which people are born, grow, live, work, and age, and the systems put in place to deal with illness" by the World Health Organization and others, SDH can be attributed to up to 80% of illness, encompassing adverse health behaviors, SES, and environmental factors of the individual [9]. The American Heart Association (AHA) reports the higher prevalence of traditional ASCVD risk factors in certain racial/ethnic groups is mostly attributable to SDH, along with suboptimal disease management as documented in blacks and an earlier age of onset of these ASCVD risk factors and diseases [10]. Nevertheless, explanations for the persistent disparities of ASCVD throughout the decades are complex and multifactorial, spanning from individual decision making to deficiencies in healthcare system management for certain populations.

Hypertension (HTN) is the most potent risk factor for ASCVD [11]. A recent meta-analysis of 51 independent studies documented the link between lower SES (measured by income, occupation, and education) and increased risk of hypertension, demonstrating a twofold higher rate of hypertension in lower-educated individuals [12]. Racial segregation, defined as living in a neighborhood with individuals that are primarily of the same race or ethnic background, has been linked to an increased prevalence of hypertension, particularly among blacks [13]. After adjustments for poverty and other risk factors, the Coronary Artery Risk Development in Young Adults (CARDIA) study found blacks had significant reductions in systolic blood pressure after moving from highly segregated to lower-segregated neighborhoods [12]. These, as well as other data, support more intense investigations into the degree and extent of impact SDH may have on cardiovascular disease (CVD) in other racial/ethnic groups.

3 Health Behaviors

Adverse health behaviors are modifiable risk factors that are known to increase risk, morbidity, and mortality for differential diagnoses. Detailing these behaviors play an essential role in the investigation of the disparity of ASCVD among racial/ethnic groups. While there have been public health campaigns that have successfully decreased the CVD burden implicated by adverse risk behaviors, personal patterns of lifestyle continue to be substantial factors affecting the degree of ASCVD disparities among all racial/ethnic groups.

3.1 Smoking

The most consistent and preventable adverse behavior for all CVD across racial/ethnic groups is cigarette/tobacco use and secondhand smoke. American Indian/Alaska Natives have the highest prevalence of smoking (31.6%), while Asian Americans and Hispanics have the lowest prevalence of smoking among minority racial/ethnic groups (9.7% and 10.7%, respectively), yet the prevalence of white and black adult smokers is similar [12].

There are also racial/ethnic differences seen in quit rates, with blacks often having lower quit rates compared to whites. There are different hypotheses regarding the lower quit rates amongst black Americans. For instance, blacks are more likely to use menthol-containing products than whites, which enhances the addictive potential of nicotine and decreases the likelihood of smoking cessation [10]. The Tobacco Use Supplement to the Current Population Survey reported that blacks used mentholated products more consistently than whites (71% vs. 21%, respectively), also reporting lower quit rates for all smokers using mentholated products overall [10].

Environmental exposure to secondhand smoke tends to be higher among black and Hispanic (Mexican) nonsmokers when compared with whites as well [10, 14, 15]. A recent study reported a higher percentage of nonsmokers exposed to secondhand smoke more commonly live below the poverty level or any rental housing when compared with nonsmokers who owned their own homes (21.1% and 19.6%, respectively). As a significant population of specified racial/ethnic groups lives below the poverty level, this may account for some of the disparities seen in secondhand smoke exposure for blacks and other racial/ethnic groups [12].

The use of electronic nicotine delivery systems (ENDS), or vaping, is also on the rise in the US population [16, 17]. According to recent survey data of youth between the ages of 13 and 18, the perceived health risk of nicotine and toxins/chemicals in electronic cigarettes differed significantly by race. The odds of perceiving harm from nicotine was 34% lower in non-Hispanic blacks versus non-Hispanic whites [18]. Other data suggest cigarette smokers perceive a higher risk of harm with ENDS use than nonsmokers, without significant racial/ethnic differences. These data, as well as other study findings, may have significant implications on the educational strategies and preventive measures to decrease nicotine use in at-risk communities.

3.2 Physical Inactivity

Although physical inactivity is a distinct risk factor for CVD, less than one-fourth of the adult population in the USA report adherence to the AHA 2019 Primary Prevention guidelines on physical activity (≥150 minutes of moderate exercise or 75 minutes or more of vigorous exercise per week) [14]. White men and women

report the highest percentage of adherence to physical activity goals (59.6% and 51.4%, respectively) [12], with black and Hispanic women having the lowest reported physical activity rates in the USA. A recent study comparing health behaviors of the third-largest American Indian population in the USA to whites found the American Indians reported a higher prevalence of leisure-time physical inactivity over the evaluation period (31.1% vs. 23.0%, respectively); American Indians also had a higher prevalence of HTN, type 2 Diabetes (T2D), obesity, and report of fair or poor health status [19]. Physical inactivity is also reported in several Asian American populations as well, associated with an increased CVD risk [20]. While recognizing the need for improvement in physical activity measures in all groups, these disparate findings strengthen the need for the multilevel behavior interventions to address physical inactivity in racial/ethnic groups at risk for ASCVD, with a significant need for improvement in physical activity measures of the entire US population.

3.3 Dietary Eating Patterns

The AHA and the American College of Cardiology (ACC) multisociety guidelines specify evidence-based lifestyle management to prevent cardiovascular disease [14]. Current recommendations include a diet that emphasizes intake of fruit, vegetables, low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils, and nuts. In addition, it is recommended for all populations to limit sweets, sugar-sweetened beverages, and red meats. Documentation of adherence to this eating plan is low among all Americans [14, 21, 22]. Regardless of the geographic location in the USA, the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study revealed that blacks are more likely to have a southern dietary eating pattern [23] with significant intake of fruit and vegetables (e.g. sweet potatoes, beans, collard greens, and corn), but also high in added fats, fatty meats, sugar, and sodium with the use of cooking techniques that add excess calories [10].

The Dietary Approaches to Stop Hypertension (DASH) diet is a dietary intervention associated with reductions in blood pressure in the USA [24]. Contemporary ACC/AHA multisociety guidelines recommend this diet to prevent cardiovascular disease through the consumption of fruit, vegetables, and low-fat dairy products. Not only does this promote healthy food products, but it also increases the intake of essential minerals that aid in the reduction of hypertension, such as potassium, magnesium, and calcium. Several studies report significant reductions in systolic blood pressure of hypertensive patients, up to 11 mmHg, as well as modest reductions in systolic blood pressure for nonhypertensive participants [14, 21, 24]. Salt sensitivity, defined as a disproportionate increase in blood pressure with high sodium intake, is common in blacks [24]. Proper adherence to the DASH diet with emphasis on lower sodium intake is particularly effective in blood pressure reductions among blacks with HTN [25]. The intake of higher DASH diet dietary potassium has been shown to lower the incidence of stroke. Potassium supplementation as an

intervention to lower blood pressure can be beneficial, especially in patients with high sodium intake and in blacks [21, 24].

Although data collection of dietary habits across racial/ethnic groups tends to prove challenging, the current evidence supports the association of culture, ethnicity, and SES to the types of food consumed in the USA. In a recent study investigating the relations among race, gender, family structure, parental SES, dietary patterns and CVD profiles among adolescents in the southeastern region of the United States, adolescents living with both parents were more often associated with a "healthy" diet pattern as compared with adolescents of a single parent home [26, 27]. The study also reported black adolescents were less likely to have a healthy diet pattern when compared with white adolescents (74% vs. 24%, respectively), and significantly less likely than white adolescents to live with both parents (78% vs. 47%, respectively) [26, 27]. Unhealthy diet patterns were associated with higher risk profiles for the future development of CVD, which included higher percentage body fat, waist circumference, systolic blood pressure, fasting insulin, homeostasis model assessment of insulin resistance, C-reactive protein, and total triglyceride ($Ps < 0.05$) [27]. These data, along with several other studies, support the need to deploy preventive measures specific to culture and family units among various racial/ethnic groups in order to diminish CVD outcomes.

3.4 Sleep

Poor sleep is a risk factor for ASCVD, including suboptimal sleep duration, sleep quality, and sleep-disordered breathing [10]. Blacks are more likely to have obstructive sleep apnea, which is directly associated with increased risk of CVD mortality and contributes to other CVD risk factors, such as type 2 Diabetes (T2D) and hypertension [12]. Sleep duration, including both prolonged and shortened sleep, is also an associated risk factor for CVD. Short and long sleepers, defined as outside 7–9 hours of sleep a night, had increased all-cause mortality of CVD. In the National Health Interview Survey (NHIS), blacks were 41% more likely to self-report as short sleepers and 62% more likely to self-report as long sleepers, compared to white participants. Blacks also had longer sleep latency and shorter sleep duration than whites. Overall, approximately 11% of the disparities in hypertension prevalence between blacks and whites appear directly attributed to the differences in sleep quality [10–12].

3.5 Nonadherence

Medication nonadherence, defined as inconsistent consumption of prescribed medications, is a significantly undermanaged problem common in approximately 50% of patients diagnosed with CVD. Around 125,000 preventable CVD deaths per year in

the USA are attributable to medication nonadherence [28]. The reasons for medication nonadherence are multifactorial, which are generally divided into four classes: social and economic factors (e.g., low health literacy, medication cost, and lack of access), healthcare system factors (e.g., provider-patient relationship, information written at too high of a literacy level, long wait times), condition-related factors (lack of symptoms, severity of symptoms, depression, psychotic disorders), and therapy-related factors (actual and perceived side effects, complexity of regimen, duration of therapy) [28].

Racial disparities in medication nonadherence are significant and therefore, many initiatives have targeted the management of these differences. The African American Health Disparity Project intended to eliminate institutional racism in San Francisco, with projects such as no-cost treatment for African Americans with breast cancer, providing educational seminars and establishment of community grants to address health disparities in disproportionally affected areas [28]. The BARBER-1 (Effectiveness of a Barbershop-Based Program to Improve High Blood Pressure Control and Awareness in Black Men) study demonstrated the effectiveness in neighborhood-based interventions rather than simply supplying literary information for review. This study cluster-randomized black men with hypertension in black-owned barbershops to an intervention involving blood pressure checks and health messaging through peers, where control participants only received AHA pamphlet on HTN management. At the completion of the study, there was a significant increase in hypertension control for the intervention arm ($p = 0.035$), demonstrating the clinical utility of these community-based programs in black men [29]. The more recent Los Angeles Barbershop study confirmed the potential benefit of applying out-of-office use of barbershops as hypertension control centers. Remarkable reduction in blood pressure and increased HTN control were documented with specialty pharmacist care, effective drug management, and the use of barbershops as a culturally sensitive source of care [30].

4 ASCVD Risk Factors

Factors that may explain health disparities in CVD outcomes across race/ethnicity are not only rooted in population-level differences in ASCVD risk factors, but also due to broader systemic and social determinants of health. Additionally, much of this public health burden may attribute to modifiable risk factors – underscored by the AHA designation of "optimal cardiovascular health," identifying seven health metrics that are critical in the reduction of incidence of ASCVD (smoking status, physical activity, healthy diet, body weight, along with optimal blood pressure, blood glucose, and total cholesterol levels) [31]. Many of these definite risk factors have been decreasing amongst the US population, yet minority racial/ethnic groups continue to have disproportionately higher rates when compared with whites. Blacks also have the lower age-standardized/specific estimates of meeting ideal criteria for five or more of the AHA's Life's Simple Seven metrics [11].

4.1 Hypertension

As previously noted, HTN is the most widely prevalent and potent risk factor in the development of ASCVD and microvascular complications, highest among US blacks than any other population in the world [11, 12]. HTN is associated with increased risk of coronary heart disease (CHD), CVA, and end-stage renal disease, further increasing the population-attributable risk of these outcomes [24]. The JNC-7 (Joint National Committee) report's threshold definition of hypertension (an average systolic blood pressure (SBP) ≥140 mmHg or average diastolic blood pressure (DBP) ≥90 mmHg) was updated in 2017 to the present definition of stage I HTN (SBP ≥130 mmHg or a DBP ≥80 mmHg) [32]. The updated 2017 HTN guideline change in the definition of HTN resulted in a substantially higher prevalence of HTN in the USA overall (46% versus 32%), with persistent race-based disparities observed [24]. In a 10-year investigation of nonhypertensive participants of the REGARDS study, black and white adults were observed in follow-up visits over 9 years (median 9.4 years) [33], which reported a higher percentage of black males and females (48% and 54%, respectively) who developed hypertension than white males and females (38% and 27%, respectively) [12].

Recent data from the CDC suggest a significantly higher prevalence of uncontrolled HTN among racial/ethnic minority groups compared with non-Hispanic whites [34]. For instance, the prevalence in non-Hispanic Asian Americans affected by uncontrolled HTN is 86.3%, while the prevalence of uncontrolled HTN within Hispanics and blacks is slightly lower (81.6% vs. 79.4%, respectively) [35] (See Table 1). The differences in the prevalence of uncontrolled HTN within racial/ethnic groups are not well understood. However, these are significant findings as HTN is related to mortality in conditions other than CVD. Results of a recent study from the CDC also notes increased rates of HTN-related mortality in American Indian/Alaska Native and white adults of advancing age from conditions such as chronic obstructive pulmonary disease, Alzheimer's and Parkinson's [36]. Thus, HTN prevention across all racial/ethnic groups has significant implications for improved survival as well as the quality of life in advancing age.

Several studies document a differential response to pharmacologic interventions in reducing high blood pressure for blacks [24]. Thiazide-type diuretics and calcium channel blockers were most effective in lowering blood pressure and stroke in blacks, while these are equally effective along with the other first-line medications for whites. Angiotensin Converting Enzyme Inhibitors (ACE-I) were less effective in blacks when compared with whites, not only in lowering blood pressure but also in the prevention of heart failure and stroke [24]. However, the guidelines recommend the addition of renin-angiotensin modulators, including an ACE-I or angiotensin receptor blockers in the setting of compelling comorbid issues such as diabetes with albuminuria, renal dysfunction, or HF. As previously noted, effective care to lower blood pressure necessitates evidence-based guideline lifestyle interventions and pharmacotherapy, often starting with two drugs as initial care, including novel community-based interventions. These collaborative efforts may also

Table 1 Hypertension rates in US population by gender, age, and race/ethnicity

	Total population	Hypertension		Uncontrolled			
				Among those with hypertension		Among those recommended medication and lifestyle modification	
Subgroup	*N, millions*	*% (SE)*	*N, millions*	*% (SE)*	*N, millions*	*% (SE)*	*N, millions*
Total	240.5	44.9 (0.7)	108	76.3 (1.2)	82.4	70.5 (1.3)	61.3
Men	115.8	47.1 (1.1)	54.5	79.4 (1.3)	43.3	73.7 (1.5)	31.4
Women	124.7	42.9 (0.9)	53.4	72.9 (1.6)	39	67.4 (1.6)	29.9
Age group, years							
18-44	112.9	22.6 (0.9)	25.5	86.7 (1.3)	22.1	75.6 (2.1)	10.5
45-64	82.6	56.8 (1.3)	46.9	74.3 (1.8)	34.9	67.8 (2.1)	25.4
≤65	44.9	76.7 (1.5)	34.4	71.5 (1.8)	24.6	71.5 (1.8)	24.6
Race/Hispanic origin							
NH White	156.7	46.1 (1.0)	72.3	74.0 (1.7)	53.5	68.3 (1.9)	40.5
NH Black	28	54.0 (1.0)	15.1	79.4 (1.4)	12	74.7 (1.7)	9.2
NH Asian	13	39.2 (1.9)	5.1	86.3 (1.7)	4.4	81.5 (2.1)	3.1
Hispanic	36.6	35.6 (1.2)	13	81.6 (1.4)	10.6	75.1 (1.7)	7.2
Other	6	43.3 (3.9)	2.6	76.7 (3.8)	2	70.1 (4.8)	1.4

Based on data from National Center for Health Statistics, Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey (NHANES), 2013–2016. Accessed January 31, 2019 from https://millionhearts.hhs.gov/data-reports/hypertension-prevalence-tables.html#Table1

positively impact adherence rates and offset healthcare access costs, such as transportation and financial challenges [37].

4.2 Type 2 Diabetes

Insulin regulation disorders, from insulin resistance to diabetes affects a large percentage of people in the United States. Specifically, T2D is a significant contributing comorbid disease to ASCVD, affecting up to 10% of the entire US population [12, 38]. Of the 30 million people with T2D in the USA, approximately one-third

of the affected people are undiagnosed. Additionally, one-third of the US population may also have prediabetes, affecting nearly half of all adults aged 65 or older. The American Indian or Native Alaska population has the highest prevalence of diagnosed diabetes (15.1%), followed by non-Hispanic blacks (12.7%), and people of Hispanic ethnicity (12.1%) [11]. The prevalence of T2D also varies significantly within racial constructs and region, from 6.0% among Alaska Natives to 22.2% among American Indians in some areas of the Southwest. Among people of Hispanic ethnicity, Mexicans had the highest prevalence (13.8%), followed by Puerto Ricans (12.0%), Cubans (9.0%), and Central/South Americans (8.5%) [12]. Among Asians, Asian Indians had the highest prevalence (11.2%), followed by Filipinos (8.9%) and Chinese (4.3%). Other Asian groups had a prevalence of approximately 8.5% [12]. According to the 2011-2012 NHANES data, the overall prevalence of T2D in the USA is 14.3%, although higher in blacks (~21.8%) [39]. Moreover, blacks were less diagnosed with T2D (~37%), less likely to be aware of their diagnoses, less likely to achieve adequate control of a hemoglobin A1c <9%, and developed T2D 1.52 times more often than white men. Black women developed T2D 2.14 times more than white women [10, 39]. These findings in diabetes prevalence contribute to a significant burden of underlying ASCVD risk, as less recognition and poor control of T2D directly contributes to the pathogenesis of other cardiovascular diseases [39].

4.3 Hypercholesterolemia

A significant prevention target in ASCVD is the treatment of lipid disorders. These lipid abnormalities, primarily elevated low-density lipoprotein (LDL-C), contribute to atherosclerotic plaque burden, which ultimately causes CHD, CVA, and sudden cardiac death from ischemia. Although blacks tend to have more favorable lipid profiles when compared to the national average, they suffer from higher rates of mortality due to CHD [10, 14]. The REGARDS study suggests blacks are less likely to be aware of their hyperlipidemia, and less likely to have adequate control [10, 23]. High-density lipoprotein (HDL) is potentially considered to have a cardioprotective effect in most populations, although the levels of HDL vary significantly between certain racial/ethnic groups [40]. Hispanic men and women have the highest overall prevalence of low HDL, although Hispanic women tend to have a higher prevalence of lower HDL levels than men. These findings likely contribute to the higher rates of metabolic syndrome seen in the Hispanic population as well. Black women have the highest percentage of obesity in the USA (~58%), followed by black men (~38%), white men (~34%), and white women (~33%) [10, 14, 40, 41]. Blacks, in general, have higher HDL and lower triglyceride values, although this does not appear to be cardioprotective based on the high rates of ASCVD in this group. Asian Americans tend to have a higher prevalence of low HDL when compared to whites, and overall higher prevalence of elevated triglycerides when compared to all racial/ethnic subgroups.

It is essential to understand the significant heterogeneity in risk according to and within different racial/ethnic groups. For instance, ASCVD risk in Hispanics tends to be higher in the Puerto Rico Hispanic population than within the Mexican American community [14]. Although the concept of race/ethnicity appears to contribute to these varying differences, country of origin, socioeconomic status, and acculturation level are among some of the critical variables of ASCVD risk burden. Disaggregation of Hispanics is essential to improved understanding of the contributions of various CVD risk and their effects on any individual population (see Table 1).

Familial hypercholesterolemia (FH) is an autosomal dominant disorder characterized by lifelong elevations in LDL-C, associated with a 20-fold increase of premature atherosclerotic disease. The CAscade SCreening for Awareness and DEtection of Familial Hypercholesterolemia (CASCADE-FH) patient registry, established in 2013, served as a national, multicenter initiative to identify patients with FH, track their treatments, and measure clinically important outcomes over time [42]. This registry was the first of its kind to provide data on the prevalence of the condition among various racial/ethnic groups. Although the prevalence of FH differs among racial/ethnic groups within this registry and may be confounded by factors such as selection bias, the data offer insight into baseline and treatment racial/ethnic differences of FH. Whites had a higher prevalence of FH within this registry (75%). The prevalence of FH was 10% in blacks and 5% in Hispanics, and 10% in others (including Asian) [43]. In an adjusted analysis from this registry, Asians and blacks with FH were significantly less likely to reach target LDL-C goals of <100 mg/dl or 50% or more significant reduction in the pretreatment LDL-C [42–45].

The 2018 ACC/AHA multisociety Guideline on the Management of Blood Cholesterol outlined evidence-based recommendations in the prevalence, risk, and treatment of ASCVD risk factors in several racial/ethnic groups. Although the overall treatment guidelines for blood cholesterol are uniform across racial/ethnic groups and associated with a calculated risk of ASCVD, there are some noted differences not clearly defined in risk estimation depending on specific groups. For instance, the risk of ASCVD in Asian Americans tends to vary by country of origin, with individuals from South Asia often carrying an increased ASCVD risk. Race and nation of origin, as well as SES, affect the ASCVD risk of Hispanics as well, with a higher risk found among Hispanics from Puerto Rico when compared with Hispanics from Mexico. In addition, Native American/Alaskan populations both carry a higher ASCVD risk than their non-Hispanic white counterparts [40] (see Table 2). Therefore, considerations of race and several other factors are essential when providing primary as well as secondary prevention in all patients.

The utilization recommendations of lifestyle and counseling interventions are again uniform across racial/ethnic groups for CVD prevention. However, the behavioral modifications needed to improve CVD outcomes through prevention measures is likely complex, involving multileveled variables of culture, environment, and behavior, requiring further study. It is also essential to understand the implications of lifestyle preferences and regional differences among racial/ethnic groups when initiating large-scale preventive measures.

Table 2 Racial/Ethnicity considerations in the evaluation of atherosclerotic cardiovascular disease risk and treatment

	Asian Americans	Hispanic/Latino Americans	Blacks/African American
Evaluation			
ASCVD issues by race/ethnicity	Risk of individuals from South Asia and East Asia varies depending on country of origin	Race, socioeconomic status, and country of origin may explain risk factor burden more specifically	Black women show increased ASCVD risk compared with white women
Lipid issues informed by race/ethnicity	Asian Americans have lower HDL-C levels than whites	Hispanic/Latino women have lower HDL-C compared to Hispanic/ Latino men	Blacks haver higher HDL-C and lower triglycerides than whites
Metabolic issues informed by race/ethnicity	Increased metabolic syndrome with lower waist circumference than in whites	Increased prevalence of metabolic syndrome and diabetes mellitus in Mexican Americans compared to whites	Increased diabetes mellitus and hypertension compared to whites
Treatment			
Lifestyle counseling	Recommend a heart-healthy diet consistent with ethnic preferences to reduce weight gain and address blood pressure and lipids	Recommend a heart-healthy diet consistent with ethnic preferences to reduce weight gain and address blood pressure and lipids	Recommend a heart-healthy diet consistent with ethnic preferences to reduce weight gain and address blood pressure and lipids
Intensity of statin therapy	Japanese patients may be sensitive to statins, as studies have shown Japanese participants had reduction of CVD events with low and moderate intensity pravastatin	No sensitivity to statin dosage compared to black or white individuals	No sensitivity to statin dosage compared to black or white individuals
Safety	FDA recommends starting rosuvastatin at lower doses (5 mg) as higher plasma levels are seen in Chinese, Japanese, Malay, and Asian Indians compared to whites	No specific safety remarks for Hispanic/ Latino patients	Serum creatine kinase levels are higher at baseline when compared to whites

Based on data from Grundy et al. [46]

Although there are no significant interactions or considerations for the use of statin treatment in blacks and Hispanics, there are some statin tolerability differences among Asian patients. Japanese patients tend to be more sensitive to statin dosing, with higher plasma levels of certain statins found, such as rosuvastatin, in Japanese, Chinese, Malay, and Asian-Indians compared to whites. The Food and Drug Administration recommends a lower starting dose in Asians when compared to whites. Blacks also tend to have higher baseline serum creatine kinase (CK)

values when compared with whites, and the 95th percentile values for race/ethnicity and sex are available for assessing changes in CK levels. Unless the baseline CK values are above these ranges, the decision to use a statin in all groups is still supported based on the ASCVD risk calculations [40, 47]. As previously noted, despite the higher levels of HDL-C and lower levels of triglycerides in blacks compared to Mexican Americans and whites, there are no observed heightened effects of statins among these groups [12].

Current guidelines note that for adults aged 40–75 with diabetes and an LDL-C level between 70 and 189 mg/dL, it is reasonable to assess the 10-year risk of an ASCVD event by using sex and race-specific pooled cohort equations, particularly in blacks. In adults aged between 40 and 75 without diabetes and an LDL-C level of 70 mg/dL and a 10-year ASCVD risk of 7.5%, a moderate-intensity statin is indicated [40]. Despite higher CVD outcomes, blacks also may have lower coronary artery calcium (CAC) scores than other racial/ethnic groups. Nevertheless, to determine the indication for, and intensity of, statin therapy, CAC is useful regardless of race/ethnicity and should be measured if ASCVD risk is uncertain. If the CAC score is 0, the guidelines recommend withholding statin therapy, except for patients with diabetes, active smokers, and those patients with a strong family history of ASCVD [14].

4.4 Overweight/Obesity

The prevalence of obesity and the metabolic syndrome (MS) in the USA is 39.6% and 34.3%, respectively [12]. Due to the significant variation of the definition of MS across data, the true prevalence between racial/ethnic groups is unknown. Thus, the definition and categorization of MS allow for disparate rates of incidence/prevalence among racial/ethnic groups, primarily due to the arbitrary cut-points for HDL and triglycerides, and lower body-mass index (BMI) cut-off values for some populations (e.g., Asians) [39]. Considering that MS is associated with a conglomeration of risk conditions discussed in this chapter, this section will focus primarily on obesity as an individual ASCVD risk factor.

The age-adjusted prevalence in obesity is much higher in black women when compared with their white counterparts, although Asian American women had the lowest age-adjusted prevalence, with similar prevalence seen in Hispanic women when compared to white women [12]. These findings are significant as obesity is associated with an increase in lifetime risk of CVD, as well as increased risk for other conditions, including type 2 DM, HTN, hyperlipidemia, and atrial fibrillation. Overall, obesity may be independently associated with a higher all-cause mortality [12, 26, 48, 49].

The concept of Metabolic Healthy Obesity (MHO) has now gained significant traction as a specific health entity that is not associated with increased cardiovascular risk. MHO is a term loosely defined as having 0–1 metabolic abnormality from the metabolic syndrome criteria. The prevalence of this condition within the USA is not well defined, although there appears to be some evidence to suggest an unstable risk of CVD progression when evaluated over time. One European study reported

44.5% of patients with MHO transitioned to metabolically unhealthy adults within 8 years [12, 50]. The Multi-Ethnic Study of Atherosclerosis (MESA) involving 6000 racially/ethnically diverse men and women of six US communities demonstrated similar results in older adults. Approximately half of the MHO patients developed the metabolic syndrome, as well as had an increased risk of CVD compared to other MHO and normal-weight patients [12]. More research in the USA may define whether the cultural acceptance of being "healthy" overweight or obese may contribute to the risk of developing CVD.

5 Race/Ethnicity and Atherosclerotic Cardiovascular Disease Outcomes

Despite prior considerable decreases in cardiovascular disease (CVD) burden, ASCVD remains the leading cause of morbidity and mortality in the USA and globally [10, 14]. The prevalence of all CVD in adults greater than the age of 20 is ~50%. Coronary heart disease (CHD), along with HTN, stroke (CVA), and heart failure (HF), attributed to over 80% of US deaths in 2016 [12]. Overall, racial/ethnic ASCVD disparities emphasize the necessity for public health research and interventions to address these issues in all populations [51].

While successful implementation of risk-reduction strategies has caused a decades-long decline in US ASCVD-related deaths, there have not been equal or comparable decreases in the incidence and mortality of ASCVD in racial/ethnic minorities compared with non-Hispanic whites in the USA [10, 12]. There are also differences in various racial groups when comparing sex outcomes. Ultimately, the causes of the disparities in ASCVD burden on black populations have been documented and researched for decades, and are complex factors with patient-, provider-, and healthcare systems-level involvement. For instance, black women had the highest overall mortality from CVD (32.8%) when compared to all racial-sex groups in 2016, followed by Asian women and men (32% and 31.6%, respectively), and black men (31.3%). The CDC estimated that CVD accounts for ~32% of the mortality difference between black and white men and ~43% between black and white women [10]. Specifically, the age-adjusted death rates were 33% higher for black men and women when compared to the whole US population in 2010 [51].

Hispanic death rates from CVD are the lowest of all groups, although this US population is also known to have a higher incidence of the metabolic syndrome when compared to other groups [11, 12]. Despite an adverse risk factor profile in Hispanics, especially Mexican Americans, marked by higher rates of traditional and nontraditional risk factors, the prevalence of CVD outcomes is lower among Hispanics relative to whites [52]. Overall, both Hispanics and non-Hispanic Asians have lower total CVD, HTN, CHD, and HF when compared with whites in the USA [12].

Due to the significantly underdeveloped investigations into other US racial/ethnic groups with ASCVD, specific race/ethnicity-based preventive measures are far more

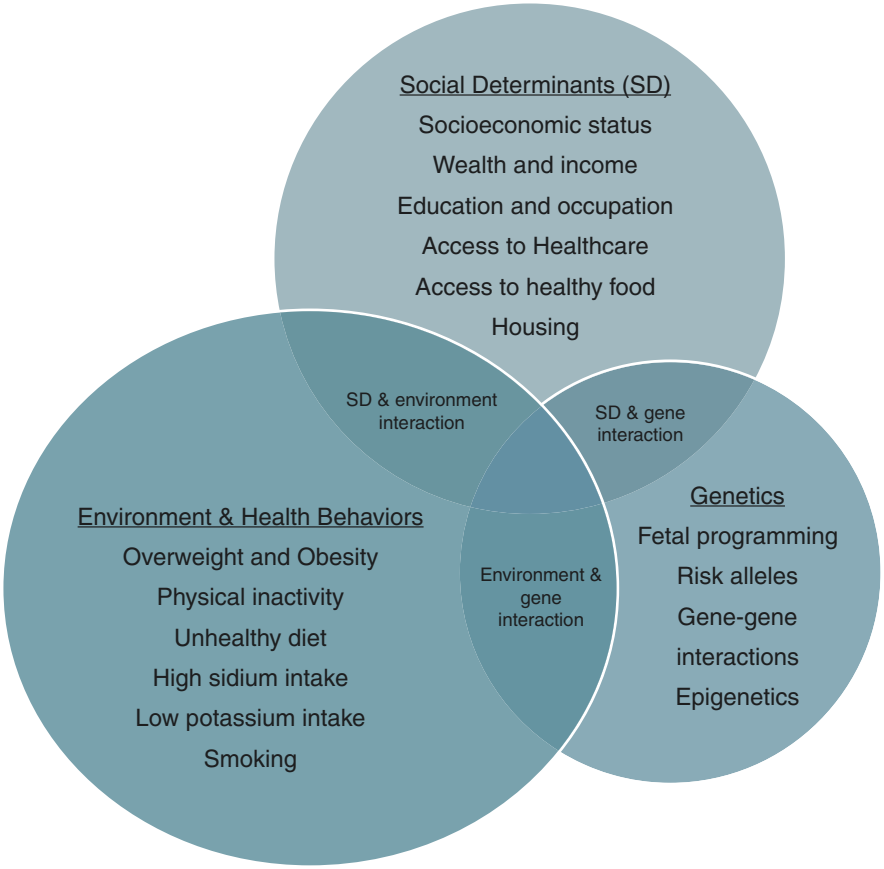

Fig. 3 Race/ethnicity factors in atherosclerotic cardiovascular disease prevention

complicated. In consideration of these challenges, ASCVD research emphasizing disparities in racial/ethnic groups continue to unmask unique factors contributing to these differences in all groups as well as group-gender, which may limit the ability to uniformly improve preventive healthcare outcomes for all Americans [51] (See Fig. 3).

5.1 Coronary Heart Disease

According to the most recent National Health and Nutrition Examination Survey (NHANES) data (2016), there are an estimated 18.2 million American adults aged ≥ 20 with coronary heart disease. According to the Atherosclerosis Risk in Communities Surveillance (ARIC) study, black men and women 35 years of age or older had the highest incidence of myocardial infarction (MI) or fatal CHD when compared with

white men and women. The study also reported a decline in CHD incidence among black men, which is only half as much as observed among white men (−3.2%/year vs 6.5%/year, respectively) [10]. Black women also had less of a decline (−4.0%/year) in CHF incidence than white women (−5.2%/year) [10, 53]. Data from the REGARDS study also suggest that black men and women have considerably higher rates of fatal CHD than whites (black men HR, 2.18; black women HR, 1.63) [10, 23], even though blacks tend to have less CAC when compared with whites [54–56]. These findings suggest the cause of CHD deaths in blacks may be related to factors other than macrovascular atherosclerotic disease, such as hypertensive heart disease.

Therefore, ASCVD-related deaths continue to be the primary cause of the lower life expectancy in blacks [57, 58]. The most recent ASCVD-related death rate is 369 and 278 per 100,000 in black and white men and 261 and 192 per 100,000 in black and white women, respectively [51]. Altogether, the disparity in the burden of ASCVD has contributed to >2.0 million years of life lost in the US black population between 1999 and 2010 [10]. Blacks disproportionately suffer a higher burden of ASCVD death relative to population size, and evaluated by disability-adjusted life-years as the possible etiology of premature death and disability [31, 51, 59]. The National Center for Health Statistics reported a US life expectancy that peaked in 2014 at 78.9 years and decreased for the following three consecutive years, reaching 78.6 years in 2017. The documented life expectancy of blacks is 74.8 years, compared with whites at 78.5 years [60]. Analysis of life expectancy by race and sex is associated with a remarkable contrast as white women have the longest life expectancy (81.2 years), followed by black women (78.1 years), white men (76.4 years), and lastly black men (71.5 years) [57].

Although there has been a significant decline in CVD mortality for blacks, Hispanics, and Asian/Pacific Islanders over the more recent decades, blacks continue to have the highest CVD mortality overall. However, increases in CVD mortality before the age of 50 in American Indian/Alaska Native individuals and death from hypertensive disease in all groups are reported from US national mortality data [26]. Overall, data pertaining to Asian Americans and CHD in the USA are scarce, although retrospective data from the state inpatient discharge details suggest Asian Americans and Hispanics are most likely to die while inpatients after an ST segment-elevation myocardial infarction (MI) [20, 61]. Asian and Hispanic Medicare patients with CHD older than the 65 years of age also utilized ambulatory services less, which was associated with a significantly higher odds of inpatient mortality from an acute MI [61]. More investigation into the causal associations of these findings is warranted.

5.2 Heart Failure

Heart failure affects an estimated 6.7 million Americans 20 years of age or older, with an expected 46% increase in prevalence over the next decade, affecting over eight million people by 2030. According to the AHA, black men and women have the highest prevalence of heart failure when compared with all racial-ethnic groups [12, 62]. The age-adjusted heart failure death rates in 2015 were 87.9 per 100,000

with variations across racial groups: 112.6 and 83.9 per 100,000 in black men and women (respectively), 107.4 and 79.4 in white men and women, 100.9 and 75.5 in American Indian/Alaska Native men and women, 47.0 and 33.3 in Asian Americans or Pacific Islanders, and 65.7 and 48.8 in Hispanics [12]. The reasons for lower HF death rates in Asians and Hispanics are not fully understood. Among blacks, a higher proportion of heart failure is attributed to modifiable risk factors, when compared with whites, such as elevated systolic blood pressure, elevated fasting glucose, left ventricular hypertrophy, CHD, and smoking. Blacks also have the highest population attributable risk of HF from HTN when compared with whites, as well as a higher prevalence of HTN at any decade of life than that of Hispanic Americans, Native Americans, or whites [11, 24]. Therefore, prevention of heart failure is possible through the modification of attributable risk for all, but especially for blacks. Increased adherence to the AHA's Life's Simple Seven guidelines (better profiles in smoking, physical activity, body mass index, diet, cholesterol, blood pressure, and blood glucose) was associated with a lower lifetime risk of heart failure in the ARIC study [63]. The ARIC study, as well as others, have also identified other, more non-traditional risk factors for heart failure, including white blood cell count, circulating N-terminal pro-Brain Natriuretic Peptide (BNP) and BNP, albuminuria, and socioeconomic status, although more investigations are needed to determine if these risk factors are associated with any racial/ethnicity-dependent HF risk [63–65].

The CARDIA study also reported disparities in the incidence of HF between blacks and whites were highest in young adults (defined as <50 years of age) [10, 62]. Of note, the MESA found that while disparities in the incidence of HF existed in older adults as well, these findings did not remain after statistical adjustment for HF risk [66]. However, this study also reported the age-adjusted 30-day case fatality rate was higher in black men (51.8%) and black women (46.1%) when compared to white men (41.2%) and white women (35.8%) [10, 66]. Multiple studies suggest that blacks also tend to have worse outcomes with HF treatment when compared with whites [10, 11, 36, 62]. Although the reasons for these data are hypothesis-provoking, more investigation into the behavioral and cultural aspects of care of minority heart failure patients is warranted.

The treatment of HF is fairly consistent across racial/ethnic groups, with the exception of the use of the hydralazine/isosorbide dinitrate combination in blacks. The African American Heart Failure Trial (A-HeFT) randomized 1050 black patients with New York Heart Association III-IV HF to a fixed dose combination of hydralazine/isosorbide dinitrate (HYD/ISDN) or placebo, in addition to standard guideline-driven HF therapy. The fixed dose of HYD/ISDN reduced relative risk for death from any cause, as well HF hospitalizations, by 33% in the treatment group when compared with the placebo group (16.4 vs. 22.4%, $p = 0.001$). The combination therapy of HYD/ISDN was also effective in improving overall quality of life in the treatment group [67]. Therefore, this therapy is included in guideline-based HF treatment of blacks, in addition to all other standard neurohormonal treatments [68].

5.3 Cerebrovascular Disease

Cerebrovascular accident (CVA) prevalence increases in the USA with advancing age, although the Behavioral Risk Factor Surveillance System (2016) suggests the highest prevalence is in blacks and American Indian/Alaska Natives [12]. Age-adjusted CVA death rates declined by ~11% in 2017, although the CVA death rates remained higher among non-Hispanic blacks than among non-Hispanic whites (52.7 per 100,000 vs. 36.4 per 100,000, respectively [11]. The annual age-adjusted incidence of first-ever CVA (ischemic, intracerebral hemorrhage, and subarachnoid hemorrhage) is also higher in blacks when compared with whites [11]. Several studies highlight the racial/ethnic disparities in utilization or access to care in the setting of acute CVAs as well. In a recent study, black and Hispanic patients with acute ischemic CVA were less likely to receive tPA or mechanical thrombectomy when compared with white patients [69]. Mortality from cerebrovascular disease (i.e., ischemic CVA, intracerebral hemorrhage, and transient ischemic attack) has decreased by 80% over the past 60 years. However, there have been no meaningful decreases in the disparity between blacks and whites in the USA, as blacks are also likely to suffer a premature death 2.5 times more when compared with whites [12]. Blacks are still less likely to receive early CVA treatment, according to the most recent AHA statistical updates, resulting in higher death rates from the condition [11].

Racial/ethnic disparities in CVA outcomes are not just related to mortality or procedural intervention. Data from the Health and Retirement Study, an ongoing longitudinal panel study, estimated higher-ranked Disability Adjusted Life Years (DALY) in blacks from CVA than Hispanics or whites [70]. These data have significant implications in rehabilitation and recovery outcomes across racial/ethnic groups. Thus, CVA preventive measures are multifaceted as in other conditions of CVD, which requires more investigation to decrease mortality as well and secondary preventive measures after an index event.

5.4 Atrial Fibrillation

Atrial fibrillation (AF) had an estimated prevalence of ~5.2 million in 2010, which is expected to increase to 12.1 million by 2030, often contributing to increased CVD outcomes such as heart failure, sudden cardiac death, and CVA [11]. However, there are limited data comparing the rate of various arrhythmias between racial/ethnic groups. Interestingly, blacks, Hispanics, and Asians all have a lower documented adjusted prevalence of atrial fibrillation according to recent cross-sectional study. Although HTN accounts for ~22% of all reported AF cases, Asians (Chinese 46.3%), Hispanics (43.9%), and blacks (33.1%) had more HTN-related AF in the MESA study [71]. Another study evaluated incident AF in 16,442,944 patients from California in the Healthcare Utilization Project (HCUP), which found significantly

lower rates of AF in American Indians when compared with whites (0.6% vs. 57.2%, respectively). However, Hispanics are reported second-highest incident AF among minority racial/ethnic groups, followed by Asians and blacks (25.6%, 8.6%, and 8.0%, respectively) [72]. These two studies underscore the challenges of selection bias and other confounding factors when interpreting the incidence and prevalence conditions in targeted or regionally selected participants.

Although the incidence of AF is 0.20–0.50 times lower in blacks versus whites, the fact remains that blacks have a lower odds of awareness of atrial fibrillation and less likely to be on treatment with warfarin [73, 74]. In a large observational study of Medicare patients with AF, Hispanics, blacks, and women were all more likely to receive rate control versus rhythm control and less likely to be given oral anticoagulant therapies for CVA prevention than white men [75]. Another study found similar results that black and Hispanic patients were more likely to receive rate control therapy rather than cardioversion, anti-arrhythmic drugs, and interventional therapies for AF (e.g., catheter ablation, surgical maze procedure), when compared with white men [71, 74, 75]. Blacks were also less likely than their white counterparts to receive novel oral anticoagulation (NOAC) if an anticoagulant was prescribed in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry after socioeconomic factor adjustments [11]. There are certain lifestyle modifications, including weight loss, which may have some benefit on decreasing symptom burden of AF, although more investigation is warranted to understand to what degree these preventive measures may have on racial/ethnic differences in AF.

5.5 Peripheral Vascular Disease

Another important disease is peripheral arterial disease (PAD), with a prevalence of 12–20% among adults over 80 years of age, globally affecting 202 million people [10, 11]. The age-adjusted death rate from PAD (per 100,000) is highest in black men and women (22.1 and 14.8, respectively), followed by white men and women (17.8 and 12.4, respectively), non-Hispanic American Indians or Alaska Native men and women (17.1 and 13.1, respectively), and Hispanic men and women (13.4 and 9.1, respectively) [11]. While it is important to note that traditional risk factors of atherosclerotic diseases, such as diabetes and smoking play a significant role in the development of PAD, statistical adjustment for these factors did not eliminate the disparity in prevalence and mortality between blacks and whites. While PAD alone is not a direct cause of mortality, it reflects the overall burden of ASCVD in the general population, accounting for 59,681 deaths in 2014 [10, 12].

Although the overall rate of lower extremity amputations has decreased significantly, blacks tend to have a 37% higher amputation risk than whites (HR 1.37 [95%CI 1.30–1.45]). A recent report from the National Inpatient Sample demonstrated that after declining trends, the rate of nontraumatic lower-extremity amputation increased by 50% between 2009 and 2015 in adults with diabetes [11]. Other risk factors of PAD include cigarette smoking, HTN, and hypercholesterolemia,

which are potentially preventable, possibly decreasing the attributed risk of these conditions.

6 Genetic Determinants of ASCVD Risk by Race/Ethnicity

It is important to consider genetic contributions that exist to describe the higher ASCVD burden in blacks. One such example is the well-studied APOL1 gene, coding for the apolipoprotein L1, in which specific alleles confer innate immunity against *Trypanosoma brucei* responsible for trypanosomiasis. The APOL1 gene variant that provides immunity for this parasitic infection is found in over 50% of African Americans, much more than people of non-African ancestry [76].

Lp(a) is a low-density lipoprotein variant that directly contributes to increased risk and development of CHD. It is an independent risk factor for atherothrombotic forms of stroke and CHD. Blacks have a 2–3 times higher median Lp(a) concentrations when compared to whites in both clinical and prospective studies, apparently related to the proportion of African ancestry [77, 78].

Transthyretin amyloid cardiomyopathy (ATTR-CM) is an underrecognized cause of heart failure (HF) and a cause of significant heart disease in elderly African Americans, resulting from myocardial deposition of misfolded transthyretin (TTR) [79]. Unfortunately, no clear evidence exists that a healthy lifestyle improves or protects from this disabling and often deadly condition.

While there have been improvements in the US health care and life expectancy, this information highlights that ASCVD reductions have not been equitable, with a significant burden that continues to disproportionately affect black Americans [41]. To summarize, blacks are at higher risk of developing T2D, obesity (especially in women), hypertension, stroke, and premature cardiac death. We also recognize the role of genetics-based on these disparities, illustrated by APOL1 gene segregation in blacks and the higher concentration of Lp(a) [41]. Although there appear to be several possible considerations for the evaluation of genotypic prevention profiles, specific customized preventive genetic approaches warrant more large-scale randomized controlled study as to whether these efforts benefit individual racial/ethnic groups.

7 Conclusion

Racial/ethnic disparities in ASCVD risk, prevalence, and outcomes are sizeable and persistent in the United States. The etiology of these disparities is complex and multifactorial, rarely due to genetic or biological associations. As much of the attributable risk of worsening disparate racial/ethnic outcomes in ASCVD is secondary to risk factor control, there are ample opportunities to improve racial/ethnic disparities through treatments and management of healthy lifestyle behaviors.

Further interventions to alleviate socioeconomic stressors or to enhance the resilience to the resulting environmental effects of SDH in minority racial/ethnic groups may strengthen health and wellness value associations in these communities (Fig. 2). Lessening barriers of healthcare access, imbalanced SDH, and differential medical treatments of minority racial/ethnic populations affected by ASCVD will further the ultimate mission to improve health equity in all populations worldwide.

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Prevention of Heart Failure

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Summary

- Heart failure is an important cardiovascular disease with enormous medical, social and economic impact.
- The Life's Simple 7™ approach to cardiovascular disease in general and prevention of heart failure, in particular, can produce major benefits in both primary and secondary prevention of heart failure.
- Healthy lifestyle choices are the foundation of the Life's Simple 7™ approach to heart failure prevention.
- Achieving and maintaining normal blood pressure is the single most important goal in heart failure prevention.
- Achieving and maintaining ideal weight (BMI) and normal blood glucose are vital in preventing heart failure.
- Because of the large number of both incident and prevalent cases of heart failure and our aging population, there is a major need to implement guideline-directed medical therapy to prevent recurrent heart failure episodes.
- Immunization against common infections such as influenza are an effective means of preventing heart failure morbidity and mortality.

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1 Introduction

Heart failure constitutes a major category of cardiovascular disease, producing high morbidity, mortality, and enormous direct and indirect socioeconomic burden throughout the world. This chapter will briefly address the epidemiology of heart failure and will mainly focus on the primary prevention of heart failure by managing risk factors known to lead to heart disease and heart failure. Emphasis will be placed on nonpharmacological interventions, especially life-style modifications known to decrease incident heart disease in general and heart failure in particular. Secondary prevention of heart failure in patients with known heart disease and future directions in the management of heart failure will also be discussed.

2 Epidemiology of Heart Failure

Heart failure is a common medical condition affecting patients with heart disease. Heart failure results in high levels of morbidity measured by either hospitalizations or diminished quality of life, and economic impact by disability and community effects [1]. In 2012, heart failure costs were $30.7 billion and projected to rise to $43.6 billion dollars in 2020 with a further increase to $69.7 billion in 2030 [2]. Further, nearly 7% of patients with heart failure are hospitalized each year, and of those who are hospitalized, 22.3% are readmitted within 30 days [3, 4]. Moreover, heart failure is a highly lethal illness with 5-year mortality reaching 50% [5]. In Western society, roughly 1/3 of the patients with heart failure have coronary artery disease and 2/3 have other disorders, including hypertension, valvular heart disease and a broad category of diseases known to produce impaired cardiac muscle function (cardiomyopathy) [5]. Beyond the nosology of heart failure according to broad disease states, the failing heart can be categorized by its gross pathology, either dilated or hypertrophic.

Clinicians and epidemiologists divide heart failure into two phenotypes: heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF) [6]. Patients with HFpEF have a left ventricular ejection fraction greater than or equal to 50%, whereas those with HFrEF have a left ventricular ejection fraction less than 50%. Persons with HFpEF are more likely to be older and female with a history of diabetes mellitus or hypertension [7]. Individuals with HFrEF tend to be younger and male, and often, a myocardial infarction has caused the decline in left ventricular ejection fraction [8]. Randomized controlled trials have defined many of our current therapies for HFrEF. Consequently, our clinical management for HFrEF is based on validated prospective, randomized, double blind trial results with a variety of interventions. Trials involving HFpEF have not revealed the same degree of clinical direction except to be aggressive in managing hypertension [9, 10]. In general, despite the lack of conclusive evidence-based direction, many providers follow the same clinical principles used for HFrEF to direct their management of those with HFpEF.

To direct both prevention and management, the American College of Cardiology/American Heart Association guidelines identify those at risk for heart failure and established heart failure patients by using a staging system [6]. Individuals who are at risk for heart failure but have normal cardiac structure are identified as stage A. Persons who have structural heart disease (left ventricular hypertrophy, prior myocardial infarction, valve disease, etc.) but no prior manifestation of heart failure are identified as being stage B. Patients who have manifested heart failure previously are identified as stage C, and those with established heart failure who are end-stage or refractory to medical therapy are identified as stage D. Heart failure patients are also identified by their New York Heart Association heart failure class [6]. Those patients with heart failure who are asymptomatic are labeled as class I. People with heart failure who only experience symptoms with moderate exertion are labeled as class II. Patients with heart failure who experience symptoms with mild exertion are labeled as class III, and finally, persons who experience symptoms at rest are labeled class IV. The combination of these staging and class-based systems enable providers to better identify individuals who would benefit from certain tailored therapies.

3 Evidence-Based Strategies to Prevent Heart Failure

3.1 Preventing New Onset Heart Failure: Intervening at Stage A

3.1.1 Life's Simple 7™

To prevent the development of cardiovascular disease, including heart failure, the American Heart Association introduced "Life's Simple 7" ™ to help people achieve ideal cardiovascular health [11]. Life's Simple 7™ consists of both optimal health behaviors (nonsmoking, body mass index <25 kg/m^2, physical activity at goal levels, and guideline-based diets) and optimal health factors (untreated total cholesterol <200 mg/dL, untreated blood pressure <120/<80 mm Hg, and fasting blood glucose <100 mg/dL). Using data from large cohort studies, such as the Nurses Health Study and the Health Professionals Follow-Up Study, investigators derived many of these benchmarks for health behaviors from results which showed strict adherence resulted in an over 80% reduction in the development of coronary artery disease [12, 13]. Investigators based their recommendations for ideal health factors on data from both the Atherosclerosis Risk in Communities (ARIC) study and the Framingham Heart Study. ARIC researchers showed an 80% reduction in cardiovascular disease when health factors were optimal, and in Framingham, researchers reported that those with optimal health factors in middle age had a significantly higher chance of living to the age of 85 years [14, 15].

While many of the studies used to develop Life's Simple 7™ focused on coronary artery disease, these same behaviors and risk factor profiles reduce new-onset

heart failure indirectly by preventing myocardial injury from incident coronary artery disease, but also, Life's Simple 7™ directly reduces the risk for incident heart failure in people without coronary artery disease. In the Multi-Ethnic Study of Atherosclerosis (MESA), a diverse cohort of over 5000 participants without prior cardiovascular disease, Ogunmoroti et al. found a 60% lower risk of heart failure with optimal Life's Simple 7™ adherence [16]. In ARIC, a cohort study of 13,462 adults ages 45–64 years enrolled in 1987–1989, the lifetime risk for developing heart failure was 14% in subjects with optimal Simple 7 behaviors and factors, but nearly 50% in those with poor adherence [17]. Following over 30,000 patients for an average of 15 years in the EPIC-NL (European Prospective Investigation Into Cancer and Nutrition-Netherlands) cohort, investigators showed that an ideal Life's Simple 7™ behavior and risk factor profile was associated with a 55% reduction in heart failure [18]. Furthermore, based on data published from the Framingham Offspring Cohort, people who practiced a strict adherence to the Life's Simple 7™ experienced a parallel decline in risk for both heart failure with preserved ejection fraction and heart failure with reduced ejection fraction [19]. Based on the aggregate results from these studies, those without established cardiac disease who had optimal adherence to the Life's Simple 7™ enjoyed a substantial reduction in new-onset heart failure. While complete adherence to the Simple 7 remains challenging, multiple studies attest to the clinical benefit of individual components being able to prevent new-onset heart failure.

Hypertension

Hypertension raises the risk of heart failure substantially. Due to the high prevalence of hypertension in the population, it deserves considerable attention for both prevention and intervention. Although there are several definitions of hypertension in use, the most commonly used for surveillance identifies hypertension from the following criteria: SBP $\geq$130 mmHg or DBP $\geq$80 mmHg, self-reported antihypertensive medicine use, or having been told previously, at least twice, by a health professional hypertension is present [20]. Latest US prevalence data from 2013 to 2016, show a population prevalence of hypertension of 46% [1]. As people age, their blood pressure rises, and in those 75 years of age or older, over 80% had hypertension [1]. With an aging population, this high prevalence of hypertension represents an existential challenge to reducing heart failure. Moreover, African Americans experience a higher burden of hypertension, approaching 60%, which may contribute significantly to recognized health disparities. In order to prevent new-onset heart failure from hypertension, the 2017 Focused Update on Management of Heart Failure endorsed a treatment goal of less than 130/80 mmHg [6]. In a meta-analysis of 18 randomized-controlled trials to reduce blood pressure, those who were treated had a 42% reduction in new-onset heart failure (Relative Risk: 0.58; 95% Confidence Interval (CI): 0.44–0.75; $p < 0.01$) [21]. Even in older patients without cardiac disease, treating hypertension resulted in a

64% reduction in the rate of new-onset heart failure (Relative Risk: 0.36; 95% CI: 0.22–0.68; $p < 0.01$) [22].

Diabetes Mellitus

Diabetes mellitus is a very powerful, independent risk factor for the development of heart failure. Individuals with diabetes are at an increased risk of developing HFpEF, but may also develop HFrEF, particularly in the setting of coronary artery disease [23]. The relative risk for heart failure in patients with diabetes ranges between 1.3 and 2.7, but may be more pronounced in younger patients [24]. Approximately 9.8% of the general population have diabetes, but 37% of those with diabetes remain undiagnosed [1]. While much attention focuses on frank diabetes, it is important to recognize that the Simple 7 uses a fasting blood glucose <100 mg/dL as the benchmark for ideal cardiac health. Nearly 38% of the population have some degree of impaired glucose metabolism, and many of these individuals have a higher risk of developing diabetes.

Many of the standard therapies to treat diabetes have been plagued with concern about possibly precipitating heart failure. Numerous studies implicated rosiglitazone both as monotherapy and in combination with insulin and sulfonylureas [25–27]. Most likely, thiazolidinediones exposed subclinical heart failure by increasing edema, and as such, their use is contraindicated in those at high risk for heart failure [28]. For most people with diabetes, metformin remains a first line agent. While to be avoided in acutely decompensated heart failure, long-term use of metformin may prevent adverse left ventricular remodeling that may lead to heart failure [29]. Sulfonylureas and insulin are often second- and third-line agents whose risk of precipitating heart failure is regarded as equivocal [28].

Newer agents continue to be developed to treat diabetes. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors represent a new way forward to optimize diabetes, and to reduce development of heart failure. In a landmark study, empagliflozin demonstrated a 35% reduction in hospitalization for heart failure (Hazard ratio (HR): 0.62; 95% CI: 0.49–0.77; $p < 0.001$) [30]. Likewise, in a randomized-controlled trial, canagliflozin reduced risk of heart failure hospitalizations by over 30% (HR: 0.67; 95% CI: 0.52–0.87) [31]. Similarly, dapagliflozin also reduced new-onset heart failure admissions by 27% in those with and without atherosclerotic disease (HR: 0.73; 95% CI: 0.61–0.88) [32]. Several mechanisms may account for how SGLT-2 inhibitors prevent heart failure: decreased preload due to osmotic diuresis and natriuresis, decreased afterload due to reduced intravascular volume, promoting ketones as an alternative cardiac energy source for myocardium, reduction in left ventricular mass, and direct inhibition of the sodium-proton exchanger in myocardium, which may decrease fibrosis and injury while promoting improved systolic and diastolic function (see Fig. 1) [33].

In addition, glucagon-like peptide 1 analogues have been introduced. Liraglutide demonstrated an improvement in cardiovascular mortality [34], but did not have

Potential Mechanisms of Cardiovascular Benefit from Sodium-Glucose Cotransport Inhibitors
1. Stimulation of natriuresis
2. Stimulation of osmotic diuresis
3. Cardiomyocyte Na^+/H exchanger inhibition
4. Increased myocardial energetics (via altered myocardial substrate metabolism
5. Reduction in left ventricular mass
6. Improved systolic and diastolic function
7. Improved cardiac filling conditions secondary to reductions in preload and afterload
8. Increased circulating proangiogenic progenitor cells
9. Increased erythropoietin
10. Improved endothelial function
11. Reduction in myocardial CaM kinase II activity
12. Improved myocardial autophagy
13. Inhibition of cardiac fibrosis
14. Increased cardiac output, HR, O_2 consumption, coronary blood flow mediated by increased levels of circulating glucagon

Fig. 1 Potential mechanisms of cardiovascular benefit from sodium-glucose cotransport inhibitors (CaM indicates Ca2+/calmodulin-dependent protein; HR, heart rate; SGLT-2, sodium-glucose cotransporter-2). (Reprinted from Lam et al. [33]. With permission from Creative Commons License 4.0: http://creativecommons.org/licenses/by/4.0/)

significant impact on heart failure hemodynamics or events [35]. Likewise, semaglutide reduced the rate of cardiovascular death and myocardial infarctions, but had no bearing on heart failure during follow-up [36]. Lastly, dulaglutide neither increased or decreased heart failure-related outcomes [37].

While most newer agents improve heart failure or have no significant relationship to heart failure, saxagliptin, an inhibitor of dipeptidyl peptidase 4, increases heart failure risk, particularly in those with chronic kidney disease or preexisting heart failure [38, 39]. In those on alogliptin, another novel dipeptidyl peptidase 4 inhibitor, higher baseline levels of troponin indicated a greater likelihood of heart failure over a 2-year follow-up period [40]. However, in those with established cardiovascular disease, sitagliptin appeared to be neutral in regard to heart failure outcomes [41]. Overall, there was no net benefit to heart failure-related outcomes in those on dipeptidyl peptidase 4 inhibitors.

Smoking

Smoking contributes to the development of heart failure through myocardial injury from acute myocardial infarctions and vascular stiffness leading to abnormal ventricular-vascular coupling. In analyzing cohort data involving nearly two million people in the United Kingdom, smokers had a 62% increase in their lifetime risk for heart failure compared to never smokers (HR = 1.62, 95% CI 1.47–1.79) [42]. The association between smoking cessation and heart failure risk reduction reaches significance at 15 years following smoking cessation, and at 30 years, the risk

approaches that of individuals who never smoked [43]. Notably, smoking increases the risk of heart failure synergistically in the presence of other established heart failure risk factors [18].

Diet-Based Prevention

Recognizing the intersection of diet with many cardiovascular risk factors, much attention has been focused on identifying diets best able to prevent cardiovascular disease, and hence, they occupy a critical role in Life's Simple 7™. In the REGARDS (REasons for Geographic and Racial Differences in Stroke) study, which is a prospective, longitudinal cohort of black and white adults followed from 2003 to 2007 through 2014, subjects who ate a higher proportion of a plant-based diet had a 41% reduction in heart failure relative to those who ate the least amount of plant-based food (HR: 0.59; 95% CI: 0.41–0.86; $p = 0.004$) [44]. Using the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam (Germany) cohort which included 24,000 middle-aged individuals, investigators found participants who ate the least amount of meat and higher proportion of fish experienced a 41% reduced risk of new-onset heart failure (HR: 0.59; 95% CI: 0.36–0.95) [45]. Reviewing cohort data from Sweden, those who adhered to the DASH diet marked by reduced dietary sodium experienced a 20–40% reduction in heart failure [46, 47]. In MESA, the DASH diet optimized LV function, which may also prevent development of clinical heart failure [48]. Not all studies, however, demonstrate a clear benefit: the Cardiovascular Health Study yielded no significant relationships between heart failure events in the elderly and dietary patterns [49]. While the Mediterranean diet promotes general cardiovascular health, its use has shown only limited benefit or no direct relationship to developing heart failure [50].

Obesity

Obesity affects a significant proportion of the adult U.S. population. According to NHANES 2015–2016, among US adults aged ≥20 years, the age-adjusted prevalence of obesity was 39.6% [51]. Among 5881 patients in the Framingham Heart Study, body mass index correlated with HF risk in a dose-dependent fashion: HF risk increased by 5% for men and 7% for women for each single unit increase in BMI, even after adjustment for demographics and other known risk factors [52]. In 21,094 participants without known coronary artery disease, the Physician's Health Study confirmed the association between BMI and HF risk in both overweight and obese participants [53]. Specifically, it demonstrated that overweight participants had a 49% increase in HF risk compared with lean participants (HR: 1.49; 95% CI: 1.30–1.71), and obese participants had a 180% increase (HR: 1.78; 95% CI: 1.43–2.23). Many different measures of obesity provide prognostic information regarding development of HFpEF. In the MESA study, using incident heart failure as the outcome, BMI, waist circumference, and visceral abdominal adiposity as

quantified by abdominal CT scan all identified risk for development of new-onset HFpEF (HR (95% CI) per 1-SD higher of each anthropometric and CT-measured adiposity measures for incident HFpEF were as follows: BMI HR: 1.66; 95% CI: 1.12–2.45; waist circumference HR: 1.59; 95% CI: 1.05–2.40; and visceral adipose tissue HR: 2.24; 95% CI: 1.44–3.49) [54]. For those who are already overweight or obese, intentional weight loss may prevent adverse cardiac remodeling and may prevent incident heart failure [55]. Prevention of obesity may be one of the most effective strategies to reduce incidence of HFpEF.

Physical Activity

Physical activity contributes to overall quality of life and may help prevent cardiovascular disease. In over 11,000 participants with a median follow-up of 19 years in the ARIC cohort, high levels of physical activity reduced the risk of incident heart failure by 31% (HR 0.69 [95% CI 0.60–0.80]) [56]. Investigators also noted that those who increased their physical activity during study follow-up experienced a 23% risk reduction in heart failure (HR 0.77 [95% CI 0.63–0.93]) [56]. In the Henry Ford Exercise Testing Project which included 66,329 patients without heart failure who underwent exercise stress testing, patients able to achieve ≥12 METs had an 81% lower risk of incident HF compared with those achieving <6 METs (HR: 0.19 [95% CI 0.14–0.29]) [57]. In addition, each 1 MET achieved was associated with a 16% lower risk (HR: 0.84 [95% CI 0.82–0.86], $p < .001$) of incident HF [57]. Lastly, in a meta-analysis including nearly 166,000 study participants, regular exercise led to a 28% risk reduction in heart failure relative to those who did not exercise (HR: 0.72; 95% CI 0.67–0.79; $p < 0.001$) [58].

3.1.2 Preventing New-Onset Heart Failure: Intervening at Stage B

The Stage B heart failure population consists of individuals with structural heart disease but who have not yet manifested any evidence of clinical heart failure [6]. Patients with Stage B heart failure present an important early opportunity to make a substantial reduction in risk for future development of heart failure (see Fig. 2). This diverse population includes subjects with left ventricular hypertrophy, asymptomatic left ventricular dysfunction, prior myocardial infarctions, and valvular heart disease. In many situations, these individuals are identified during other routine health care settings.

Left Ventricular Hypertrophy

Under most clinical circumstances, left ventricular hypertrophy occurs in situations where the left ventricular systolic pressure is increased—usually because of hypertension. Most often identified from electrocardiograms or echocardiograms, left

Recommendations	Class[a]	Level[b]
Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life.	I	A
Treatment with statins is recommended in patients with or at high-risk of CAD whether or not they have LV systolic dysfunction, in order to prevent or delay the onset of HF and prolong life.	I	A
Counselling and treatment for smoking cessation and alcohol intake reduction is recommended for people who smoke or who consume exces alcohol in order to prevent or delay the onset of HF.	I	C
Treating other risk factors of HF (e.g. obesity, dysglycaemia) sholud be considered in order to prevent or delay the onset of HF.	IIa	C
Empagliflozin sholud be considered in patients with type 2 diabetes in order to prevent or dealy the onset of HF and prolong life.	IIa	B
ACE-I is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction in order to prevent or delay the onset of HF and prolong life.	I	A
ACE-I is recommended in patients with asymptomatic LV systolic dysfunction without a history of myocardial infarction in order to prevent or delay the onset of HF.	I	B
ACE-I sholud be considered in patients with stable CAD even if they do not have LV systolic dysfunction, in order to prevent or delay the onset of HF.	IIa	A
Beta-blocker is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction, in order to prevent or delay the onset of HF or prolong life.	I	B
ICD is recommended in patients: a) with asymptomatic LV systolic dysfunction (LVEF ≤30%) of ischaemic orgin, who are at least 40 days after acute myocardial infarction, b) with asymptomatic non-ischaemic dilated cardiomypathy (LVEF ≤30%), who receive OMT therapy, in order to prevent sudden death and prolong life.	I	B

ACEI = angiotensin-converting enzyme inhibitor; CAD = coronary artery disease; HF = heart failure; ICD = implantable cardioverter-defibrillator; LV = left ventricular; LVEF = left ventricular ejection fraction; OMT = optimal medical therapy
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Fig. 2 Recommendations to prevent or delay the development of overt heart failure or prevent death before the onset of symptoms from the 2016 European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. (Reprinted from Ponikowski et al. [127]. With permission from Oxford University Press)

ventricular hypertrophy identifies increased risk for new-onset heart failure [59, 60]. Development of left ventricular hypertrophy identifies patients who are at a higher risk of developing heart failure within several years [61]. Lowering blood pressure prevents the development of heart failure in those with left ventricular hypertrophy [22, 60, 62]. In patients whose blood pressure is aggressively treated, left ventricular hypertrophy can regress, and those who experience regression may have a lower risk of incident heart failure [63].

Asymptomatic Left Ventricular Systolic Dysfunction

In general, nearly 5% of the general US population may have some degree of impaired left ventricular systolic function [64]. Of these individuals, half are asymptomatic; in spite of their asymptomatic state, this sample of the population is at high risk of experiencing cardiac events and mortality [65, 66]. To prevent further decline in left ventricular function and prevent development of clinical heart failure, inhibiting angiotensin-converting enzyme (ACE) provides the highest clinical utility to limit pathological ventricular remodeling and prevent clinical progression to overt

heart failure [67]. Patients with asymptomatic left ventricular systolic dysfunction given an ACE inhibitor experienced a 20% reduction in heart failure death or hospitalization (Reduction in Risk: 20%; 95% CI: 9–30%; $p < 0.001$) [67]. Adverse remodeling and prevention of clinical deterioration may also be achieved by preventing excess sympathetic stimulation through use of beta adrenergic blocking medications [68]. In patients who cannot tolerate ACE inhibitors, angiotensin-receptor blockers may be substituted [69, 70].

Post-Myocardial Infarction without Clinical Heart Failure

Myocardial infarctions account for a substantial proportion of patients with left ventricular systolic dysfunction. Individuals with left ventricular dysfunction after a myocardial infarction have a significant risk for developing heart failure. In persons with left ventricular systolic dysfunction, ACE inhibitors reduce development of subsequent heart failure by 20–30% [71, 72]. In initiating a beta-blocker in the post-MI setting, caution is recommended since beta-blockers have the potential to exacerbate low output states. With judicious care, however, post-myocardial infarct patients who can tolerate beta-blockers have an improvement in survival (HR 0.77; 95% CI 0.60–0.98; $p = 0.03$) and less adverse remodeling [73, 74].

3.1.3 Preventing Heart Failure Morbidity and Mortality: Intervening at Stage C

Stage C heart failure patients include those who have clinically manifested heart failure. While clinicians continue to implement the measures previously discussed, more intensive therapies are often selected to improve survival and prevent hospitalization.

Pharmacological Approaches

ACE Inhibitors

Inhibition of the renin-angiotensin-aldosterone system (RAAS) remains one of the primary targets for medications used to treat heart failure, and ACE-inhibitors constitute the best initial approach for most heart failure patients. From the Study of Left Ventricular Dysfunction (SOLVD) trial, participants randomized to enalapril experienced a 22% risk reduction in heart failure deaths (Relative Risk: 0.78; 95% CI: 0.65–0.94; $p = 0.005$). In addition, they had a 26% risk reduction in heart failure hospitalization (Relative Risk: 0.74; 95% CI 0.66–0.92; $p < 0.001$) [75]. In the Assessment of Treatment with Lisinopril and Survival (ATLAS) study, the patients in the high-dose lisinopril group had a nonsignificant 8% lower risk of death ($p = 0.128$) but 24% fewer hospitalizations for heart failure ($p = 0.002$) [76]. These

results should encourage achieving higher ACE-inhibitor dosing to prevent acute exacerbations and improve survival.

Angiotensin Receptor Blockers

Not all patients can tolerate ACE inhibitors. Inhibiting the RAAS axis may still be accomplished with angiotensin-receptor blockers. In the Valsartan Heart Failure Trial (Val-HeFT), valsartan reduced the relative risk of hospitalization by 53% (Relative Risk: 0.47; 95% CI 0.29–0.78; $p < 0.001$). Subjects taking valsartan experienced a 17.3% mortality rate compared to 27.1% in the group who were not receiving any RAAS axis blockade (Relative Risk: 0.66; 95% CI 0.42–1.06; $p = 0.017$) [77]. In a head-to-head trial between losartan and captopril, patients randomized to losartan experienced similar outcomes to those on captopril, but fewer patients on losartan had to discontinue therapy due to side effects [78, 79]. ARBs may, therefore, be used in patients who are not able to tolerate ACE-inhibitors. ARBs and ACE-inhibitors should not, however, be used concurrently, as the risk of acute renal injury and hyperkalemia is high [80].

Beta-Blockers

Overstimulation of the beta-adrenergic receptor promotes adverse left ventricular remodeling and heart failure progression. Blocking beta-adrenergic receptors provides a second pathway to improve long-term outcomes in heart failure. In the Carvedilol Heart Failure Study, the reduction in mortality risk attributable to carvedilol was 65% (95% CI, 39–80%, $p < 0.001$). Subjects randomized to carvedilol also experienced a 27% reduction in the risk of hospitalization for cardiovascular causes (95% CI, 3–45%, $p = 0.036$) [81]. From the MERIT-HF trial, the relative risk for mortality was 0.66 [95% CI 0.53–0.81; $p < 0.001$] in the metoprolol group compared to the placebo group, and there was a marked reduction in deaths from worsening heart failure (RR: 0.51; 95% CI: 0.33–0.79; $p = 0.002$) [82]. As such, beta-blockers represent a critical component of heart failure management. Beta-blockers are, however, best introduced in euvolemic patients as their introduction in low-output states may exacerbate underlying fluid retention.

Aldosterone Antagonists

In patients with class III-IV NYHA heart failure with an LV ejection fraction less than 35%, aldosterone antagonists improve survival and reduce hospitalizations [6]. In the Randomized Aldactone Evaluation Study (RALES), investigators found a 30% risk reduction for death in subjects randomized to spironolactone (Relative Risk: 0.70; 95% CI: 0.60–0.82; $p < 0.001$) [83]. Further, the frequency of hospitalization for worsening heart failure was 35 percent lower in the spironolactone group than in the placebo group (Relative Risk: 0.65; 95% CI: 0.54–0.77; $p < 0.001$). Subjects who received spironolactone had a significant improvement in heart failure symptoms, as assessed on the basis of New York Heart Association functional class

($p < 0.001$) [83]. Based on these results, individuals who are class III-IV heart failure in the setting of HFrEF already on an ACE-inhibitor and beta-blocker should be considered candidates for aldosterone antagonism.

Angiotensin Receptor Blockade with Neprilysin Inhibition (ARNI)

The introduction of neprilysin inhibition represents the most recent significant development in clinical heart failure. Inhibiting neprilysin prevents degradation of endogenous B-natriuretic peptides (BNP), an endogenous hormone secreted to improve the heart failure state. By increasing BNP, ARNI promotes natriuresis and vasodilatation and inhibits myocardial fibrosis [84, 85]. In a landmark study enrolling patients with a left ventricular ejection fraction less than 40% and class II-IV heart failure, PARADIGM-HF investigators reported that subjects who were randomized to sacubitril-valsartan demonstrated a 20% risk reduction for cardiovascular mortality compared to enalapril Relative Risk: 0.80; 95% CI, 0.71–0.89; $p < 0.001$) [86]. In addition, sacubitril-valsartan also reduced the risk of hospitalization for heart failure by 21% (HR: 0.79; 95% CI, 0.71–0.89; $p < 0.001$) and decreased the symptoms and physical limitations of heart failure ($p = 0.001$) [86]. Patients on sacubitril-valsartan did experience more episodes of hypotension but had similar rates of angioedema. In subsequent routine clinical practice, those taking sacubitril-valsartan enjoyed a 20% risk reduction for all-cause mortality compared to those on either an ACE-inhibitor or ARB-alone (HR: 0.80, 95% CI: 0.66–0.97; $p = 0.027$) [87]. Importantly, individuals on ARNIs should not take ACE-inhibitors as the combination substantially increases the risk of angioedema. At present, newer class agents are being evaluated, and the results of many studies on sacubitril-valsartan remain outstanding. Depending on the results of these and further studies, ARNI use may continue to grow and redefine our clinical practice in heart failure and beyond. At present, for those patients with HFrEF who have class II-III heart failure, the 2017 ACC/AHA heart failure guideline update endorses ARNI use to ACE-inhibitor or ARB-alone as a class I indication [88]. Its role in class I heart failure or in Stage A or B heart disease remains to be established.

Sodium-Glucose Cotransporter-2 (SGLT-2) Inhibitors

As discussed previously, SGLT-2 inhibitors are emerging as novel hypoglycemic agents that also significantly reduce the risk of developing heart failure in patients with diabetes. However, given their substantial impact, recent studies evaluated whether SGLT-2 inhibitors, specifically dapagliflozin, may have a role in treating heart failure in those without diabetes. In a randomized-controlled trial enrolling nearly 5000 patients with class II, III, or IV heart failure with a left ventricular ejection fraction <40%, investigators found fewer hospitalizations (HR: 0.70; 95% CI: 0.59–0.83) and less cardiovascular mortality (HR: 0.82; 95% CI: 0.69–0.98) in those who were given dapagliflozin [89]. Further analyses also showed that those on dapagliflozin demonstrated an improvement in quality of life as demonstrated by a

3 point increase in the Kansas City Cardiomyopathy questionnaire score ($p < 0.001$) [90]. Additional studies on other SGLT-2 inhibitors may be forthcoming. Given the strength of the findings in optimizing heart failure in those patients without diabetes, future guidelines may incorporate SGLT-2 inhibitors into a more comprehensive treatment strategy to reduce incident heart failure in those with diabetes and prevent further recurrence in those with established heart failure irrespective of their diabetic status.

Hydralazine-Isosorbide Dinitrate Combination

Added to standard, guideline-based therapy as detailed above, hydralazine-isosorbide increased survival in African American patients with heart failure [Mortality: 10.2% (Placebo) vs. 6.2% (Hydralazine-Isosorbide Dinitrate), $p = 0.02$] [91].

Diuretics

While diuretics are a mainstay of heart failure therapy, they do not improve mortality [92–94]. Ideally, the lowest dose that maintains a normal volume status is preferred. Diuretic dosing may be adjusted based on daily weights to address volume overload prior to worsening symptoms.

Hypertension Management in Patients with Stage C Disease

Researchers continue to debate the optimal blood pressure goal to prevent development of acute heart failure. In the ACCORD trial, investigators targeted a systolic blood pressure <130 mmHg, and in identifying heart failure events, the intensive control group was not statistically different from those managed with a target of 140 mmHg (HR 0.94; CI 0.70–1.26) [24]. However, in SPRINT, subjects who were targeted to a systolic blood pressure <120 mmHg had a 38% risk reduction for the development of heart failure (HR 0.62; CI 0.45–0.84; $p = 0.002$) [95]. SPRINT has generated significant interest and debate about the optimal blood pressure level; further studies may be needed to clarify and validate these findings.

Nonpharmacological Approaches

Implantable Cardioverter Defibrillators

Individuals with a left ventricular ejection fraction <35% have an increased risk of sudden cardiac death. For patients with class II/III heart failure and LVEF <35% due to ischemic or nonischemic etiology, there was a 23% decrease in mortality over a 5-year period with ICDs (HR: 0.77; 97.5% CI: 0.62–0.96; $p = 0.007$) [96]. Before an ICD is placed, patients should be maintained on guideline-directed medical therapy for 3–6 months to allow time for recovery of LV systolic function [6, 97].

Due to its widespread availability and lower cost, providers often use echocardiograms to readily assess for left ventricular recovery prior to placing an ICD.

Exercise Training

Patients with heart failure may experience limitations in exercise tolerance. In HF-ACTION, 2331 subjects were enrolled and underwent randomization to dedicated exercise training or standard therapy [98]. Accounting for baseline and prognostic characteristics, exercise training was associated with a modest benefit in mortality, subsequent hospitalization, and improvement in functional status (HR: 0.89; 95% CI, 0.81–0.99; $p = 0.03$) [98].

Diet and Dietary Supplementation

For persons with heart failure, dietary changes often emphasize restricting sodium consumption. Increased sodium intake leads to fluid retention, particularly in those with heart failure. In a prospective study following outpatient heart failure patients, individuals who consumed the most sodium had the highest risk of hospitalizations and mortality (HR: 2.55; 95% CI: 1.61, 4.04; $p < 0.001$) [99]. Most providers focus on limiting sodium to less than 2 gm/day, but maintaining a sodium consumption less than 3 gm/day may also confer clinical benefit [100].

For patients with heart failure who are overweight or obese, weight loss by caloric restriction may lead to improved remodeling and hemodynamics. Intentional weight loss improves exercise capacity, particularly in HFpEF [101]. Even in heart failure patients who were morbidly obese, weight loss leads to reverse remodeling and improved cardiac hemodynamics [102]. While weight loss usually represents a positive change, in patients with advanced heart failure, unintended weight loss may signal the development of cardiac cachexia which strongly forecasts clinical deterioration and mortality [103].

Many patients seek relief through dietary supplements, and while most supplements lack clinical trial data, n-3 polyunsaturated fatty acids improve clinical outcomes in heart failure. Patients with reduced left ventricular ejection fraction experience a much higher risk of sudden death, but in a trial enrolling over post-myocardial infarction 9000 patients, 1 g daily of n-3 polyunsaturated fatty acids reduced the risk of sudden death by 58% in those left ventricular systolic dysfunction (RR 0.42 (0.26–0.67)) [104]. In addition, in a randomized-controlled trial involving nearly 7000 patients with chronic heart failure (GISSI-HF), supplementation with 1 gram daily of n-3 polyunsaturated fatty acids reduced the risk of mortality and hospitalization (HR 0.92 [99% CI 0.849–0.999], $p = 0.009$) [105]. While many patients use fatty acids to control abnormal triglyceride levels, the anti-inflammatory effects of n-3 polyunsaturated fatty acids most likely mediate the observed effects [106]. In several randomized-controlled trials, however, high-intensity statins showed no significant impact on heart failure outcomes [107, 108].

This observation may mean that the anti-inflammatory properties of n-3 polyunsaturated fatty acids provide more benefit to heart failure patients than the demonstrated anti-inflammatory effects of statins.

4 Biomarkers as Targets for Heart Failure Prevention

Over the past several decades the growing interest in "biomarkers" has fostered an entire industry devoted to identifying objective variables of proven utility in the diagnosis and management of many medical illnesses, including heart failure. These biomarkers can not only help diagnosis, but they also establish prognosis and are used to help tailor interventions to improve outcomes. Biomarkers may be determined through blood testing as simple as hemoglobin A1c to establish diagnosis and follow the management of diabetes mellitus or may be as sophisticated as imaging measurements of anatomy (left ventricular hypertrophy) or left ventricular systolic function (crudely depicted as left ventricular ejection fraction). Beyond their established diagnostic, prognostic, and management utility, can biomarkers serve as suitable targets for prevention of heart failure, either in a primary prevention setting or a secondary prevention scenario? A number of cohort studies have established that blood-based biomarkers such as natriuretic peptides, high sensitivity troponins, and hemoglobin A1c predict the incident development of heart failure and therefore might be useful targets for prevention of heart failure [109, 110]. Moreover, the identification of elevated pro-BNP in a population of at-risk patients has been shown to have benefit for more aggressive control of their risk factors with subsequent demonstration of lower incident heart failure compared to similar patients managed more conservatively [111].

5 Role of Immunization as Strategy to Prevent Heart Failure

It has been known for decades that populations with cardiovascular disease are at risk for development of heart failure. Similarly, immunization against influenza was associated with a 27% decrease in hospitalizations for heart failure in the general population ((Odds Ratio: 0.73, 95% CI: 0.64–0.84; $p < 0.001$) and 19% decrease in all-cause mortality in those with established heart failure (HR: 0.81, 95% CI: 0.67–0.97; $p = 0.015$) [112–114]. More recently, it has been demonstrated that influenza immunization prevents a variety of cardiovascular disease events, including myocardial infarction, stroke, and heart failure [115]. Through prevention of these important outcomes, immunization indirectly prevents incident and recurrent heart failure. Therefore, universal immunization should be a vital public health goal for the prevention of heart failure.

6 Cardiotoxins

6.1 Alcohol

Historically, heavy alcohol consumption (more than 4 g of pure alcohol daily for more than 5 days per week for more than 5 years) may lead to dilated cardiomyopathy in individuals who have susceptibility [116]. Interestingly, light-to-moderate consumption in the general population is associated with a slight decline in risk of heart failure development [117].

6.2 Chemotherapeutic Agents

Many different chemotherapy agents lead to cardiac dysfunction. The most common offenders include anthracyclines and HER-2 inhibitors [118]. The advent of newer classes of therapy, including immune checkpoint inhibitors has brought with them recognition of new toxicities, including those of the cardiovascular system [119]. As the field of cardio-oncology grows, more clinically relevant experience becomes available to guide our understanding and management of clinical and subclinical cardiotoxicity and, thereby, to prevent heart failure in this unique population. The most effective means currently available to prevent cardiotoxicity is to monitor left ventricular ejection fraction and left ventricular strain during and after therapy to detect early signs of cardiotoxicity [120].

6.3 Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Over-the-counter NSAIDs are among the most used and abused medications by patients, and evidence continues to associate their use with increased risk of heart failure development [121]. Interestingly, the risk varies depending upon the specific NSAID with selective COX-2 inhibitors carrying the highest risk, such as rofecoxib (HR: 4.61; 95% CI: 1.50–18.83; $p < 0.001$) [122, 123].

7 The Future of Heart Failure Prevention

Where will the next era of epidemiological study and cardiovascular intervention take the field of prevention of heart failure? This area is primed for exciting new developments, some to focus on population intervention through public health measures and others to address individual needs. Population-based measures include emphasis on lifestyle changes to decrease incident cardiovascular disease. Evidence

cited above suggests that the greatest value comes from achieving and maintaining ideal body mass index and control of high blood pressure. Achieving and maintaining normal blood glucose and prevention of the development of impaired glucose tolerance and diabetes mellitus are also of enormous value.

A particular future direction in heart failure prevention may be through a critical reassessment of heart failure classification. One such approach is the introduction of the concept of heart failure with mid-range ejection fraction (HFmEF; LVEF between 35% and 50%) [124]. With the wealth of cohort and trial data available, epidemiologists may reevaluate their previous results in light of newer classification schemes, such as HFmEF. By redefining these categories, it may allow health care providers to be more specific in the choice of agents to optimize heart failure outcomes.

The proliferation of home genetic testing may allow for an unprecedented level of information to identify relationships between genotype, phenotype, and environment. By identifying asymptomatic patients with genetic indicators of cardiomyopathies or high risk of heart failure, this information may afford epidemiologists the opportunity to identify strategies best able to prevent development of heart failure, improve quality of life, and optimize survival.

At the individual level, a Poly-Pill is likely to be a futile and misdirected approach from several aspects. First, achieving ideal total cholesterol levels has been demonstrated to be of little value in the prevention of incident heart failure. The use of statins is also not without significant problems with side effects, including development of arthralgias, myopathy and diabetes mellitus. Second, increasing evidence has shown the failure of aspirin in primary prevention of atherosclerotic cardiovascular disease, mostly because its benefits are far outweighed by the burden of bleeding complications [125, 126]. Even if a Poly-Pill containing other agents could be developed, its use would be inherently limited by cost and the widespread barrier of nonadherence to the habit of taking medicines over years or decades. Lastly, as we look toward the new era of patient-centered precision medicine, it is clear that the spectrum of a given individual's risk is quite broad. Therefore, the composition of a single Poly-Pill would need to be tailored to fit the needs of a heterogeneous phenotype manifesting the results of epigenetic influences on individual genetic make-up. The best approach appears to be two-pronged, a population emphasis on Life's Simple 7™ and a highly refined precision approach to those at highest risk.

8 Conclusion

Heart failure is an important cardiovascular disease with increasing prevalence that presents a significant medical and societal burden. Different risk factor profiles lead to different phenotypes of heart failure (HFpEF and HFrEF) with similar risk of morbidity and mortality. Life's Simple 7™ evidence-based approach to prevention of heart failure can produce major benefits in both primary and secondary prevention of heart failure. Recognizing structural heart disease early enables clinicians to

intervene to prevent further clinical deterioration towards heart failure. For those with heart failure, blockade of augmented sympathetic tone and the RAAS axis provides the failing heart with reduced stress and promotes reverse remodeling. Nonpharmacological approaches through diet and cardiac rehabilitation may also be used to augment evidence-based pharmacological strategies to prevent mortality and hospitalization.

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Prevention of Peripheral Arterial Disease

Elsie Gyang Ross, Jonathan T. Unkart, and Matthew Allison

Summary

- Peripheral arterial disease (PAD) is a relatively common, but underdiagnosed, atherosclerotic disease process that increases the risk of cardiovascular morbidity and mortality.
- Major risk factors for PAD include smoking, diabetes, hypertension, hyperlipidemia, and family history.
- Vigilance in identifying those at risk of PAD include assessing smoking status, physical activity limits, diminished pulses or evidence of lower extremity wounds.
- Lifestyle factors are important in risk factor modification for PAD and newer pharmaceutical agents show considerable promise in further reducing the rates of limb loss and cardiovascular events in those with established disease.
- Surgical consultation should be considered in those with PAD with any evidence of pain at rest in the feet, tissue loss or lifestyle-limiting pain with walking.

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1 Introduction

Peripheral arterial disease (PAD), defined as atherosclerosis of the lower extremities, affects 200 million individuals worldwide and independently increases risk of cardiovascular morbidity and mortality. Major risk factors include smoking, diabetes, hypertension, hyperlipidemia, and family history. Diagnosing PAD can be difficult as many patients are asymptomatic or have atypical symptoms. In addition to lifestyle modifications as the cornerstone of PAD prevention, many newer pharmaceutical agents are now approved to produce further reductions in cardiovascular and limb events. In this chapter we detail the most up-to-date literature on traditional and novel risk factors for PAD and strategies for diagnosis and review the latest recommendations for primary and secondary prevention.

Lower extremity PAD is associated with significant morbidity and mortality. Globally, 200 million people are affected by PAD [1]. In the United States, the estimated prevalence of PAD in those aged 40 years and older is 4.3% and increases to 14.5% in those aged 70 years and older [2]. It is estimated that, as of the year 2000, 8.5 million people living in the United States have PAD, with the largest burden seen in those of African American race/ethnicity [3].

The classic symptom of PAD is intermittent claudication (IC), i.e., ischemia-induced leg pain in the calf that starts after ambulation and resolves shortly after rest. However, extensive research has shown that individuals with PAD may be asymptomatic or present with a range of leg pain symptoms [4, 5]. These symptoms, often lifestyle limiting, result in significant functional impairment [6]. Beyond these, symptomatic or asymptomatic PAD is associated with a significantly increased risk for cardiovascular disease events and mortality, which increases with the burden of disease [7, 8].

The most common initial and noninvasive technique to evaluate for PAD is the ankle brachial index (ABI). The ABI is the ratio of systolic blood pressure measured at the ankles divided by the highest systolic blood pressure in the arms. The highest ABI for each leg is recorded. An ABI ≤ 0.9 is considered to be positive for PAD. Currently, the United States Preventive Services Task Force (USPSTF) states that there is insufficient evidence to assess the balance of benefit and harm in screening for PAD with the ABI in asymptomatic individuals [9]. However, the American College of Cardiology (ACC)/American Heart Association (AHA) state the measurement of the resting ABI is reasonable in asymptomatic individuals with increased risk for PAD [10]. Those at increased risk include individuals age 65 years or older, or who have a history of diabetes mellitus, smoking, hyperlipidemia, and/or hypertension.

2 Risk Factors for PAD

2.1 Nonmodifiable Risk Factors

2.1.1 Age

Rarely seen in individuals 40 years of age or younger, older age is a strong risk factor for PAD. The incidence of PAD substantially increases after age 65 with the highest prevalence in those older than 70 years of age (Fig. 1) [2, 11].

2.1.2 Gender

When PAD is defined by an ABI of ≤0.9, many studies have found that the prevalence of PAD is equivalent between genders (approximately 3–4.5% among those ≥40 years) [2, 12], or slightly higher in women (2.5% prevalence in men versus 3.5% prevalence in women ≥40 years) [3, 13]. In a majority of studies of symptomatic PAD, defined as symptoms of intermittent claudication, the prevalence and incidence appear to be much higher in men. For example, in a study of over 15,000 individuals from the Atherosclerosis in Communities (ARIC) study, although women had a higher prevalence of ABI <0.9, men had a higher prevalence of intermittent claudication (1% versus 0.6%). Furthermore, in the Framingham Heart Study, the incidence and prevalence of symptomatic PAD is nearly twice that in men as in women [14, 15].

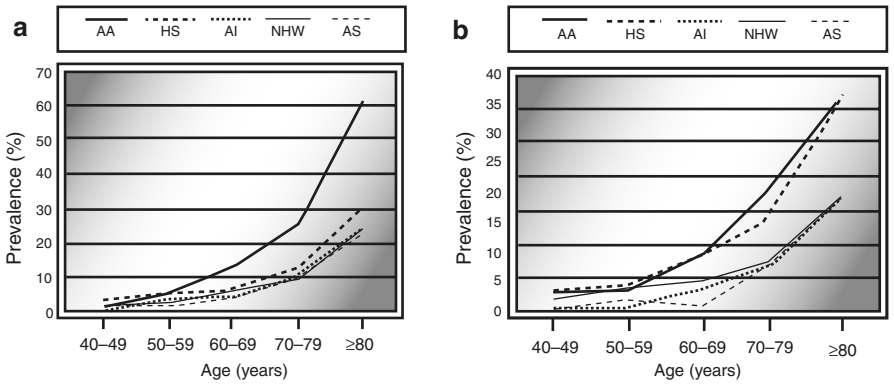

Fig. 1 Prevalence of peripheral arterial disease by race in men (**a**) and women (**b**). (Reprinted from Allison et al. [3]. With permission from Elsevier)

2.1.3 Ethnicity

In studies evaluating multi-ethnic populations, African Americans are disproportionally affected by PAD [2, 3, 12]. Evaluating data from seven community-based studies, African American men have the highest rates of prevalent PAD from age 50 years and greater (Fig. 1). Prevalence at ages 50–59 years is about 5%, 13.2% at age 60–69, and 59% at ≥80 years compared to approximately 1.9%, 5.4%, and 22.6% in non-Hispanic whites at similar ages, respectively. Similarly, in women, the rates of PAD are much higher in African American women compared to other racial and ethnic groups, though these higher rates are observed a decade later compared to men, starting around age 60 years.

Differences in PAD prevalence have also been explored among Hispanic subgroups. In one study of subclinical cardiovascular disease in adult Hispanic ethnic groups, Puerto Rican Americans had a higher prevalence of ABI <1.0 (13%) [16]. Compared to Mexican Americans, Hispanics who did not identify as Mexican, Puerto Rican, or Dominican were the least likely to have an ABI of <1.0. In another study looking at an even more diverse population of Hispanics, after adjusting for multiple risk factors such as age, smoking, and hyperlipidemia, compared to Mexican Americans, Cuban Americans were found to have the highest risk of PAD (OR 2.9, 95% CI 1.9–4.4), followed by Puerto Rican Americans, those with a Central American background, and Dominican Americans [17].

2.2 Behavioral Risk Factors

2.2.1 Cigarette Smoking

Compared to other atherosclerotic diseases such as coronary disease, cigarette smoking portends a greater risk for the development of PAD [18, 19]. The deleterious effects of smoking act both through lifestyle factors and abnormal physiology. For instance, cigarette smoking is associated with reduced dietary intake of antioxidants and increased alcohol intake. On the other hand, physiologically, cigarette smoking is known to induce endothelial dysfunction and is associated with lower high-density lipoprotein cholesterol, higher triglycerides, blood viscosity, and can induce a prothrombotic state – all of which contribute to the development of PAD [18, 20].

Smoking increases risk for both symptomatic and asymptomatic PAD. In a large multi-country meta-analysis, current smokers were found to have 2–10 times the odds of developing symptomatic PAD compared to nonsmokers [21]. In former smokers, the risk was still elevated with the odds of developing symptomatic PAD 2–5 times more likely in former smokers compared to never smokers. Furthermore, a significant dose-response between number of cigarettes and years of smoking has also been observed in multiple populations, with heavy smokers (>25 pack year history) having the highest risk of developing symptomatic PAD [18, 21].

2.2.2 Physical Activity

Moderate physical activity is believed to exert beneficial cardiovascular effects through molecular changes that reduce oxidative stress and improve endothelial function [22]. As a primary risk modifier for the development of PAD, physical activity is relatively understudied. Even so, a few epidemiologic studies demonstrate a positive benefit of increased physical activity and the detrimental effects of a sedentary lifestyle.

Specific to PAD, in 1592 men and women aged 55–74 years enrolled in the Edinburgh Artery Study, higher levels of physical activity in early middle age (35–45 years) were associated with higher ankle brachial indices in men who smoked [23]. In another study of 12,513 men and women aged 45–64 years free of cardiovascular disease at baseline, engagement in recommended weekly moderate and vigorous exercise was associated with lower risk of hospitalization for PAD (HR, 0.68; 95% CI, 0.54–0.85) compared to those reporting low levels of such exercise [24]. Although this difference attenuated with adjustment for lifestyle factors, when vigorous activity was analyzed separately from moderate activity, vigorous activity demonstrated a robust protective association with PAD hospitalizations. In contrast to high physical activity, a sedentary lifestyle, defined as engagement in light or minimal daily work and leisure activities, was associated with a 1.6 higher odds of developing asymptomatic PAD in a large longitudinally followed cohort [25].

2.3 Comorbidities

2.3.1 Hypertension

Hypertension is a well-known risk factor for many atherosclerotic diseases. The induced endothelial dysfunction, hypercoagulable state, and abnormal flow dynamics from hypertension significantly contribute to PAD development [26]. In population-based studies evaluating incident asymptomatic and symptomatic PAD, the presence of hypertension typically confers a ~1.5 to >2-fold increased risk of both conditions [14, 25]. Of both systolic and diastolic pressures, systolic hypertension appears to be more closely associated with the risk of PAD development [14, 27, 28].

2.3.2 Hyperlipidemia

The role of dyslipidemia and atherosclerosis has been well described, especially in the setting of acute coronary events [29, 30]. A similar process of subendothelial retention of circulating low-density lipoproteins (LDL) has traditionally been viewed as a primary driver for peripheral atherosclerotic plaque development and propagation. And, while elevated total cholesterol and LDL can be reasonable

surrogate markers for PAD risk, more specific lipid and lipoprotein measurements may have greater importance in understanding disease risk [11]. In this regard, scientists have challenged the notion that low-density lipoprotein-cholesterol (LDL-C) is as important to PAD development as it is for the development of coronary and cerebrovascular atherosclerotic disease. Using data from the prospective Women's Health Study, including 27,888 individuals ≥45 years of age, the authors compared the lipid profiles of women who developed incident symptomatic PAD versus those who did not over a median period of 15.1 years [31]. The results indicate that total cholesterol and LDL-C were not significantly associated with incident PAD but were associated with incident cardio- and cerebrovascular disease. Notably, higher total and small LDL particle concentrations (LDL-P), concentrations of very low-density lipoprotein particle subclasses (VLDL-P), triglycerides, total cholesterol to high-density lipoprotein (HDL) ratio, and lower HDL and low HDL particle concentrations were significantly associated with PAD. In age-adjusted analyses, these individual factors were associated with a two to three times higher risk of incident PAD. While these results are provocative, they remain to be replicated in more diverse cohorts.

2.3.3 Diabetes Mellitus

Similar to cigarette smoking, diabetes mellitus is considered to be a more important risk factor for PAD than for coronary artery disease (CAD) [32]. The pathophysiology of how diabetes instigates and potentiates PAD is multifactorial. Hyperglycemia and insulin resistance promote vascular inflammation, activation of immunologic factors leading to thrombogenesis and promotion of leukocyte migration and adhesion, increasing atherosclerotic plaque burden and instability [33]. The elevated levels of free fatty acids in diabetics also have deleterious vascular effects such as endothelial dysfunction leading to poor vasodilatory capacity, impaired angiogenesis, increased blood viscosity, hypercoagulability, and platelet dysfunction causing increased aggregation.

In the Framingham Study, glucose intolerance conferred a 2.4-fold increased relative risk of incident symptomatic PAD in men and 4.0-fold increased relative risk in women [14]. Interestingly, the finding of glucosuria was associated with even higher risks (3.5 relative risk in men and 8.6 relative risk in women). Diabetes has also been shown to increase risk of asymptomatic PAD nearly twofold [25] and is associated with higher prevalence of ABIs ≤0.9 (20.9% prevalence vs 7.0% in non-diabetics) [34].

In addition to intraluminal plaque formation seen in PAD, diabetes and the resultant insulin resistance, glycolates, and a complex cascade of biological mechanisms can lead to a condition known as medial artery calcification (Fig. 2) [35, 36]. Calcium in the medial layer of the arterial wall leads to stiffened arteries and confers an independent risk for all-cause mortality and mortality from cardiovascular

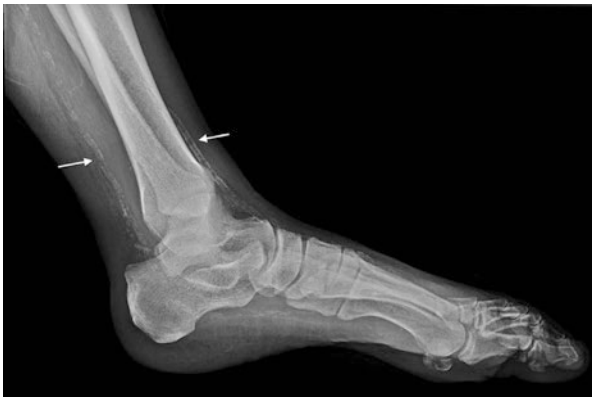

Fig. 2 Example of medial artery calcification seen in diabetes and chronic kidney disease (white arrows). Such findings are linked to increased risk of all-cause mortality and can lead to findings of noncompressible ABIs or ABIs ≥1.4

disease in particular. Additionally, while PAD is traditionally defined as an ABI ≤0.9, those with medial calcification often seen in diabetic patients will often have noncompressible vessels or an ABI ≥1.4. Thus, it is important to recognize that these findings are abnormal, are indicators for increased mortality risk, and may warrant further testing.

2.3.4 Chronic Kidney Disease

Though many individuals with chronic kidney disease (CKD) have concomitant cardiovascular risk factors associated with PAD, renal dysfunction confers its own distinct hazards. Individuals with CKD have hormonal and metabolic dyscrasias that have been linked to the potentiation of vascular disease. While more robust studies are needed, conditions often encountered in CKD and end-stage renal disease (ESRD) patients including protein malnutrition, hypoalbuminemia, and hyperphosphatemia have been linked to increased clinical vascular events in small observational studies [37]. Further, hyperparathyroidism and vitamin D deficiency are associated with higher prevalence of PAD. Similar to diabetes, those with CKD are at high risk of developing medial calcification (Fig. 2) with hyperphosphatemia being a principal catalyst for abnormal arterial calcifications.

Epidemiologic studies have shown a strong independent association between CKD and incident PAD. In the ARIC study individuals with stage 3–4 CKD (estimated glomerular filtration rate (eGFR) of 15–59 ml/min per 1.73 m^2) had a relative risk (RR) of PAD of 1.56 (95% CI 1.13–2.14) compared to those with normal function after adjusting for known cardiovascular risk factors [38]. In an even larger collaborative meta-analysis of 21 international cohorts that included over 800,000 individuals without baseline PAD, compared to normal function, the RR of PAD for those with an eGFR of 45 ml/min per 1.73 m^2 was 1.22 (95% CI 1.14–1.3) and 2.06 (95% CI 1.7–2.48) for those with an eGFR of 15 ml/min per 1.73 m^2 [39].

2.4 Novel Risk Factors

PAD and its associated comorbidities such as hypertension, hyperlipidemia, diabetes, and CKD are known to induce pro-inflammatory and hypercoagulable states. Table 1 lists selected biomarkers associated with PAD.

Table 1 Novel risk factors for peripheral arterial disease

Markers	Association with peripheral arterial disease
Inflammatory markers	
C-reactive protein	1.3–2.1 relative risk of incident PAD in men for every quartile increase in CRP level [119]
	2.1 hazard ratio for incident symptomatic PAD in highest levels of high sensitivity CRP in women [120]
Cellular adhesion molecules	4.0 adjusted hazard ratio for risk of incident symptomatic PAD in women for every tertile increase in sICAM-1 level [120]
	2.7–3.9 increased odds of incident symptomatic PAD in men for every quartile increase in sICAM-1 level [121]
Beta2-microglobulin	Plasma level associated with increased arterial stiffness [122] and independently associated with ABI level [123]
Interleukin-6	32% higher odds of PAD for every standard deviation increase in level [124]
	Independently associated with atherosclerosis progression and ABI change at 5 and 12 years [125]
Thrombotic markers	
Fibrinogen	1.35 relative risk of incident PAD for every tertile increase in serum level [126]
von Willebrand factor	1.31 relative risk of incident PAD for every tertile increase in serum level [126]
Lipoprotein markers	
Lipoprotein(a)	1.37 adjusted hazard ratio for incident symptomatic PAD for every 1 standard deviation increase in LPA [127]
	LPA gene risk allele (rs10455872) associated with decreased ABI (Beta-coefficient − 0.016, $P = 0.03$) [128]
High-density lipoprotein cholesterol	0.4 adjusted hazard ratio for risk of symptomatic PAD in women for every tertile increase in serum level [120]
Others	
Homocysteine	Higher levels of homocysteine independently associated with lower ABI in African Americans [129]
	1.13 increased adjusted odds of PAD in multi-ethnic cohort [124]
Cystatin-C	2.5 adjusted hazard ratio for risk of incident PAD when comparing highest to lowest quintile levels in elderly patients [130]
	1.54 relative risk for symptomatic PAD in men per standard deviation increase in level [131]

2.4.1 Genetics

Family history is a known risk factor for PAD, which implicates genetics, and possibly shared environmental factors [40]. In one twin registry study, in monozygotic twin pairs, individuals with a twin with PAD had a 17.7 increased odds of PAD compared to individuals without an affected twin [41]. The odds ratio for dizygotic twins was 5.7. While many risk loci have been identified for coronary disease, relatively little is known regarding specific genetic risks for PAD. Recent advances in genetic analysis as well as the development of large biobanks have enabled more in-depth analysis of genetic risk factors associated with PAD.

Early genome-wide association studies (GWAS) identified the 9p21 locus as an important risk factor for multiple cardiovascular diseases including PAD [42]. These results were later confirmed in observational studies. Specifically, variants of 9p21 have been associated with differences in ABIs and PAD prevalence [43]. Furthermore, the addition of 9p21 risk alleles has been shown to significantly improve PAD risk prediction when added to traditional cardiovascular risk factors [44].

The latest GWAS study of PAD was conducted using multi-ethnic data from the Million Veterans Program. Analyzing data from 31,307 PAD cases and 211,753 controls, 19 loci were identified as having significant associations with PAD [45]. Eleven of these risk loci were also associated with risk of diabetes (*TCF7L2*), hypertension (*PTPN11*, *ALDH2*), and generalized atherosclerosis of the coronary and cerebral vasculature (*LDLR*, *LPA*, *LPL*, *TWIST1*, *HDAC9*, *SORT1*, *COL4A*, and *FAM20*). Other risk loci included candidate genes (*CHRNA3*, *CHRNA5*, *CHRNB4*), which are associated with nicotine dependence; a variant of Factor V Leiden (*F5*) associated with risk of thrombosis; *IL6*, a known inflammatory biomarker associated with PAD; and a risk variant for the *ABO* gene, which has been associated with deep venous thrombosis, type 2 diabetes, and hyperlipidemia. Many of the discovered risk loci maintained their directionality when compared across different ethnic groups. Furthermore, they have important implications for targeting preventive and treatment strategies for PAD.

3 Prevention

As previously mentioned, individuals with PAD can range from having no symptoms to mild claudication (pain or cramping in the calf with walking, relieved with rest) to critical limb ischemia (such as numbness/tingling or pain in the foot at rest with or without tissue loss). PAD is also associated with significant cardiovascular morbidity and mortality, increasing the rate of major adverse cardiovascular events up to fivefold, even in patients who are asymptomatic [8, 46] (Fig. 3). This section

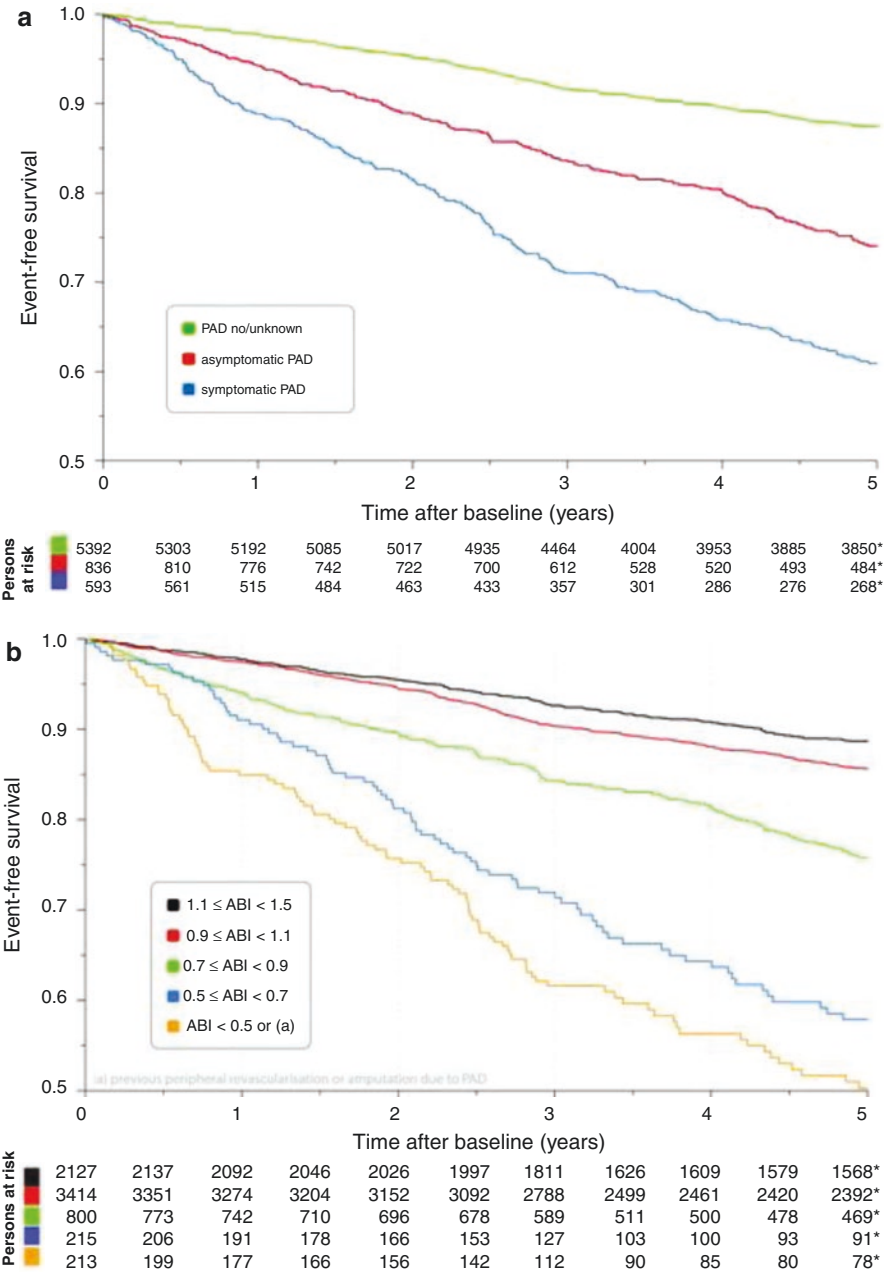

Fig. 3 Risk of all-cause mortality or major adverse cardiovascular or limb event based on symptom status (**a**) and ABI (**b**). (Reprinted from Diehm et al. [8]. With permission from Wolters Kluwer Health)

is split into two parts – Primary Prevention and Secondary Prevention. Primary prevention will focus on the management of patients with high risk of having PAD due to other cardiovascular risk factors (e.g., history of hypertension, hyperlipidemia, and/or diabetes), as well as those with signs of PAD such as diminished pulses, or other indicators suggestive of PAD, but without symptoms. The Secondary Prevention section will focus on the management of patients with a definitive diagnosis of PAD with and without symptoms.

3.1 Primary Prevention

PAD often goes unrecognized in general medical practice [5, 47]. This is partially due to lack of patient/provider awareness of the disease and a relatively low rate of symptoms. In fact, only about 5–30% of patients with PAD report classic symptoms of claudication, with another 30–62% reporting atypical symptoms and the remainder reporting no symptoms at all [5, 47]. In the absence of symptoms, individuals with a high risk of PAD may be identified in routine practice through diminished lower extremity pulse exam, ABI $\leq$0.9, or incidental CT or radiologic findings of peripheral atherosclerosis. It is important to note that even without symptoms, the presence of PAD is a marker of more systemic atherosclerosis that can increase risk of major adverse cardiovascular events. For example, data from the Framingham Study showed that the hazard ratio (HR) for 10-year cardiovascular mortality in men with an ABI $\leq$0.9 is 4.2 (95% CI 3.3–5.5) compared to men with normal ABIs [7]. For women the HR is 3.5 (95% CI 2.4–5.1). Further research has confirmed that the elevated risk of major adverse cardiovascular events from PAD is also observed in those with asymptomatic disease [8, 48]. Thus, recognition of the need to initiate aggressive prevention strategies is important for cardiovascular outcomes in these high-risk patients.

3.1.1 Screening

Currently there is some controversy as to the utility of screening for PAD in asymptomatic individuals. While organizations such as the United States Preventive Services Task Force (USPSTF) and the American College of Preventative Medicine recommend against routine screening, other societies such as the American Diabetes Association, ACC/AHA, and the Society for Vascular Surgery recommend consideration of screening in high-risk groups (Table 2). While the former cite a lack of sufficient evidence that the benefits of routine screening outweigh the harm, the latter groups assert that ABI screening can significantly improve cardiovascular risk stratification.

Table 2 Summary of Society recommendations for screening ankle brachial indices

Organization	Screening recommendation	Recommendation class	Year
American College of Preventative Medicine	Do not recommend routine ABI screening in asymptomatic adults, though providers should be alert for risk factors (aged >50 years, smokers, and diabetics)	Not reported	2011 [132]
American Diabetes Association	1. Perform ABIs for diabetics aged >50 years, if normal repeat every 5 years 2. Perform ABIs in diabetes <50 years old with other risk factors 3. Perform ABIs in those with symptoms of PAD	Not reported	2003 [133]
American Heart Association/ American College of Cardiology	1. Recommend resting ABI in patients with history or physical exam suggestive of PAD	1. I	2016 [10]
	2. Reasonable to measure ABI for those at increased risk of PAD without history or physical examination suggestive of PAD	2. IIa	
	3. ABI not recommended in those not at increased risk of PAD and without history or physical exam suggestive of PAD	3. III: No benefit	
European Society of Cardiology/ European Society of Vascular Surgery	1. Patients with clinical suspicion of PAD should undergo ABI testing	1. Not reported	2017 [134]
	2. Patients at risk of PAD due to history of other atherosclerotic diseases (e.g., CAD) should undergo ABI testing	2. IIb	
	3. Asymptomatic individuals with risk factors should undergo testing: Individuals >65 years Individuals <65 years classified as high CV risk Age >50 with family history of PAD	3. Not reported	
Society for Vascular Surgery	1. Recommend ABI in individuals with symptoms or signs suggestive of PAD	1. IA	2015 [135]
	2. Reasonable to obtain ABI in asymptomatic individuals who are at increased risk (e.g., age >70, diabetics, other CV disease) to improve risk stratification	2. IIC	
USPSTF	1. Recommend against routine ABI screening	1. D	2006 [136] 2013 [137], 2018 [9]
	2. Insufficient evidence to make recommendations	2. Indeterminate	

3.1.2 Diet and Nutrition

Relatively little has been published regarding dietary recommendations specific for PAD. Even so, studies have demonstrated that for men, increasing cereal fiber may help prevent PAD [49] and high intake of antioxidants such as vitamin E, beta-carotene, vitamin C, and dietary carotenoids may be protective against incident symptomatic PAD [50]. In the Rotterdam Study of over 4000 men and women aged 55–94 years without cardiovascular disease at baseline, vitamin C intake in women was protective against PAD (defined as ABI ≤0.9) (highest vs. lowest quartile RR of 0.64 95% CI 0.48–0.89) [51]. Similarly, in a mixed-cohort of men and women included in the cross-sectional NHANES study, increased fiber, omega-3 fatty acid, vitamin C, vitamin E, vitamin A, vitamin B6, and folate were associated with a reduced prevalence of PAD [52]. In one multicenter randomized trial conducted in Spain, researchers found that compared to the control group, a Mediterranean diet supplemented with extra-virgin olive oil significantly decreased risk of incident PAD (HR 0.36, 95% CI 0.21–0.65) as did a Mediterranean diet supplemented with nuts (HR 0.54, 95% CI 0.32–0.92) [53]. In a case-control study of type 2 diabetic patients, researchers found that those with a higher Mediterranean diet score had a lower risk of having PAD (Odds Ratio = 0.44, 95% CI 0.24–0.83) [54].

While dietary findings specific to PAD are promising, there currently are no guidelines recommending specific diets or nutrients for PAD prevention. Instead, the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease offers general advice on dietary recommendations for cardiovascular risk reduction [55]. Recommendations include diets that accent vegetable, fruit, legume, nut, whole grain and fish intake. Saturated fats should be replaced by monounsaturated and polyunsaturated fats. Low-sodium and low-cholesterol diets are recommended, as is reducing intake of refined carbohydrates, sweetened beverages, processed meats, and avoidance of trans fats.

3.1.3 Physical Activity

Aerobic exercise increases the growth and development of arterial capillaries, improves endothelial function, decreases inflammation, and improves vascular smooth muscle function [56]. For those with preexisting cardiovascular risk factors, exercise also improves blood pressure in hypertensive patients, improves insulin sensitivity in diabetic patients, and increases HDL-C [57]. As a primary preventive strategy, exercise has been shown to prevent and/or slow the progression of subclinical atherosclerotic plaque [57].

3.1.4 Smoking Cessation

Smokers are up to ten times more likely than nonsmokers to develop PAD, making smoking one of the most important modifiable risk factors for PAD [33]. Although there is a residual effect of smoking and risk of development of atherosclerotic

diseases, longer durations of smoking cessation are associated with decreased risk of PAD development [19]. Compared to current smokers, those who quit smoking at <31 years of age had a lower adjusted risk of PAD than those who quit when over the age of 48 (HR 0.23 95% CI 0.18–0.29 vs HR 0.52, 95% CI 0.38–0.7, respectively).

The ACC/AHA Guidelines for Primary Prevention for Cardiovascular disease currently recommend assessing patients' smoking status at every visit (Class IA recommendation) [55]. Furthermore, patients should be advised to quit smoking and offered both behavioral and pharmacotherapy to improve smoking cessation rates. In addition, secondhand smoking should be avoided.

3.1.5 Lipid Management

In those with a high risk of cardiovascular disease, high-intensity statin therapy can help reduce the risk of incident PAD. In a study of nearly 9000 post-myocardial infarction patients who were randomized to high- or moderate-dose statins, researchers found that high-intensity statin therapy significantly reduced risk of incident PAD (HR 0.70, 95% CI 0.53–0.91) [58]. In light of this evidence, though the ACC/AHA guidelines do not make specific recommendations for statin therapy for primary PAD prevention, general guidelines for assessing cardiovascular risk and deciding when to place patients on statins are likely helpful for reducing risk of PAD.

3.1.6 Blood Pressure Control

There are no specific guideline recommendations for blood pressure management for prevention of PAD. However, research indicating that higher blood pressures, particularly systolic blood pressure >140–160 mmHg and associated increased risk of incident and prevalent PAD, indicate that hypertension is an important risk factor requiring control [27, 59, 60]. Current recommendations include targeting a blood pressure of <130/80 mmHg in adults with confirmed hypertension and 10-year atherosclerotic cardiovascular disease (ASCVD) risk of 10% or higher [55]. One caveat is that a re-analysis of the ALLHAT trial (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack) showed that for PAD events specifically, a systolic blood pressure <120 mmHg was associated with a 26% higher hazard of PAD events (CI 5–15%) compared to systolic blood pressures ranging from 120 to 129 mmHg [59]. Furthermore, a diastolic blood pressure <60 mm Hg was associated with an increased risk of PAD events (HR, 1.72, CI 1.38–2.16). Thus, while a target blood pressure goal of <130/80 is reasonable, targeting blood pressures <120/60 may be harmful, though more research is needed.

In addition to initiation of antihypertensive medicines, lifestyle modifications are also recommended and include: weight loss, a heart-healthy diet, reducing sodium intake, dietary potassium supplementation, increased physical activity, and limiting alcohol intake.

3.1.7 Glucose Control

Similar to smoking, hyperglycemia and the development of diabetes act as major catalysts for the development of PAD [14, 61]. For those with prediabetes (i.e., fasting plasma glucose of 100–125 mg/dL or Hgb A1c of 5.7–6.45), the American Diabetes Association guidelines recommend referral to intensive behavioral lifestyle intervention programs that focus on losing 7% of initial body weight and increasing moderate-intensity physical activity to at least 150 minutes per week [62]. Multiple studies, including randomized, controlled trials have found that these interventions can reduce risk of progression to diabetes and improve control of other cardiovascular risk factors such as hyperlipidemia, hypertension, and general inflammation. For older adults with diabetes, in addition to important lifestyle management goals, general guidelines recommend maintaining a Hgb A1c of <7.5%. For those with multiple comorbidities, cognitive impairment, or functional dependence, an A1c <8.0–8.5% is recommended [63].

3.2 Secondary Prevention

For individuals with a diagnosis of PAD, intensive management of this disease is extremely important to improve longevity and quality of life. Approximately 10–20% of individuals who are diagnosed with PAD go on to experience disease progression that can include need for vascular surgery and/or the complication of limb loss [64]. In addition to limb events, those with PAD have an up to five-fold increased risk of major adverse cardiovascular events [8, 46]. Furthermore, risk of cardiovascular mortality and morbidity is highest for those with symptomatic disease, especially those presenting with tissue loss [65]. It should be mentioned that there is some controversy as to whether those with asymptomatic PAD benefit from the same intensive therapies as symptomatic patients given the lack of clinical trials evaluating outcomes in this specific patient population. This section will distinguish recommendations based on symptom status.

3.2.1 Diagnosis

Individuals at increased risk of PAD include those who are:

1. ≥65 years of age
2. 50–64 years of age with other risk factors for atherosclerosis such as diabetes, hypertension, hyperlipidemia, and/or history of smoking
3. <50 years with diabetes and one additional risk factor for atherosclerosis
4. Individuals with known atherosclerotic disease in a different vascular bed such as coronary, carotid, subclavian, renal, or mesenteric artery stenosis or those with an abdominal aortic aneurysm [10]

For those with increased risk of PAD, a thorough history and physical exam to assess extent of risk factors, status of any lower extremity symptoms, or tissue loss is important to help establish a diagnosis of PAD. Important symptoms to elucidate include pain with walking that improves with rest, symptoms of "leg fatigue" or other impaired walking symptoms, burning pain in the foot at rest, or history of poorly healing lower extremity wounds. Examination should include palpation of the bilateral femoral, popliteal, dorsalis pedis, and posterior tibial arteries. Noninvasive blood pressure measurements in both arms are also important to initial evaluation as this can diagnose subclavian stenosis, which is a known manifestation of upper extremity PAD [10]. In those with signs or symptoms suggestive of PAD, a resting ABI with or without waveforms and/or segmental pressures is recommended to establish a diagnosis. It is also reasonable to obtain ABIs in those who have a high risk of PAD but for whom there are no signs or symptoms suggestive of PAD.

In those with an ABI >1.4, noncompressible vessels or with wounds, it is reasonable to obtain toe-brachial indices (TBI) with waveforms. Toe-brachial indices involve measurement of pressures of the bilateral 1st toes and dividing this blood pressure by the highest brachial pressure. A TBI <0.7 is considered positive. Given that diabetics and those with CKD are more likely to have falsely elevated ABIs due to medial artery calcifications (Fig. 2), TBIs represent an important alternative measurement that has significant cardiovascular prognostic value [66]. For those with normal (1.0 to <1.4) or borderline ABIs at rest (0.91–0.99) with exertional leg symptoms, a treadmill ABI test is reasonable, as those with occlusive disease concentrated in the aorto-iliac system can sometimes have normal resting ABIs. More invasive studies such as CT, MR, or invasive angiography should be reserved for those for whom revascularization is being considered.

3.3 Risk Factor Modifications

Intensive management of comorbid conditions can lead to significant improvement in life expectancy in PAD patients and decrease progression to more severe disease [67, 68].

3.3.1 Smoking Cessation

Although underutilized in the PAD population, evidenced-based smoking cessation treatments are important to PAD management [69]. Even for those who are successful in quitting, the rate of relapse at 3 months can be nearly 40% and the rate increases over time. Furthermore, those with PAD who smoke have a higher rate of progression of disease and poorer postoperative outcomes when revascularization is attempted [70–72]. Thus, it is important to assess an individual's smoking status at every visit and provide guidance and develop a plan for quitting. Formal smoking

cessation counseling, as well as pharmacologic agents such as bupropion, varenicline, and/or nicotine replacement agents have all been shown to be effective for smoking cessation [10].

3.3.2 Physical Activity

Structured walking exercise therapy has been shown to improve cardiorespiratory fitness and walking distance, and decrease functional decline in individuals with PAD [73–76]. Moreover, poor exercise capacity in patients with PAD has been linked with increased risk of all-cause mortality [77].

As of 2017, the Centers for Medicare and Medicaid Services (CMS) provide coverage for a 12-week supervised exercise program for those with symptomatic PAD [78]. These sessions include 30–60 minute sessions of therapeutic exercise conducted face to face with qualified personnel and supervised by a physician 3 times a week. Those with persistent symptoms are eligible for an additional 36 sessions after the 12-week program. While the coverage of supervised exercise by CMS is definitely welcome, many patients find supervised exercise programs to be inconvenient in location and/or hours and many refuse to participate for other reasons [79]. An alternative for patients who refuse or who cannot conveniently participate in supervised exercise is home-based therapy. Three of four randomized trials evaluating home-based exercise therapy have found them to be successful in improving walking distance, functional status, and vascular function and reducing inflammatory markers in PAD patients [80–83].

4 Pharmacotherapy for Management of Co-morbidities

While lifestyle modification is a cornerstone of cardiovascular health, a diagnosis of PAD warrants more aggressive therapy, including initiation and maintenance of certain agents to help reduce burden of major adverse cardiovascular and limb events. Table 3 outlines specific therapy goals for those with PAD.

4.1 Antiplatelet Therapy

A single antiplatelet regimen – aspirin (75–325 mg daily) OR clopidogrel (75 mg daily) – is recommended to reduce major adverse cardiovascular events in individuals with symptomatic PAD [10]. In asymptomatic patients with ABI $\leq$0.9, antiplatelet therapy is recommended as a reasonable approach to decreasing risk of major adverse cardiovascular events.

The newest antiplatelet agent with Food and Drug Administration (FDA) indication for reduction of cardiovascular events in PAD patients is vorapaxar – a selective

Table 3 Summary of guideline recommendations for secondary prevention measures for peripheral arterial disease

Risk factor	Target goal	Specific agents
Smoking	Cessation	Counseling + pharmacologic agent better than single strategy [69, 71]
Sedentary lifestyle	Moderate activity for 30–60 minutes a day, 3 times per week	Supervised exercise therapy most effective [138]
Hypertension	<130/80 mmHg	No specific evidence that 1 antihypertensive agent better than another [139, 140]
Hyperlipidemia	LDL reduction of ≥50% or <70 mg/dL in very high risk PAD patients (acute coronary syndrome, history of multiple cardiovascular events, and/or multiple risk factors)	Statin therapy as first line therapy [10] Can consider adding a PCSK-9 inhibitor if LDL goal not achieved [90]
Diabetes	Hgb A1c <7.0%* *<8.5% in older, more disabled patients	No specific evidence that one anti-glycemic agent is better than another [63]

Protease-Activated Receptor-1 (PAR-1) inhibitor [84]. In subgroup analyses, vorapaxar has also been shown to decrease risk of acute limb ischemia and need for revascularization in PAD patients [85, 86]. However, clinical trials have also shown increased bleeding risk with vorapaxar, particularly in patients with prior cerebrovascular events. Thus the clinical role for vorapaxar in PAD patients will need to be studied in more detail to best understand which patient groups derive the most clinical benefit with the least amount of bleeding risk.

4.2 Statin Therapy

Statin therapy has been shown to decrease cardiovascular and limb events, such as amputation, and improve functional status in those with PAD [87–89]. Thus, statin therapy is currently recommended for all patients with diagnosed PAD [10]. Per AHA guidelines, those with PAD placed on statins for secondary prevention of cardiovascular disease should be initiated on high-dose statin therapy [90]. High-intensity statins are expected to reduce baseline LDL-C by ≥50%.

4.3 Non-statin Lipid Lowering Therapy

The ACC/AHA guidelines recommend reduction in LDL to <70 in "very high risk" individuals, including those with acute coronary syndrome, multiple cardiovascular events, or history of prior cardiovascular event with multiple risk factors. While

guidelines recommend the addition of ezetimibe for increased LDL-C reduction, there is some controversy in this approach for those with PAD. Two trials evaluating the addition of ezetimibe to statin monotherapy or statin therapy with niacin found that although ezetimibe led to further significant reductions in LDL-C, there was an unexpected increase in atherosclerotic plaque in the superficial femoral artery [91] and increased carotid-intima-media thickness [92], respectively.

While guidelines recommend consideration of PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor as a second-line agent to ezetimibe, the data for outcomes in PAD patients may be stronger for PCSK9 treatment. A subanalysis of the FOURIER trial (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) found that among 3542 patients with PAD followed for a median of 2.2 years, the addition of a PSCK9 to statin therapy reduced the composite risk for cardiovascular death, myocardial infarction, stroke, hospital admission for unstable angina or coronary revascularization (HR 0.79, 95% CI 0.66–0.94) [93]. Compared to those without PAD, those with PAD had a larger absolute risk reduction (1.6% versus 3.5%, respectively). In all patients (with and without PAD), the addition of a PCSK9 significantly reduced risk of major adverse limb events (HR 0.58, 95% CI 0.38–0.88).

4.4 Oral Anticoagulation

Generally, the use of anticoagulation for secondary prevention in PAD has been recommended against due to the potential for harm [10]. However, newer anticoagulants are demonstrating improvement in cardiovascular and limb outcomes in PAD patients. The COMPASS trial (Cardiovascular Outcomes for People Using Anticoagulation Strategies) included 27,395 individuals with coronary artery disease and/or PAD from 33 countries and 602 hospitals. Of the initial cohort 7470 had stable PAD. The salient findings were that those on rivaroxaban and aspirin, compared with aspirin alone, experienced reduced composite death, myocardial infarction, and stroke events (HR 0.72, 95% CI 0.57–0.9) and major adverse limb events (HR 0.54, 95% CI 0.35–0.82) [94]. These findings led to FDA approval of an additional indication for rivaroxaban as an agent to reduce major adverse cardiovascular and limb events in those with PAD and CAD in conjunction with aspirin therapy. Current dosing recommendations for this indication are 2.5 mg of rivaroxaban twice daily with aspirin (75–100 mg) once daily.

4.5 Glycemic Agents

In those with PAD, the presence of diabetes increases odds of premature all-cause mortality by up to twofold [95]. The severity of PAD is greater in diabetics, and revascularizations may be more likely to fail [96–98]. Furthermore, lower extremity

polyneuropathy associated with diabetes can lead to infections and wounds that are more difficult to treat in the setting of concomitant PAD [99]. Generally, aggressive glycemic control is a cornerstone of PAD management in those with diabetes.

There has been keen interest in whether there are particular glycemic agents that can specifically improve outcomes for diabetics with vascular disease. Newer anti-diabetic agents known as SGLT2 inhibitors (sodium-glucose co-transporter 2 inhibitors) and GLP1-RA (glucagon-like peptide-1 receptor agonists) have shown promising results in reducing cardiovascular events and mortality in those with diabetes [100–103]. Unfortunately, certain SGLT2 inhibitors have been found to not only increase risk of amputations in diabetics, but the risk of below knee amputations has been found to be highest in those with a history of PAD [104]. Thus, caution should be taken in prescribing these agents in those with PAD.

4.6 Other Agents

There are few other pharmaceutical agents with FDA approval for treatment of PAD. Cilostazol is a phosphodiesterase-3 inhibitor and has both antiplatelet and vasodilatory properties. It is currently approved for and recommended for treatment of symptomatic PAD, as it has been shown to improve walking distance and decrease claudication symptoms [105]. Of note, Cilostazol has an FDA black box warning against use in those with heart failure.

Pentoxifylline is another phosphodiesterase inhibitor that has been studied for treatment of claudication symptoms in PAD. Its properties include decreased blood viscosity, increased erythrocyte flexibility, and improved tissue oxygen concentration and flow in the microcirculation. Unlike cilostazol, the data is more mixed as to the utility of pentoxifylline for claudication, and it is not currently recommended for treatment [10, 106].

4.7 Invasive Treatments

For individuals with symptomatic PAD, revascularization may be necessary to improve quality of life and ability to engage in work-related activities and improve exercise capacity. However, prior to any revascularization, medical therapy and lifestyle modification should be optimized. Recent research shows that early revascularization, rather than conservative management for symptomatic PAD is actually associated with increased risk of amputation [107].

We are currently in what many describe as an “Endovascular First Era.” That is, for most patients who are medically optimized with persistent lifestyle limiting claudication, endovascular therapies are likely to be discussed and initiated before more invasive procedures. Endovascular approaches include use of angioplasty balloons, stents and atherectomy to treat hemodynamically significant occlusions and

stenoses [108]. An increasing number of population-based studies are finding that an "endovascular first" approach to treatment of significant PAD lesions may improve amputation-free survival, even in those with critical limb ischemia [109, 110]. Even so, endovascular therapy is not recommended as a strategy to prevent limb loss in patients with claudication symptoms only, as only 1–2.5% of those with claudication progress to critical limb ischemia including amputation or tissue loss [111]. Comparatively, for those with critical limb ischemia, risk of amputation is as high as 40% at 1 year [65]. Thus, earlier, more aggressive intervention is warranted in this group for prevention of limb loss in appropriately selected patients.

Surgical procedures for symptomatic PAD and critical limb ischemia include endarterectomy (removal of occlusive atherosclerotic plaque) or bypass surgery. Patients recommended for surgical procedures may have failed endovascular therapies or may not be suitable anatomical candidates for endovascular repair. Furthermore, in younger individuals with fewer comorbidities, surgical repair may be offered first since open repair is associated with longevity of patency and lower rates of re-interventions [109, 112]. More and more, surgeons may perform hybrid procedures where stenting, endarterectomy, and/or bypass procedures may all take place in the same setting [113].

Post endovascular or surgical intervention, antiplatelet therapy is generally indicated to improve patency [114]. Though there are little data to support use of dual antiplatelet therapy after surgical or endovascular intervention, it is common practice for those undergoing endovascular intervention to be placed on dual antiplatelet therapy for 1–3 months post-procedure [115]. Though there continues to be emerging data supporting dual antiplatelet use after revascularization [116], larger randomized controlled trials would help elucidate the true impact of this practice on post-procedural outcomes.

The role of anticoagulation after peripheral revascularization is similarly understudied. There is evidence that routine anticoagulation after vascular intervention has mixed results. The Dutch Bypass Oral Anticoagulants or Aspirin Study was one of the largest studies to evaluate postoperative anticoagulation and found that oral anticoagulation was better at preventing occlusions of infrainguinal vein bypasses, while aspirin alone was better at preventing occlusions of infrainguinal prosthetic graft bypasses [117]. However, the risk of bleeding was significantly higher in those treated with anticoagulants than with aspirin. Further research in this area is needed. Currently, low dose rivaroxaban in addition to antiplatelet therapy is being evaluated as a strategy to reduce vascular events after endovascular or surgical interventions [118].

5 Conclusion

Peripheral arterial disease affects millions of Americans, confers significantly increased risks of morbidity and mortality, yet there is a relative lack of awareness of the disease. This lack of awareness contributes to low diagnosis rates. However,

improving diagnosis can improve outcomes for those with PAD given the multiple approaches to primary and secondary prevention available. Simple screening measures can be instituted in the outpatient clinic setting such as review of patients' smoking history, symptoms with walking, family history, evaluation of their pedal pulses, and noninvasive measures such as the ankle brachial index. Those at high risk of having PAD or those with diagnosed but asymptomatic disease should be counseled about important lifestyle modifications while those with symptomatic disease may need more aggressive pharmacologic treatments, supervised exercise therapy, and surgical intervention.

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Prevention of Atrial Fibrillation

Jelena Kornej and Emelia J. Benjamin

Abbreviations

AA	African Americans
AF	Atrial fibrillation
ARIC	Atherosclerosis Risk in Communities Studies
BMI	Body mass index
BP	Blood pressure
CKD	Chronic kidney disease
CPAP	Continuous positive airway pressure
CVD	Cardiovascular disease
DM	Diabetes mellitus
FHS	Framingham Heart Study
HF	Heart failure
HFpEF	HF with preserved ejection fraction
LA	Left atrial
LV	Left ventricular
MI	Myocardial infarction

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OSA	Obstructive sleep apnea
PA	Physical activity
RAS	Renin-angiotensin axis
TGF	Transforming growth factor
VTE	Venous thromboembolism

Summary

- AF incidence is increasing substantially worldwide mostly because of aging populations and the rising prevalence of chronic comorbidities associated with higher AF risk. Becoming a global epidemic, targeted prevention programs for AF are necessary but largely missing. There is an unmet epidemiological and clinical need to start AF prevention at younger ages and at the population level.
- AF incidence and prevalence rates are higher in individuals of European ancestry compared to other ethnic populations, although prevalence of comorbidities related with AF risk are higher in African Americans. Racial and ethnic variations in AF incidence and prevalence are explained by genetic factors, socioeconomic and environmental determinants of health, and AF ascertainment biases.
- Identification and prevention of modifiable risk factors – such as smoking, alcohol consumption, sedentary lifestyle, overweight/obesity, high blood pressure, and diabetes – should be considered as a major priority for AF prevention.
- Cardiac adaptation to moderate physical activity is beneficial and should be used for AF prevention. However, it should be understood that extreme physical activity leads to cardiac "overadaptation" or even "maladaptation" and pathophysiological changes facilitating AF initiation and perpetuation.
- There is an unmet epidemiologic and clinical necessity to define the relation of AF burden to clinical outcomes and healthcare costs.
- With the exception of stroke, there is a lack of data to guide prevention of complications after AF. There is an urgent requirement for studies analyzing the prevention of myocardial infarction, heart failure, venous thromboembolism, and chronic kidney disease after the onset of AF. Conversely, because of complex bidirectional relations, additional research is needed to effectively prevent AF after myocardial infarction, heart failure, stroke, venous thromboembolism, and chronic kidney disease.

1 Introduction

1.1 Epidemiology

Both the incidence and prevalence of atrial fibrillation (*AF*) are increasing globally [1–3]. Aging populations, increased life expectancy, and longer survival with varied chronic diseases are probably the most important driving mechanisms explaining the twenty-first-century AF epidemic [1, 4]. Many concerns relate to AF-associated complications leading to increasing healthcare costs despite scientific and clinical innovations [5, 6].

In the United States, AF prevalence ranged from 2.7 to 6.1 million a decade ago [7, 8], and prevalence is estimated to reach 12.1 million by 2030 [9]. In the European Union (*EU*), AF was diagnosed in almost nine million adults older than 55 years in 2010 and is expected to rise up to 18 million by 2060 [10]. According to the Global Burden of Disease project, AF prevalence was 33.5 million in 2010 worldwide, with five million new AF cases each year [1]. AF epidemiological assessment beyond Europe and North America is scarce, with estimated AF prevalence from <1% in India and Africa, 3% in Middle East, and ~4% in Australia [11, 12]. It was estimated that by 2050 AF will be diagnosed in at least 72 million individuals in Asia with ~three million AF-related strokes [13].

1.2 Secular Trends

Based on the Framingham Heart Study (*FHS*) and Rotterdam Study data, the lifetime risk for AF development was previously estimated to be 1 in 4, but more recent FHS, European BiomarCaRE Consortium, and Atherosclerosis Risk in Communities Studies (*ARIC*) cohorts reported lifetime risk of approximately 1 in 3 for individuals of European ancestry [14, 15] and 1 in 5 for African Americans (*AA*) [16]. Observational studies reported AF prevalence increased fourfold over 50 years, and after age adjustment the incidence was threefold higher [2]. Several decades ago, AF diagnosis was possible only based on ECG recording, whereas recent diagnostic tools facilitate more frequent detection of paroxysmal AF diagnosis. It is important to highlight recent advances in the prevalence of most relevant risk factors, which also have changed over time (e.g., diabetes and obesity) contributing to increasing AF rates [2]. In addition to increasing anticoagulation in individuals with AF, trends in risk factors (improved hypertension treatment, smoking cessation) may contribute to the considerable decrease in stroke and mortality associated with AF by 75% and 25%, respectively [2]. Also, despite constant hospital length of stay,

the mortality and hospital readmissions declined by 4% and 1% per year [17]. However, the median Medicare inpatient costs increased from $2900 to $4700 per hospitalization [18].

Based on the FHS data, the lifetime risk of AF in individuals older than 55 years is 37% depending on their clinical and genetic risk [19]. Additionally, recent data indicated that AF lifetime risk depended on risk factor burden with lower AF lifetime risk experienced by individuals in the optimal compared to borderline and high-risk profile (23%, 33%, and 38%, respectively) [20].

1.3 Outcomes and Public Health Burden

Asymptomatic AF remains an important clinical challenge, which is becoming more complicated by often silent AF initiation and progression [21]. Asymptomatic AF often remains undiagnosed until development of serious complications (e.g., stroke and heart failure). Turakhia et al. estimated a 13% US prevalence of undiagnosed AF with 56% of individuals at moderate to high risk for thromboembolic complications estimated using the $CHADS_2$ score [22]. Although the benefits and potential harms of screening for AF remain uncertain, some experts contend that the majority of undiagnosed AF could be identified using mass screening [23]. That means that the global AF burden is very likely understated. Within the last decade, novel innovations and technologies such as smartphones and wearables became very popular for longitudinal rhythm monitoring and are expected to increase the prevalence of diagnosed AF [24].

AF is not a harmless electrocardiographic disturbance, as it is associated with relevant comorbidities, higher mortality rates, and consequently expanding healthcare costs. Adverse outcomes associated with AF compared to patients in normal sinus rhythm include fivefold higher risk of heart failure (*HF*) [25], twofold risk of myocardial infarction (*MI*) [26], 1.9-fold risk of sudden cardiac death [25], 2.4- to fivefold risk of stroke [25, 27], ~fivefold risk of systemic arterial embolism [28], 2.2-fold risk of pulmonary embolism [29], 1.7-fold risk of venous thromboembolism (*VTE*) [29], up to twofold risk of dementia [30, 31], 1.6-fold risk of renal dysfunction [25], impaired quality of life [32], and 1.5- to twofold increased risk of death [25, 33]. All these sequelae and comorbidities are associated with estimated US healthcare costs of $28.4 billion (2016 USD), which are estimated to have a population standardized annualized rate of change of 3.4%. It had been recently estimated that the adjusted annual incremental cost for individuals with AF was $18,601 (2009 USD) [34]. In Denmark, the 3-year economic costs of AF were €20,403–26,544 per person and €219–295 million for Denmark as a whole [35].

In this chapter, we summarize and discuss the current knowledge on primordial, primary, and secondary AF prevention and focus on relevant factors associated with AF. In addition, we spotlight future directions toward precision AF risk assessment and prevention.

2 Primordial, Primary, and Secondary Prevention of AF

2.1 Definitions

Primordial AF prevention is defined as prevention of the emergence of risk factors associated with AF development – such as obesity, sedentary lifestyle, smoking, alcohol consumption, and psychological stress.

Primary AF prevention is concerned with preventing AF onset by addressing comorbidities predisposing to AF such as hypertension, diabetes, myocardial infarction, heart failure, stroke, sleep apnea, renal dysfunction, peripheral embolism, etc.

Secondary AF prevention aims to improve quality of life, reduce symptoms, and prevent AF recurrence and complications of already diagnosed AF. In addition, secondary prevention's goal is to ensure the appropriate treatment is delivered to the appropriate individual, at the optimal time to improve prognosis, and minimize treatment-related complications.

2.2 Typically Non-modifiable Risk Factors

2.2.1 Age

Age is the most important risk factor for AF. It is associated with increased incidence and prevalence of AF with a sharp incline after the age of 65 years. It is expected that the population over 65 years will double from 12% in 2010 to 22% in 2040 [36].

In AF, many risk factors act over decades. For example, chronic subclinical inflammation, defined as continuous low-grade activation of the systemic immune response, is a hallmark of biological aging across multiple organ systems. Its origin is multifactorial; most of the classical cardiovascular disease (*CVD*) risk factors (e.g., smoking, obesity, hypertension, diabetes) correlate with higher levels of inflammatory markers [37]. Further, inflammation is associated with increasing reactive oxygen species, endothelial dysfunction, collagen catabolism, transforming growth factor (*TGF*)-ß1 activity, and changes in the extracellular matrix [38]. Aging of the myocardium and vasculature comprises changes at cellular, structural, and functional levels. Age-related cardiac comorbidities and arterial stiffening are strong predictors of AF. Therefore, "healthy" aging should be considered a goal in primordial and primary AF prevention. Controlling known AF risk factors might slow these degenerative processes and promote fit longevity.

2.2.2 Sex

AF epidemiology in men and women diverges substantially [39], especially in individuals of European ancestry. Per 1000 person-years, AF incidence is 4–12 in men compared to 2–9 in women [2, 15]. The multiracial ARIC study demonstrated

significantly higher AF lifetime risk in white men than women (36% and 30%). Although AA had lower lifetime risk of AF than their white counterparts, AA males (21%) and females (22%) had similar risks [16]. In Asian populations, AF incidence was also higher in men [1], although the AF lifetime risk was similar in males and females (17% and 15%, respectively) [40]. Also, AF risk in Asians was much lower compared to white Americans [41]. Although higher AF incidence in men was observed globally in high-, middle-, or low-income countries [1], the data in Asian population are less consistent [42].

The CHARGE-AF Consortium demonstrated no association between sex and AF incidence after adjustment for AF-related risk factors, particularly height and weight [43]. However, the population attributable risk of the risk factors varied by sex: whereas the population attributable risk of coronary disease was higher in men, high blood pressure and valvular disease were more important in women [39, 44].

2.2.3 Race

The overall prevalence of AF in the United States is 1–2% [7]. Compared to individuals of European ancestry, the prevalence, incidence, and risk factors for AF in other ethnic/racial populations are understudied due to their underrepresentation in observational and clinical studies [45, 46]. Because risk factors associated with AF are higher in AA than in whites, it is reasonable to postulate that AF incidence would be higher in AA. However, in the Multi-Ethnic Study of Atherosclerosis analysis, the AF incidence was 46–65% lower in AA, Asians, and Hispanics >65 years compared to non-Hispanic whites [46]. In a study with 600,000 Veteran Affairs patients, the AF prevalence was 5.7%, 3.4%, 3.6%, and 3.0% in non-Hispanic whites, AA, Asians, and Hispanics, respectively [45].

The lower AF incidence in individuals not of European ancestry has had several explanations. One concern is that non-whites have under-detection compared to whites because of worse access to healthcare [47] and more frequent paroxysmal AF [48]. For instance, based on pacemaker interrogation, individuals of non-European ancestry had lower AF incidence [49, 50]. Nevertheless, a recent Multi-Ethnic Study of Atherosclerosis analysis reported that using 14 days of continuous ECG monitoring, the proportion of detected AF was similar among four ethnic groups (7.1%, 6.4%, 6.9%, and 5.2% for whites, AA, Hispanics, and Chinese, respectively; $p > 0.50$) [51].

The lower AF prevalence in white Americans compared to AA partially may be explained by up to 2 mm smaller left atria (*LA*) in AA compared to white Americans [52] and genetic differences in racial/ethnic distribution of AF risk-associated polymorphisms [53]. Notably, the Cardiovascular Health (CHS) and ARIC studies reported higher risk of AF development in AA with increasing levels of genetic markers associated with European ancestry [54].

A similar paradox was observed in the South Asian population including ethnic groups from India, Pakistan, Nepal, Sri Lanka, and Bangladesh and representing

one fifth of the world's population [1, 55]. However, specific data analyzing electrophysiological parameters in different ethnic groups and any potential variations among them remain an unmet research need.

2.3 Primordial Prevention

2.3.1 Weight

The prevalence of overweight and obesity has increased dramatically over the last few decades worldwide [56]. It had been estimated that by 2030 up to 40% of the global adult population will be obese [57]. Obesity is a common risk factor for many chronic diseases including CVD, diabetes, several types of cancer [58], and AF [59, 60]. Based on FHS data, the adjusted risk of incident AF was almost 4% for every 1-unit increase in body mass index (*BMI*) [61]. Similar findings were made in >3000 participants from the Olmsted County study [62].

Importantly, compared with stable BMI, weight increase [63–65] and weight trajectories with BMI changes over time are associated with increased AF risk [60]. A causal association between obesity and AF is supported by a Mendelian randomization study; a polygenic risk score associated with obesity was associated with AF [66]. Sustained obesity was associated with higher blood pressure [67], diabetes [68], metabolic syndrome [69], coronary artery disease [70], and obstructive sleep apnea [71], which provide a substrate for atrial remodeling and contribute to AF initiation and perpetuation. Some experimental studies demonstrated increased atrial volume and LA pressure, atrial interstitial fibrosis, inflammation, myocardial lipid accumulation, slower atrial conduction, and increased conduction heterogeneity in obese animals [72]. Other studies confirmed that BMI is one of the most powerful determinants of LA size [73] and diastolic dysfunction [74] and found enhanced neurohormonal activation [75], which modulates LA enlargement and electrical instability. Obesity also is related to low-grade inflammation [76] and greater epicardial fat pad thickness [77], which also contribute to alterations in atrial electrophysiology and risk of AF [78], in part through increased oxidative stress [79] or lipoapoptosis [80].

Finally, there are some intriguing findings describing an association between AF and high lean body mass, also known as fat-free mass [81]. Skeletal muscles are the main part of the lean body mass [82] and are also a secretory organ due to production and release of different cytokines and peptides with endocrine effects [83]. Muscles promote follistatin synthesis in the liver [82], which is a myostatin's contra-player. Myostatin is a peptide involved in metabolic homeostasis and modulation of adipose tissue function [82] as well as regulation of cardiomyocyte growth [84]. In the experimental setting, inhibition of myostatin was associated with ventricular hypertrophy, LA enlargement, LA fibrosis, and spontaneous AF [84].

2.3.2 Nutritional Factors

The data analyzing the impact of nutritional factors on AF incidence and prevalence in large cohorts are incomplete and potentially susceptible to confounding. Some beneficial effects of lifestyle and dietary modification for cardiovascular risk reduction may be explained by modulation of inflammation and oxidative stress especially in metabolic syndrome [85]. Mediterranean-type diet is associated with benefits on cardio-metabolic health [86] potentially due to anti-inflammatory and antioxidant effects [86, 87]. The randomized PREDIMED study observed that Mediterranean diet with extra-virgin olive oil was associated with almost 40% AF risk reduction compared with the control group, in a post hoc analysis [88]. However, a recent observational cohort study with >18,000 participants did not find any association between Mediterranean-type diet with intensified olive oil use and AF during 10-year follow-up [89]. Other case-control study demonstrated higher incidence of AF conversion to sinus rhythm in patients with higher adherence to a Mediterranean diet [90].

2.3.3 Physical Activity

Regular and moderate physical activity (*PA*) is a cornerstone of a healthy lifestyle, inversely associated with adjusted clinical AF incidence and progression [91, 92]. Healthy PA is 150 minutes of moderate or 75 minutes of vigorous exercise per week [93]. The next lowest PA level, involving recreational walking, cycling, or other forms of activity >4 h/week, was associated with a 20% risk reduction of AF [94]. Similarly, walking at least 20 min/day seems to be protective against AF compared to the least active individuals [95]. Moderate PA is associated with multiple beneficial effects on weight, insulin resistance, endothelial dysfunction, and reduced blood pressure [96]. Furthermore, in overweight and obese individuals, moderate PA reduces systemic inflammation adjusting for weight loss, minimizing atrial arrhythmogenesis [97].

Investigators have reported an association between moderate PA and decreased AF risk [98, 99], while vigorous aerobic PA is associated with increased AF [100]. A meta-analysis reported a J-shaped relationship between exercise intensity and incident AF, with intermediate levels being associated with lowest risk [101]. In the Tromsø Study, compared with individuals without regular exercise history, individuals with moderate PA had a 28% lower AF risk [94].

Compared with referents, extreme endurance exercise in elite athletes is associated with an almost fivefold increased AF risk [102]. This might be partly explained by awareness of body symptoms during AF episodes, possibly resulting in earlier diagnosis of AF. Cardiac adaptation to vigorous exercise is known as *athlete's heart* and is characterized by increased vagal tone, resting heart rate reduction, and increased stroke volume, with consequent left ventricular (*LV*) dilatation and hypertrophy [103, 104]. Animal experimental studies described exercise raising atrial pressure with subsequent LA dilation, atrial refractory period reduction, and higher

exposure to AF [105]. In elite athletes, regular stretch of the atrial myocardium over long periods leads to LA enlargement, stretch-induced microtrauma, and pro-inflammatory and pro-fibrotic changes predisposing to AF [104]. Furthermore, a systemic inflammatory response is a common contributor to higher AF prevalence in athletes [106, 107], especially after intensive, long-term exercise [108].

2.3.4 Smoking

In the United States, up to 38 million people are current smokers [109]. Despite a consistent decline of cigarette use in the United States among adults and youth, considerably higher tobacco use is observed in underrepresented groups (e.g., American Indian/Alaska Natives, LGBT populations) and among individuals with lower socioeconomic status [17]. Furthermore, sharp growth in e-cigarette use was found over the last decade among adolescents from 1.5% to 20.8% between 2011 and 2018 [17].

Compared to nonsmokers, the risk for AF in current smokers was significantly higher in the CHARGE-AF Consortium, although the association was not as strong as with other CVD [43, 110]. A meta-analysis of smoking studies reported that the relative risk of AF associated with current smoking was 1.32 and former smoking was 1.09 [111]. The relation between secondhand smoke and AF is much less well studied, but a small case-control study reported that secondhand smoke was associated with an adjusted increased risk of AF.

A central component in tobacco products is nicotine, a substance that activates pro-fibrotic mechanisms and blocks potassium channels. Thus, smoking may be directly involved in the development of an electro-anatomical substrate for AF [112, 113]. Indirectly, smoking may increase systemic catecholamine release and promote coronary vasospasm leading to myocardial ischemia and, secondarily, to AF [114]. Furthermore, smoking increases inflammation, oxidative stress, endothelial dysfunction, and other pro-thrombotic conditions facilitating atherosclerotic changes and contributing to atrial ischemic processes [115].

It has been suggested that vaping also leads to pro-inflammatory changes and endothelial dysfunction. Although data regarding e-cigarettes' adverse cardiovascular effects are sparse, a recent retrospective study reported that e-cigarette use was associated with an almost twofold risk for myocardial infarction [116]. Whether vaping is associated with increased risk for AF needs to be examined.

2.3.5 Alcohol

Approximately 50% of the American population regularly consumes alcohol [117]. The American Heart Association recommends limiting alcoholic beverages to a daily maximum of two drinks for men and one drink for women, ideally consumed with meals. A recent meta-analysis reported an 8% increase in AF risk with each additional daily alcoholic drink suggesting a linear dose-response relation [118].

The results of the ARIC cohort indicate duration- and dose-dependent association with higher risk of developing AF [119]. Importantly, lower AF incidence was associated with longer duration of alcohol abstinence among former heavy drinkers. Every decade of alcohol abstinence was associated with an almost 20% decreased risk of incident AF (about 2% per year) [120]. Furthermore, a recent randomized controlled trial reported that alcohol abstinence significantly reduced AF burden in regular alcohol drinkers [121].

In the United States, over 17% of adult drinkers (~37 million) are binge drinkers with ≥4 (women) or ≥5 (men) drinks consumed per drinking occasion [122]. Long-term alcohol consumption initiates supraventricular and ventricular arrhythmias particularly after periods of heavy drinking. Chronic ethanol exposure leads to electrical remodeling with HV interval and QRS duration prolongation and predisposition to arrhythmia in experimental models [123, 124]. In the FHS, alcohol consumption was associated with LA size enlargement and incident AF, elucidating a possible mechanism for the relationship [125]. Furthermore, high alcohol consumption has direct toxic, inflammatory, and oxidative effects on the LA myocardium, promotes LV remodeling, and increases LV pressures facilitating diastolic dysfunction [126]. Therefore, restriction or abstinence should be considered as a potentially effective strategy for preventing AF.

2.3.6 Psychological and Psychosocial Factors

Although the prevalence of chronic stress is ~8% in the United States, in some populations (e.g., military deployment, sexual assault, natural disaster, gun violence, etc.), it reaches 40% [127]. Recently, it had been demonstrated that posttraumatic stress disorder was associated with a 13% higher risk of incident AF in a nationwide study with >1 million young and middle-aged veterans [128]. Also, both animal and human experimental studies reported that social and environmental stresses (e.g., work stress or long-term experience of destructive emotion) are associated with increased AF risk [129, 130]. In addition, a Danish study with >85,000 participants found an almost 40% higher risk of incident AF working 55 h or more a week compared to standard <40 h week [131]. Recent ARIC analysis reported that vital exhaustion – but not anger – was a risk factor associated with an incident AF [132].

The association of psychologic stress with AF incidence is complex. Psychological stress is associated with unhealthy behavior with higher prevalence of smoking, alcohol consumption, and obesity. If exposure becomes chronic, stress impairs autonomic tone and affects the hypothalamic-pituitary-adrenal axis [133]. Also, chronic changes in autonomic tone impair atrial electrophysiological pattern and facilitate AF initiation [134]. Furthermore, psychosocial stress leads to dysregulations in hormonal imbalance to catecholamine overload altering LA electrophysiology [133] and facilitating atrial fibrosis formation [135, 136]. Finally, psychological stress leads to sleep disorders including disturbances in the sleep-wake cycle, disruption of sleep patterns, and deteriorating malfunction of the hypothalamic-pituitary-adrenal axis [137, 138]. Sleep deprivation impairs the physiological balance in

circadian cortisol concentrations resulting in increased sympathetic [139] and decreased vagal activity [133]. Of note, there is evidence that relaxation techniques such as prayer, yoga, and meditation transiently modify indices of autonomic activation [140] and improved quality of life in AF patients [141].

2.3.7 Social and Socioeconomic Factors

Humans are highly social beings, and their social ties and relations may play a critical role in the determination of health status [142, 143]. Social isolation is an important risk factor for obesity, inactive lifestyle, and alcohol consumption [144]. Social integration, which describes the presence of close personal relationships to family members and friends as well as social binding to community, was associated with prediction of cardiovascular disease incidence and mortality [145]. However, a recent analysis based on 11,445 participants from the ARIC study did not find significant associations between social support or social network and incident AF [132].

Education and total family income are established socioeconomic factors and are inversely associated with CVD [146]. The ARIC study confirmed an inverse association between incident AF and socioeconomic status [147]. In adjusted models, the authors found that lower education and higher total family income were associated with elevated AF risk. Although this association was stronger in women, it diminished or even disappeared in models adjusting for relevant CVD risk factors, suggesting a mediating character of cardiovascular risk factors. Similar findings were observed in a Swedish study analyzing the association between neighborhood and AF [148].

2.4 Primary Prevention

AF has complex bidirectional associations with HF, MI, stroke, chronic kidney disease (*CKD*), and VTE. There also is evidence suggesting associations between cancer and the gut microbiome in AF initiation. Coexistence of AF with other disorders is associated with substantially increased morbidity and mortality, emphasizing the urgent need to control the imminent epidemic of AF (Fig. 1).

2.5 Elevated Blood Pressure and Hypertension

Elevated blood pressure (BP) is a major risk factor for cardiovascular and cerebrovascular complications [149]. The prevalence of elevated BP in adults >20 years is over 116 million, with 26% among individuals <44 years, 59% among those 45–64 years of age, and 78% among ≥65 years [17]. Furthermore, the prevalence of

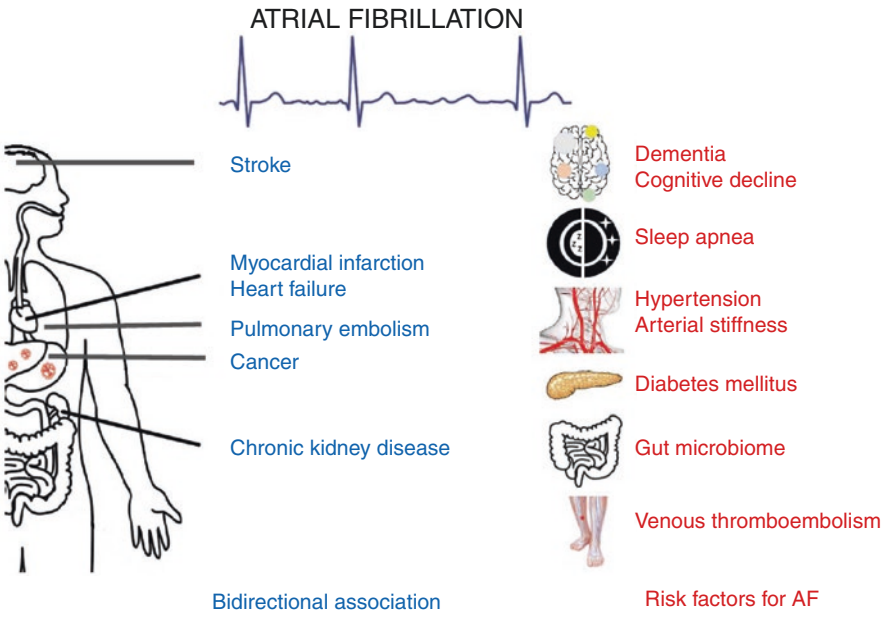

Fig. 1 Clinical risk factors associated with AF development. Atrial fibrillation (AF) is associated with other comorbidities through complex pathomechanisms and leads to increased mortality. Patients usually do not die from the arrhythmia but rather of coexisting comorbidities and related complications. A refined understanding of these interactions would improve risk assessment and management of AF and its comorbidities in the future

elevated BP in AA – 58% among males and 53% among females – is one of the highest worldwide. The prevalence of elevated BP is also higher in AA and by 55 years reaches 76% for both genders, whereas the prevalence in individuals of European ancestry is 55% and 40% in males and females, respectively [150]. The Cardiovascular Lifetime Risk Pooling Project reported that the lifetime risk for hypertension was highest for both AA males and females (86%) and lowest in females of European ancestry (69%) [151]. Furthermore, recent retrospective analysis of the healthcare data in South Korea with approximately 9.8 million participants reported a continuous increase in AF incidence with advancing hypertension stage [152]. Thus, compared to non-hypertensive individuals, AF incidence for individuals with prehypertension, hypertension without antihypertensive treatment, and hypertension with antihypertensive treatment <5 years and ≥5 years was 1.15, 1.39, 1.85, and 2.34 for each stage, respectively.

Hypertension carries the largest population attributable risk for AF development worldwide. The CHS demonstrated increased AF risk by 11% with each 10 mmHg systolic blood pressure elevation [153]. In the ARIC study, the hypothetical elimination of risk factors including borderline values would have avoided more than half of diagnosed AF cases [154]. Hypertension played the central role here – while it explained up to 25% of AF cases if borderline hypertension was included, only 3% of AF cases were referable to diabetes [154]. In FHS, 20 mmHg higher mean pulse pressure was associated with 1.3-fold adjusted hazard of incident AF [155].

Chronic elevated blood pressure is associated with LA and LV structural remodeling due to cardiac pro-fibrotic changes [156]. In an experimental study, the renin-angiotensin system (*RAS*) axis and upregulated TGF-ß1 expression and activated production of aldosterone and nicotinamide adenine dinucleotide phosphate oxidase remain the main contributors for these changes [157]. Although some post hoc analyses suggested that inhibition of RAS could be considered as an upstream therapy for AF prevention, the observational or randomized data were inconclusive [158, 159]. However, analyzing association between antihypertensive treatment and AF, a meta-analysis of ~215,000 participants reported 10% risk reduction of AF [160]. In a subgroup analysis, almost 20% of AF risk reduction was achieved in patients with HF, who had larger benefit of antihypertensive treatment compared to patients with coronary heart disease or with no history of previous heart disease.

2.5.1 Diabetes Mellitus

Insulin resistance and glucose intolerance are the main pathophysiological characteristics in diabetes mellitus (*DM*) and modulators in AF substrate development [161]. DM is associated with a 1.4- to 1.6-fold increased risk of AF [44, 162, 163]. Experimental studies reported that oxidative stress and inflammation are leading modulators of mitochondrial dysfunction and related DNA damage, creating a structural substrate for AF initiation in metabolically stressed hearts [164, 165]. Also, human and animal studies demonstrated that TGF-β1, RhoA-ROCK (*Rho*-associated protein kinase) pathway, and AGE-RAGE axis (advanced glycation end products and their receptor for advanced glycation end products, RAGE) are activated in DM and contribute to AF initiation [166]. Nevertheless, the association of DM with AF is not as strong as with other CVD. Very likely, this could be explained by significant overlap with prevalence of other AF risk factors, through which DM may lead to atrial dysfunction and pathophysiological changes necessary for the genesis of AF.

Glycemic disbalance reflected by elevated HbA1c levels is another risk factor associated with AF [167]. Despite some controversies, a meta-analysis of eight prospective and six retrospective studies with ~160.000 participants reported a 10% increase of AF risk in individuals with elevated serum HbA1c levels, suggesting that HbA1c might be considered as a prognostic biomarker in AF [168]. Low-grade systemic inflammation and oxidative stress are the most relevant underlying pathomechanisms explaining this relationship [169].

2.5.2 Sleep Apnea

According to the American Academy of Sleep Medicine and the Sleep Research Society, at least 7 hours of sleep per night is important to support optimal health [170]. Meta-analyses reported significant associations between short sleep duration <7 hours/night with CVD, coronary heart disease [171], and hypertension [172], which are known risk factors for AF. Another study with over 30,000 individuals

reported that each 1-h reduction in sleep duration was associated with both prevalent and incident AF [173].

Obstructive sleep apnea (*OSA*) is most common type of sleep apnea and occurs in 21–74% of patients with AF [174, 175]. Some experimental studies demonstrated significant atrial conduction abnormalities and relevant atrial fibrosis [176]. There is evidence that large negative intrathoracic pressure fluctuations cause acute atrial distension and dilatation [177] as well as significant electrophysiological changes with atrial refractoriness as a substrate for AF vulnerability [178]. On a molecular basis, permanent de- and reoxygenation cycles are comparable with ischemic myocardial damage leading to vascular inflammation and increased reactive oxygen species production [179].

The prevalence of both OSA and AF increases with advancing age and obesity, which are common underlying risk factors for both diseases. In patients with OSA and AF, nocturnal AF paroxysms are often related temporally to respiratory obstructive events [180, 181], suggesting acute transient arrhythmogenic changes during apnea and their contribution to AF initiation [182].

Several clinical studies considered OSA as a modifiable risk factor mostly in secondary AF prevention and analyzed the impact of OSA treatment as a target to improve rhythm outcomes after catheter ablation [183]. The positive effects of continuous positive airway pressure (*CPAP*) therapy are largely explained by anti-inflammatory and anti-fibrotic CPAP effects [184]. Also, decreasing the frequency of hypoxic episodes, CPAP therapy at least partially diminishes adverse autonomic [185] and acute structural effects caused by OSA [186].

2.5.3 Chronic Kidney Disease

Albuminuria, mild renal impairment, and declining renal function are associated with higher AF incidence [187, 188]. Up to one third of patients with glomerular filtration rate of 30–59 ml/min had higher risk for new-onset AF compared to individuals with normal renal function, while for those with glomerular filtration rate <30 ml/min, the risk was 57% higher [188].

Despite similar risk factors for AF and CKD, their association remains significant also in individuals without hypertension or diabetes [188]. The main pathophysiologic contributor is the RAS activation. In CKD patients, RAS upregulation promotes fibrogenesis, oxidative stress, and an impairment of kidney function. Similar mechanisms have been described in AF – with atrial fibrosis, increased atrial pressure, and modulation of ion channels due to RAS activation [189]. Furthermore, systemic inflammatory response contributes to both diseases' pathophysiology [190]. Nevertheless, AF may directly contribute to CKD development by impaired hemodynamics with reduced cardiac output and/or peripheral embolism.

As in many comorbidities with bidirectional character, the coexistence of AF and CKD has a poorer prognosis. Thus, in CKD patients, AF is associated with increased risk for myocardial infarction (MI), HF, and all-cause mortality especially directly after AF diagnosis [191]. As demonstrated in a single-center study, compared to

29% in patients without AF, patients with end-stage CKD and AF had 81% mortality rate during 4-year follow-up [192].

2.5.4 Bidirectional Nature Between AF and Comorbidities

Myocardial Infarction

There is evidence of bidirectional relations between AF and MI. While the risk of MI is ~twofold increased in AF patients [193], patients in the first year after MI have ~8% risk of developing AF [194]. Furthermore, almost one third of patients with implantable cardiac devices developed AF within 12 months post-MI [195].

Both AF and MI share risk factors. In addition, there are several mechanisms by which AF predisposes to MI. Tachycardia in AF directly contributes to type 2 MI due to inadequate coronary artery perfusion and increased myocardial oxygen demand [196]. Furthermore, AF may lead to coronary thromboembolism resulting in MI [197]. Finally, AF is associated with systemic inflammation and endothelial dysfunction promoting MI development [198].

On the other hand, there are specific mechanisms contributing to AF development in patients with MI. In acute MI, LV dysfunction, LV hypertrophy, and elevated heart rate predispose to AF initiation [199]. Also, AF may be caused by atrial ischemia in the early post-MI stage [200]. Acute HF after MI contributes further to atrial stretching and increased atrial excitability [201]. Furthermore, oxidative stress during ischemic disturbances caused by MI leads to systemic inflammation and cytokine release, which facilitates AF initiation [202]. Finally, there is an association between MI-related pericarditis and AF [203].

In a meta-analysis of patients with MI compared to individuals with a sinus rhythm, both new-onset and prior AF were associated with at least 40% higher risk of mortality [204]. Possible mechanisms explaining mortality are worsening of ischemia by hemodynamic impairment and increased vulnerability for fatal ventricular arrhythmias [205].

2.5.5 Heart Failure

The combination of HF and AF can be fatal [206, 207]. Incidence of both diseases increases steeply after the age of 60 years [36, 208]. In the FHS, 37% of participants with newly diagnosed AF had previously diagnosed HF. Conversely, 57% of participants with HF had previously diagnosed AF [207]. In FHS, among individuals with both conditions, 21% had HF and AF diagnosed on the same day [206]. Furthermore, the study found that HF becomes manifest in ~50% of AF patients.

Compared to the general population, the risk of AF is four to six times higher in HF patients [44]. The prevalence of AF in HF patients correlates with HF stage and increases from <10% in NYHA class I up to 50% in patients with HF symptoms accordingly to the NYHA class IV [208, 209]. There is evidence that not only

patients with reduced ejection fraction but also the subgroup of HF with preserved ejection fraction (*HFpEF*) is at higher risk of AF [207, 210].

The mechanisms underlying the association between AF and HF are complex and multifactorial. HF is accompanied by structural and electrical remodeling as shown by electrophysiological mapping in HF patients and in some experimental studies [211, 212]. Another explanation is the renin-angiotensin-aldosterone (RAS) axis activation in HF patients that facilitates AF development [213]. Other mechanisms include irregular heart rate, shortened diastole, and loss of atrial contraction, resulting in a modest cardiac output decline, but which are largely reversible after sinus rhythm restoration [214, 215]. In the long term, AF leads to structural and hemodynamic changes largely caused by inadequately controlled tachycardia.

2.5.6 Stroke

Stroke is a major thromboembolic complication associated with AF. The underlying pathophysiological mechanisms of thrombus formation and stroke in AF include atrial fibrosis [216, 217], LA enlargement [218], and alterations in blood flow. Patients with AF have four- to fivefold higher risk for stroke compared to individuals without AF, and at least 15% of all strokes are related to AF [158]. Persistent AF appears to carry higher risk of stroke compared to paroxysmal AF [219, 220]. Importantly, subclinical AF is associated with significantly increased risk of ischemic stroke or systemic embolism [221].

Interestingly, incidence of new-onset AF is increased after stroke, indicating that there may be an association with stroke beyond its role as origin of thrombus formation. In fact, episodes of AF in the first few days after stroke are common and disappear in the course of time [222]. The assumption that incident AF can also be a result of stroke is further supported by the fact that new-onset AF is also increased after hemorrhagic stroke [223], which cannot be a result of previous AF. Pathophysiological mechanism may include dysregulation of autonomous nervous system and inflammation [224].

There have been multiple risk prediction scores for stroke after AF diagnosis. Currently, the CHA_2DS_2-VASc score is most widely used [158, 159, 225], and the more detailed ATRIA score represents an alternative [226, 227]. Nevertheless, there are risk factors that are not included in the CHA_2DS_2-VASc score but lead to higher frequency of stroke in patients with AF. These include, in particular, OSA [228] and CKD [229]. Notably, none of the currently available scores has good discriminatory ability. Whether polygenic risk scores or blood biomarkers including high-sensitivity troponin T, N-terminal B-type natriuretic peptide, or growth differentiation factor-15 may improve the performance of stroke risk prediction is not established [19, 230].

AF burden is another factor associated with increased risk of stroke and higher mortality [231]. There are several definitions of AF burden – from the AF episode duration or number during predefined monitoring period to a proportion of an individual time in AF expressed as a percentage. Several studies reported an association between increasing AF burden and the risk of stroke [221, 232, 233]. While in ASSERT study subclinical episodes of atrial tachycardia episodes longer than 6 minutes were associated with almost twofold risk of ischemic stroke [221],

Turakhia et al. demonstrated that the risk of the short-term stroke increased four- to fivefold with AF burden of ≥5.5 hours [233]. Notably, the risk of stroke was highest at 5–10 days after AF initiation.

2.5.7 Venous Thromboembolism

Although VTE and AF are distinct diseases, both are closely related, often co-occur, and share similar pathophysiological patterns. The AF incidence in patients with VTE as well as VTE incidence after the diagnosis of AF is ≥70% higher compared to the general population. Especially within first 6–12 months after diagnosis of AF and VTE, individuals are susceptible to the other diseases [234].

There are multiple pathophysiological interactions between AF and VTE. In patients after pulmonary embolism, AF initiation may be caused by changed hemodynamics leading to increased right cardiac pressure and consequent dilation [235]. Also, neurohormonal mechanisms and platelet activation have been suggested as contributing factors in the pathogenesis of both diseases [236]. Finally, hypercoagulability has been linked to initiation of LA fibrosis in an experimental model [237]. Importantly, the authors were able to demonstrate attenuation of pro-fibrotic changes after use of anticoagulants [237].

Notably, pulmonary embolism occurs in AF patients more frequently than VTE [238]. The most important denominators are shared risk factors and comorbidities. Age is the main contributor for both AF and VTE development [239]. Also HF, obesity, sepsis, and autoimmune diseases are other risk factors contributing to systemic inflammation with increased platelet activation and endothelial dysfunction, resulting in a pro-thrombotic state [44, 240–242].

As with other bidirectional comorbidities, the co-occurrence of AF and pulmonary embolism or VTE has vital prognostic implications and is associated with higher mortality [243]. Although this seems to be common for primary (AF→VTE) and subsequent AF (VTE→AF), it is unclear whether AF is the cause of the increased mortality or merely a bystander indicating a subset of patients with more severe embolism [244].

2.6 Secondary Prevention

The secondary prevention of recurrent AF remains challenging despite advances in pharmacological and technological strategies, and none of the presently used therapies are consistently effective long term. Available therapies are targeting mostly one pathophysiological mechanism, which at least partly explains the lack of success of available therapies for AF.

During the last decade, several studies analyzed the impact of lifestyle modification on AF occurrence after catheter ablation (e.g., weight reduction, alcohol consumption, hypertension, and OSA treatment, Table 1) [121, 245–248]. Patel et al. found that after catheter ablation, sinus rhythm maintenance in patients with OSA

Table 1 Selected observational studies and randomized trials in primary and secondary AF prevention

Author	Year	Study cohort	Outcome	Follow-up	Main findings	Comments
Primary prevention						
Observational data						
Jamaly [264]	2016	SOS (Swedish obese subjects) with 4021 obese individuals and no history of AF Surgery group – 2000 patients underwent bariatric surgery Control group – 2021 matched obese control subjects received usual care	First-time atrial fibrillation	19 years	Individuals having bariatric surgery had a 29% lower risk (HR, 0.79 [95% CI, 0.60–0.83]; $P < 0.001$) of developing AF	Better effect in young individuals
Secondary prevention						
Observational data						
Hess [265]	2013	National outpatient registry of AF patients (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation, ORBIT-AF), $n = 10{,}096$ enrolled patients	Measurement of guideline-recommended therapies for cardiovascular comorbid conditions and risk factors	Cross-sectional analysis	There were 94% patients with indications for guideline-based primary or secondary prevention in addition to oral anticoagulant drugs, while only 47% received all guideline-indicated therapies Predictors of *not receiving* all guideline-indicated therapies included frailty, comorbid illness, geographic region, and antiarrhythmic drug therapy Factors most strongly associated with the OAC discontinuation rate included hospitalization because of bleeding (OR, 10.9, 95% CI 7.9–15.0), prior catheter ablation (OR, 1.8, 95%CI 1.4–2.4), noncardiovascular/nonbleeding hospitalization (OR, 1.8, 95% CI 1.4–2.2), cardiovascular hospitalization (OR, 1.6, 95% CI 1.3–2.0), and permanent AF (OR 0.25, 95% CI, 0.17–0.36)	The study population from this voluntary registry may not mirror AF patients in the United States

Pathak [246]	2014	Patients undergoing AF ablation (total $n = 281$), $n = 149$ patients with BMI ≥ 27 kg/m^2 and ≥1 cardiovascular risk factor: RFM group ($n = 62$) and control group ($n = 88$) RFM = blood pressure, weight, lipid, glycemic, OSA, smoking, and alcohol management	Arrhythmia-free survival	41.6 ± 12.5 in RFM and 42.1 ± 14.2 months in the control group	In individuals referred for catheter ablation, those who agreed to aggressive risk factor modification had lower symptom burden in follow-up and higher adjusted AF-free survival (HR, 4.8 [95% CI, 2.0–11.4]; $P < 0.001$	Single-center, observational study, RCT are needed
Pathak [245]	2015	Patients undergoing AF ablation (total $n = 1415$), $n = 355$ with BMI ≥ 27 kg/m^2 and weight reduction management	Arrhythmia-free survival	5 years	In adjusted analyses, overweight and obese individuals with paroxysmal or persistent AF with ≥10% weight reduction were six-fold more likely to be AF free (86.2% AF free; HR, 5.9, 95%CI, 3.4–10.3) than those with <3% weight loss (39.6% AF free) Individuals losing at least 10% weight reported fewer symptoms	Single-center, observational study. RCT are needed
Pathak [247]	2015	Patients undergoing AF ablation (total $n = 1415$), $n = 308$ with BMI ≥ 27 kg/m^2 included into tailored exercise program	Arrhythmia-free survival	49 ± 19 months	Among consecutive overweight and obese patients with AF who agreed to participate in an exercise program, those who achieved less improvement in cardiorespiratory fitness (<2 METs gain) had lower AF-free survival (40%; HR, 3.9, 95%CI, 2.1–7.3) than those with greater improvement in fitness (≥2 METs gain, 89% AF free)	Single-center, observational study. RCT are needed

(continued)

Table 1 (continued)

Author	Year	Study cohort	Outcome	Follow-up	Main findings	Comments
Holmqvist [266]	2015	National outpatient registry of AF patients (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation, ORBIT-AF) with n = 10,132 patients. There were n = 1841 with OSA	Hospitalizations, mortality, major adverse cardiovascular outcome, and AF progression	2 years	In adjusted analyses, patients with OSA had higher risk of hospitalization (HR 1.12, 95% CI 1.03–1.22) Treatment of OSA has been noted to decrease risk of progression to permanent AF (HR, 0.66; 95% CI, 0.46–0.94)	Diagnosis of OSA was made based on physician report and medical records. RCT are needed
Qureshi [267]	2015	Meta-analysis of eight studies with OSA patients undergoing AF catheter ablation (one RCT and seven cohort studies) with n = 1247 patients (n = 698 CPAP and n = 549 non-CPAP users)	AF recurrences		CPAP was reported to be associated with a 44% reduced risk of recurrent AF after ablation (pooled risk ratio 0.58; 95% CI 0.47–0.70) CPAP benefits were stronger for younger, obese, and male patients ($p < 0.05$)	Relatively small studies, only one RCT. OSA was not examined by severity
Pathak [268]	2017	Patients undergoing AF ablation (total n = 1415), n = 355 with BMI $\geq$ 27 kg/m^2 included into risk factor management program (n = 208 RFM group, n = 147 controls)	Cost-effectiveness and AF burden	4 years (47 ± 18 months for RFM and 49 ± 18 months for controls)	Overweight and obese individuals with symptomatic AF, who participate in weight loss and aggressive risk factor management interventions, had fewer hospitalizations, cardioversions, and ablation procedures than their counterparts, who declined enrollment. The risk factor management group was associated with a predicted 10-year cost savings of $12,094 per patient	

Silberberg [269]	2017	Two national Canadian AF primary care physician chart audits (FREEDOM AF and CONNECT AF): n = 11,264 patients	Use of cardiovascular evidence-based therapies in Canadian AF outpatients	Cross-sectional	There were 84.3% individuals eligible for ≥1 cardiovascular evidence-based therapy. The proportions receiving evidence-based therapy varied by diagnosis, at 40.8% of those with CAD, 48.9% of those with DM, 40.2% of those with HF, and 96.7% of those with hypertension	
Secondary prevention						
Randomized data						
Healey [251]	2005	Meta-analysis of 11 studies with n = 56,308 patients (four trials in HF, three in hypertension, two in patients following cardioversion for AF, and two in post-MI patients)	Effect of ACEIs and ARBs on AF prevention		BP lowering might be useful in prevention of AF in trials of hypertension, after MI, in HF, and after cardioversion	
Emdin [160]	2015	Meta-analysis of 27 trials with n = 214,763 randomized participants and n = 9929 AF events	Effect of antihypertensive agents on AF risk		Antihypertensive therapy was modestly associated with AF risk reduction. Larger benefits were observed in patients with HF	The studies were primarily secondary or post hoc analyses, the intervention duration was modest, and the results were heterogeneous

(continued)

Table 1 (continued)

Author	Year	Study cohort	Outcome	Follow-up	Main findings	Comments
Rahimi [252]	2011	Meta-analysis of 13 short-term (n = 4414 randomized patients, n = 659 events), 22 long-term (statins vs controls: n = 105,791 randomized patients, n = 2535 events), and 7 long-term trials (intensive statin treatment vs standard dose, n = 28,964 randomized patients and n = 1419 events)	Effect of statins on AF risk reduction		The use of statins might prevent AF in short-term trials. However, larger longer-term studies do not provide support for the concept that statins are effective in AF prevention	Significant heterogeneity ($P < 0.001$) between short-term trials
Swedberg [270]	2012	EMPHASIS-HF trial (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) with n = 911 in eplerenone and n = 883 in the placebo group	Incidence of new AF or atrial flutter	21 months	Eplerenone was nominally observed to reduce the incidence of new-onset AF by 42%	The number of AF events was modest
Abed [248]	2013	Overweight and obese ambulatory patients (n = 150) with symptomatic AF (intervention group and controls, 75 patients in each)	Symptom burden and symptom severity	15 months	Lower symptom burden in individuals randomized to a weight loss intervention	Single-center, partially blinded, randomized controlled study

Fatemi [271]	2014	Patients from the ACCORD study with diabetes (n = 10,082); randomization to an intensive therapeutic strategy (HbA1c < 6.0%, n = 5040) or a standard strategy (HbA1c 7.0%–7.9%, n = 5042)	AF incidence	Median 4.68 years	Intensive glycemic control was not associated with incident AF prevention, but patients with diabetes and incident AF had higher risk for cardiovascular morbidity and mortality with non-AF	Unknown anticoagulation treatment, association with thromboembolic complications or bleeding not possible
Martínez-González [88]	2014	PREDIMED randomized primary prevention study (n = 6705 participants without AF)	AF incidence	Median 4.7 years (IQR 2.8–5.8)	Significant reduction in incident AF with the Mediterranean diet including extra-virgin olive oil (HR 0.62, 95% CI 0.45–0.85)	Post hoc analysis
Alonso [272]	2015	Look AHEAD randomized trial of individuals with type 2 diabetes mellitus (n = 5067 overweight or obese individuals)	AF incidence	Mean 9.0 years	An intensive lifestyle intervention associated with modest weight loss did not significantly affect the rate of incident AF (6.1 versus 6.7 cases per 1000 person-years of follow-up; multivariable HR 0.99, 95% CI 0.77–1.28)	AF was not prespecified as a primary or secondary outcome

was worse than in non-OSA group [249]. Furthermore, rhythm outcomes after catheter ablation were significantly better in patients with OSA with CPAP treatment use compared to CPAP nonusers [249, 250]. Other studies investigated the role of angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, aldosterone antagonists, statins, and polyunsaturated fatty acids showing potential benefits on AF progression [251, 252]. However, there are still more controversies and speculations of beneficial "antiarrhythmic effects" of these drugs, and the clinical implication of these agents is controversial.

A summary of most relevant observational and randomized trials in primary and secondary AF prevention is presented in Table 1.

3 Conclusions

Despite the global burden of AF and other forms of CVD, cardiovascular pharmaceutical development has stagnated over the last two decades for many reasons, including high failure rates [253], regulatory burden, exorbitant costs of CVD outcome trials, and increasing payer forces [254, 255]. While short- and intermediate-term risk factors and risk prediction for AF are well investigated [43, 44, 256–258], the predictors of the lifetime risk of AF remain uncertain. The genetic variants associated with AF in individuals of non-European ancestry also are largely unknown. The evidence base to guide the prevention of AF is incompletely understood, leading the NHLBI [259], AHA [260], Heart Rhythm Society [261], and European Societies [262] to issue calls to action. For secondary prevention, a rigorous evidence base exists for stroke/systemic embolism and AF recurrence and stroke-related death. There is virtually no robust evidence on how to prevent HF [263], MI, CKD, dementia, and impaired quality of life in individuals with AF. Similar to the disease itself, AF primary and secondary prevention is complex and must be multifactorial. Precision medicine approaches are needed to identify those at higher risk for AF and its sequelae as well as to implement the most resource-effective strategies to determine which subgroups of patients to screen and which patients to target for preventive and therapeutic management.

In conclusion, the exploding incidence, prevalence, and high lifetime risk render AF as a relevant disease in the population with high morbidity, mortality, and significant healthcare costs. The epidemic of AF motivates research in modifiable AF risk factors and improved precision in AF prevention and management.

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Prevention of Ischemic Stroke

Wayneho Kam and Nada El Husseini

Abbreviations

ACC	American College of Cardiology
ACCORD	Action to Control Cardiovascular Risk in Diabetes trial
ACCORD BP	Action to Control Cardiovascular Risk in Diabetes blood pressure trial
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation trial
AF	Atrial fibrillation
AHA	American Heart Association
ARRIVE	Aspirin to Reduce Risk of Initial Vascular Events trial
ASA	American Stroke Association
ASCEND	A Study of Cardiovascular Events in Diabetes trial
ASCVD	Atherosclerotic cardiovascular disease
ASPREE	Aspirin in Reducing Events in the Elderly trial
BMI	Body mass index
CAPRIE	Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events trial
CHANCE	Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events trial
CI	Confidence interval
CVD	Cardiovascular disease
DASH	Dietary approaches to stop hypertension
FDA	Food and Drug Administration
FOURIER	Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk trial

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GLP-1RA	Glucagon-like peptide-1 receptor agonist
HbA1c	Glycated hemoglobin
HDL-C	High-density lipoprotein cholesterol
HOPE-3	Heart Outcomes Prevention Evaluation-3 trial
HPS	Heart Protection Study
HR	Hazard ratio
LAA	Left atrial appendage
LDL-C	Low-density lipoprotein cholesterol
MET	Metabolic equivalent
NOAC	Non-vitamin K oral anticoagulant
ODYSSEY-OUTCOMES	Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab trial
PCSK9	Proprotein convertase subtilisin/kexin type 9
POINT	Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke trial
PREDIMED	Prevención con Dieta Mediterránea trial
PREVAIL	Evaluation of the WATCHMAN LAA Closure Device in Patients with Atrial Fibrillation Versus Long-Term Warfarin Therapy trial
PROTECT-AF	WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation trial
PY	Patient-years
REDUCE-IT	Reduction of Cardiovascular Events with Icosapent Ethyl – Intervention Trial
RR	Relative risk
SAMMPRIS	Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis trial
SBP	Systolic blood pressure
SGLT2	Sodium-glucose cotransporter-2
SPRINT	Systolic Blood Pressure Intervention Trial
TIA	Transient ischemic attack
TNT	Treating to New Targets study
WHO	World Health Organization

Summary

- Ischemic stroke is a leading cause of death and disability worldwide, and effective prevention remains the best approach in mitigating the burden of this disease.
- Ischemic stroke is considered to be a clinical atherosclerotic cardiovascular disease (ASCVD) equivalent, sharing much of the same risk factors as acute coronary syndromes, myocardial infarction, stable or unstable angina, and peripheral arterial disease of atherosclerotic origin.

- Adequate prevention of ischemic stroke entails modification of vascular risk factors (hypertension, hyperlipidemia, diabetes), promotion of healthy lifestyle behaviors (exercise, healthy diet, smoking cessation, limitation of alcohol intake), and adherence to antithrombotic therapy in select patients.
- Among individuals with a prior ischemic stroke, prevention of a subsequent event may require initiation or escalation of antithrombotic therapy and continued aggressive control of vascular risk factors. Investigations into the less common causes of stroke should be pursued if clinically indicated.
- This chapter provides the latest evidence-based guidelines on the prevention of ischemic stroke as recommended by major professional societies.

1 Introduction

Stroke is a leading cause of death and disability worldwide, and ischemic strokes represent the vast majority (>80%) of all strokes [1]. Every year, there are over 9.5 million new cases of ischemic stroke. Over 2.7 million will die annually as a result of this devastating condition, and 51.9 million years of healthy life is lost per year due to ischemic stroke-related death and disabilities [2]. Despite advances in reperfusion therapies for patients who present with an acute ischemic stroke, effective prevention remains the best approach in mitigating the burden of this disease [3]. Primary prevention is especially important because over 75% of strokes are first events [4]. Effective prevention strategies include targeting the modifiable risk factors of the disease (Table 1).

In addition to the modifiable risk factors listed in Table 1, which account for approximately 80–90% of all ischemic strokes, several nonmodifiable risk factors also contribute to stroke risk (Table 2). These include age, low birth weight, race/

Table 1 Modifiable risk factors of ischemic stroke

Risk factor	Population-attributable risk of ischemic stroke (%)
Hypertension	45.7
Physical inactivity	33.4
Dyslipidemia (apolipoprotein ApoB/ApoA1 ratio)	34.0
Diet risk score (unhealthy cardiovascular diet)	22.4
Abdominal obesity (waist-to-hip ratio)	20.4
Current smoking	15.1
Atrial fibrillation	9.0
Diabetes mellitus	7.5
Alcohol consumption	4.6

Based on data from Ref. [11]

Table 2 Nonmodifiable risk factors of ischemic stroke

Risk factor	Association with ischemic stroke risk
Age	The incidence of stroke increases with age due to the cumulative effects of aging on the cardiovascular system and the higher occurrence of stroke-related risk factors with older age. The incidence of stroke doubles each decade after the age of 55.
Low birth weight	The odds of stroke and stroke mortality are higher among people with lower birth weights. It is uncertain if this association is causal. Mothers of low-birth-weight babies often have poorer overall health.
Race/ethnicity	Blacks and Hispanic/Latino Americans have higher incidences of stroke and stroke mortality compared to whites of the same age. It is unclear if the racial differences are genetic, environmental, or a combination of the two.
Genetic factors	Genetic influences of stroke may occur through their influences on individual stroke risk factors or, less commonly, as inherited monogenic causes of stroke, which include: Sickle cell disease CADASIL Fabry disease

Based on data from Ref. [5]

ethnicity, and genetic factors. The specific impact of these factors on cerebrovascular risk is detailed in the 2014 American Heart Association (AHA)/American Stroke Association (ASA) Guidelines for the Primary Prevention of Stroke [5]. Additional recommendations on the prevention of stroke in special populations are further provided in Table 3.

The main focus of this chapter is on the common modifiable risk factors of stroke. Ischemic stroke is considered to be a clinical atherosclerotic cardiovascular disease (ASCVD) equivalent, sharing much of the same vascular risk factors as acute coronary syndromes, myocardial infarction, stable or unstable angina, and peripheral arterial disease of atherosclerotic origin. Targets for stroke prevention are therefore aligned with the AHA's most recent scientific guidelines and public health campaigns that promote ideal cardiovascular health [6].

2 Determinants of Stroke Etiology

Stroke is a heterogeneous disease that can be classified into multiple types and subtypes based on the clinical presentation and the results of ancillary tests, including brain imaging, neurovascular studies, cardiac evaluations, and laboratory data. The specific type of stroke carries important implications on prognosis, outcome, and treatment strategies [7]. It also provides an understanding of how subsequent events can be prevented. The two broad categories of stroke are ischemic and hemorrhagic. Ischemic stroke results from an insufficient supply of blood to provide an adequate amount of oxygen and nutrients to parts of the brain, leading to reduced tissue viability and neuronal death, often due to arterial occlusion or stenosis. Hemorrhagic stroke, on the other hand, is characterized by an abnormal accumulation of blood

Table 3 Recommendations on the prevention of ischemic stroke in special populations

Risk factor	Preventive recommendations
Cardiac causes other than AF	*Acute myocardial infarction*: Among patients with STEMI, anticoagulant therapy with a vitamin K antagonist is reasonable for individuals with concurrent asymptomatic left ventricular mural thrombus and may be considered for those with anterior apical akinesis or dyskinesis *Cardiomyopathy*: Anticoagulants or antiplatelet agents are reasonable for patients with heart failure who do not have AF or a previous thromboembolic event, but selection of one therapy over the other should be individualized *Valvular heart disease*: The choice of antithrombotic regimen for prosthetic valve, and the INR goal when a vitamin K antagonist is used, depends on the type of valve (mechanical vs bioprosthetic), location of valve (aortic vs mitral), and the presence or absence of additional thromboembolic risk factors *Infective endocarditis*: Anticoagulant therapy should be avoided in individuals with infective endocarditis due to an increased risk of intracranial hemorrhage; rather, management should focus on treating the underlying infection
Patent foramen ovale	No specific treatment is recommended for the primary prevention of stroke in people with PFO
Asymptomatic carotid artery stenosis	Patients with asymptomatic carotid atherosclerosis should receive intensive medical therapy to include statin therapy, antiplatelet therapy, blood pressure control, and lifestyle modification Carotid endarterectomy may be considered in individuals with high-grade stenosis (>70%) if the risk of perioperative stroke, MI, and death is low (<3%)
Sleep-disordered breathing	Because of its association with stroke risk, screening for sleep apnea should be considered
Sickle cell disease	Children with sickle cell disease should be screened annually with transcranial Doppler, and those at elevated risk should receive transfusion therapy to target reduction of hemoglobin S to <30%
Drug abuse	Referral to a drug rehabilitation program is reasonable for patients who abuse cocaine, amphetamines, and other recreational drugs that are associated with stroke risk
Migraine	Among women who have migraine headaches with aura, smoking cessation is strongly recommended, and alternatives to oral contraceptives, especially those containing estrogen, should be considered

Based on data from Ref. [5]

within the intracranial cavity due to leakage or rupture of an artery. Ischemic and hemorrhagic strokes, in turn, have additional subtypes based on their precipitating cause.

The TOAST criteria is one widely used classification scheme that organizes ischemic stroke by their major pathophysiologic mechanisms [7]:

- Large-artery atherosclerosis: These patients have evidence of a significant (>50%) stenosis or occlusion of a major intracranial or extracranial artery supplying the territory of their infarct, presumably due to atherosclerosis.
- Cardioembolism: These patients have an arterial occlusion that is presumed to be from an embolus arising from the heart, with thrombogenic sources including

atrial fibrillation, mechanical prosthetic valve, left atrial thrombus, left ventricular thrombus, recent myocardial infarction, akinetic left ventricular segment, dilated cardiomyopathy, atrial myxoma, and infective endocarditis, among others.
- Small-vessel occlusion: These patients often have a history of hypertension and diabetes. Over time, segmental arterial disorganization and fibrinoid degeneration of the small penetrating arterioles occur due to chronically elevated blood pressures (also termed lipohyalinosis). It is postulated that microatheroma formation may be an alternative causative mechanism. Small and deep subcortical (lacunar) infarctions are seen.
- Stroke of other determined etiology: These patients may have one of the less common causes of stroke, such as nonatherosclerotic vasculopathies, hypercoagulable states, or hematologic disorders.
- Stroke of undetermined etiology: In many cases, the cause of stroke cannot be determined with any degree of confidence because of a negative evaluation, incomplete evaluation, or the presence of two competing causes.

Hemorrhagic strokes may be classified as an intracerebral hemorrhage, referring to bleeding directly into the brain parenchyma, or subarachnoid hemorrhage, referring to bleeding into the cerebrospinal fluid within the subarachnoid space. Causes of intracerebral hemorrhages include trauma, hypertension, bleeding diatheses, amyloid angiopathy, illicit drug use, vascular malformations, aneurysmal rupture, and bleeding into tumors. The most common causes of subarachnoid hemorrhage include trauma, aneurysmal rupture, and vascular malformations. Of all the types of intracranial bleeds, the subcortically located hypertensive hemorrhage is thought to share a similar pathophysiologic mechanism with small-vessel lacunar infarcts (i.e., chronic hypertension causing lipohyalinosis and microaneurysms of the small penetrating arteries) [8]. Prevention of hypertensive intracerebral hemorrhages primarily hinges on long-term management of hypertension.

3 Primary Prevention of Ischemic Stroke by Risk Factor

3.1 Hypertension

3.1.1 Definition and Epidemiology

According to the World Health Organization (WHO), 1.13 billion people in the world had hypertension in 2015 [1]. Hypertension was previously defined as having blood pressures ≥140 mmHg systolic and/or ≥90 mmHg diastolic. However, in 2017, the American College of Cardiology (ACC) and the AHA published new guidelines that lowered the threshold for the diagnosis of hypertension. With the new definition, individuals with blood pressure measurements between 130–139 systolic or 80–89 diastolic have stage 1 hypertension, and those with ≥140 systolic or ≥90 diastolic have stage 2 hypertension. Normal blood pressure is still defined as less than 120/80 mmHg, but individuals with blood pressures of 120–129 systolic and less than 80 diastolic are considered to have elevated blood pressures [9]. The

change in guidelines was based on a review of studies that showed that complications may occur at lower blood pressure numbers, with an increased risk of death from stroke, heart disease, or other vascular diseases with every incremental increase in blood pressure from as low as 115/75 [10]. High blood pressure induces functional and structural changes in the vasculature that promote atherosclerosis in the large intracranial and extracranial arteries and lipohyalinosis in penetrating arterioles. Hypertension is in fact the leading risk factor for ischemic stroke, with a population-attributable risk of 45.7%. This means that approximately 45.7% of ischemic stroke cases would not occur if this risk factor is eliminated [11].

3.1.2 What Is the Evidence?

Some studies support the use of intensive blood pressure control (systolic blood pressure [SBP] < 120 mmHg) over standard blood pressure control (SBP < 140 mmHg) in the primary prevention of stroke.

In the Action to Control Cardiovascular Risk in Diabetes blood pressure (ACCORD BP) trial, 4733 diabetic individuals who were considered to be at high risk for cardiovascular events were randomized to receive either intensive therapy (initiation/adjustment of blood pressure medications to achieve a goal of less than 120 mmHg systolic) or standard therapy (adjustment of BP medications to achieve a goal of less than 140 mmHg systolic). The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. After the first year, the mean systolic blood pressure was 119.3 mmHg in the intensive-therapy arm and 133.5 mmHg in the standard-therapy arm. The study found that the annual rate of the primary endpoint and death from any cause did not differ significantly between the two groups. However, the annual rate of stroke, a prespecified secondary outcome, was lower in the intensive-therapy arm (0.32% vs 0.53%; hazard ratio [HR], 0.59; 95% confidence interval [CI], 0.39–0.89; $P = 0.01$). This benefit was accompanied by an increased rate of serious adverse events related to a lower blood pressure target, driven by hypotension, arrhythmia, and hyperkalemia (3.3% vs 1.3%; $P < 0.001$) [12].

Similarly, the Systolic Blood Pressure Intervention Trial (SPRINT) randomized 9361 individuals with a systolic blood pressure of 130 mmHg or higher and an increased cardiovascular risk to the same intensive- versus standard-treatment arms. A notable difference in this study was that it excluded patients with diabetes. The primary outcome was a composite of myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes. After the first year, the mean systolic blood pressure was 121.4 mmHg in the intensive-therapy arm and 136.2 mmHg in the standard-therapy arm. The trial was stopped early after it was determined that there was a significantly lower annual rate of the primary endpoint in the intensive-therapy group (1.65% vs 2.19%; HR, 0.75; 95% CI, 0.64–0.89; $P < 0.001$). All-cause mortality was also found to be significantly lower among patients treated with a lower blood pressure target (HR, 0.73; 95% CI, 0.60–0.90; $P = 0.003$). However, the rate of stroke as one of the secondary endpoints was not statistically different between the two groups, and rates of serious adverse

events, including hypotension, syncope, electrolyte abnormalities, and acute kidney injury, were higher in the intensive-therapy arm [13].

In contrast to the ACCORD BP and SPRINT trials, the Heart Outcomes Prevention Evaluation (HOPE)-3 trial randomized 12,705 participants at intermediate cardiovascular risk to undergo blood pressure lowering with candesartan and hydrochlorothiazide or to receive placebo. These individuals did not have any prior established cardiovascular disease. The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The mean baseline systolic blood pressure of the participants was 138.1 mmHg. During follow-up, there was a 6.0 mmHg greater systolic reduction in the active-treatment group than in the placebo group. No significant difference in the primary composite outcome was found between the two groups. However, in the analyses of one of three prespecified subgroups, participants in the subgroup for the upper third of systolic blood pressures (mean SBP >143.5 mmHg) did benefit from antihypertensive therapy for reduction of stroke risk (HR, 0.58; 95% CI, 0.37–0.90). These findings suggest that individuals without high cardiovascular risk will still benefit from antihypertensive therapy, though with a more liberal SBP goal of less than 140 mmHg [14].

In review of these and other studies, the clinician should weigh the risks and benefits of intensive blood pressure control to help guide its applicability in select patient populations. The following recommendations are in concordance with the guidelines published by the ACC/AHA in 2017 [9].

3.1.3 Recommendations for Management

1. The use of BP-lowering medications is recommended for the primary prevention of stroke in adults with evidence of clinical cardiovascular disease (CVD), or no history of CVD but an estimated 10-year ASCVD risk of ≥10%, to achieve a blood pressure goal of less than 130 mmHg systolic and 80 mmHg diastolic [9].
2. The use of BP-lowering medications is recommended for the primary prevention of stroke in adults with no history of CVD and an estimated 10-year ASCVD risk <10% to achieve a blood pressure goal of less than 140 mmHg systolic and 90 mmHg diastolic [9].
3. Refer to Sects. 3.5 and 3.6 for nonpharmacologic interventions to reduce high blood pressure.

3.2 Dyslipidemia

3.2.1 Definition and Epidemiology

Hyperlipidemia or dyslipidemia has been estimated to cause 2.6 million deaths annually and is a major driver of disease burden in both the developed and developing world [1]. Epidemiological studies have shown a direct relationship between

high cholesterol and ischemic stroke risk, with association strongest for strokes due to large artery atherosclerosis [15]. Cholesterol contributes to the buildup of plaque along the walls of large- and medium-sized arteries. These plaques become fragile and prone to rupture and lead to subsequent thrombus formation. Dyslipidemia has a population-attributable risk for ischemic stroke of 34% [11]. Total cholesterol and low-density lipoprotein cholesterol (LDL-C) appear to carry the greatest influence on risk compared to other components of the lipid profile [15].

Strict numerical cutoffs between normal and abnormal lipid levels do not exist. A continuous relationship probably occurs between lipid levels and cardiovascular risks such that many people with "normal" cholesterol levels may still benefit from achieving even lower levels depending on their risk profile. The ACC/AHA published updated lipid guidelines in 2018 which individualized the threshold of initiating statin and non-statin therapy. The selection of cholesterol-lowering therapy depends on various patient characteristics, which include age, baseline LDL-C levels, presence or absence of clinical CVD, presence or absence of diabetes, and overall 10-year ASCVD risk [16].

The details of the ACC/AHA lipid guidelines for the primary prevention of CVD are beyond the scope of this chapter. The remainder of this section will highlight a few trials that studied the efficacy of statin and non-statin lipid-lowering therapies for the prevention of ischemic stroke.

3.2.2 What Is the Evidence?

Statins are the mainstay of pharmacologic therapy for primary and secondary stroke prevention. In the Heart Protection Study (HPS) published back in 2002, more than 20,000 patients aged 40–80 years with coronary disease, other occlusive arterial disease, or diabetes were randomly allocated to receive 40 mg of simvastatin daily or matching placebo. The mean baseline LDL-C was 131 mg/dL among the participants. Intention-to-treat analyses showed an average difference in LDL-C of 39 mg/dL during the 5-year study period. Primary outcomes were mortality and fatal or nonfatal vascular events. The study showed that all-cause mortality was significantly reduced with statin use (12.9% vs 14.7%; $P = 0.0003$). The first event rate for fatal or nonfatal stroke was also found to be significantly reduced (4.3% vs 5.7%; $P < 0.0001$) [17]. Other trials showed that more aggressive lipid lowering was associated with a further reduction in risk [18, 19]. Based on a meta-analysis of studies looking at lipid management and stroke prevention, there was a ~20% relative risk reduction in ischemic stroke with each 39 mg/dL reduction in LDL-C [18]. In the Treating to New Targets (TNT) study, atorvastatin 80 mg daily was associated with a 25% reduction in stroke risk compared to atorvastatin 10 mg daily [19].

The evidence for the use of non-statin therapies in the primary prevention of stroke is not as robust. Although niacin helps increase high-density lipoprotein cholesterol (HDL-C) levels, and fibric acid derivatives can lower triglycerides and increase HDL levels, the use of these agents in reducing the risk of cerebrovascular events remains uncertain [20–22]. On the other hand, ezetimibe, when added to simvastatin therapy, was shown to reduce the rate of ischemic stroke by 21%

compared to simvastatin alone [23]. Ezetimibe is a medication that inhibits the intestinal absorption of cholesterol, thereby reducing LDL-C and triglyceride levels.

Alirocumab and evolocumab are two inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9) approved by the Food and Drug Administration (FDA) for treatment of high cholesterol. PCSK9 is a naturally occurring enzyme in the body whose action is to promote the lysosomal catabolism of hepatic LDL receptors and in effect increase serum LDL-C levels. PCSK9 inhibitors block the activity of this enzyme, making more LDL receptors available on the cell surfaces of hepatocytes; this allows for an increase in clearance of LDL-C from the circulation. In the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial, 27,564 patients with atherosclerotic CVD and LDL-C levels of ≥70 mg/dL while on statin therapy were randomized to receive evolocumab or matching placebo. Compared to placebo, the group who received evolocumab had their LDL-C reduced by an additional 59% from an average baseline of 92 mg/dL after 48 weeks. The rates of the primary and key secondary efficacy endpoints, which were varying composites of fatal and nonfatal CVD-related events, were significantly reduced by evolocumab treatment relative to placebo. Notably, the risk of ischemic stroke alone, one of the secondary endpoints in the study, was reduced by 25% [24]. The Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab (ODYSSEY OUTCOMES) was a similar randomized, double-blind, placebo-controlled trial. It assigned patients who had a recent acute coronary syndrome and a suboptimal lipid profile despite statin therapy to receive alirocumab or matching placebo. The study found that a primary composite endpoint of fatal and nonfatal CVD-related events was also significantly reduced in the treatment group relative to placebo, with risk of ischemic stroke reduced at similar rates seen in the FOURIER trial (HR for fatal or nonfatal stroke, 0.73; 95% CI, 0.57–0.93) [25]. Both alirocumab and evolocumab are administered by subcutaneous injection at a frequency of once every 2 weeks or once monthly, depending on dosage.

Icosapent ethyl is a highly purified omega-3 fatty acid that has been shown to lower serum triglyceride levels [26, 27]. In the recent Reduction of Cardiovascular Events with Icosapent Ethyl – Intervention Trial (REDUCE-IT), a total of 8179 patients with established cardiovascular disease, or with diabetes and other risk factors, were randomly assigned to receive 2 g of icosapent ethyl twice daily or placebo. These individuals were already on statin therapy with a median baseline LDL-C level of 75 mg/dL, but their median baseline fasting triglyceride level was 216 mg/dL. Compared to placebo, the use of icosapent ethyl led to a 19.7% greater reduction in triglycerides after 1 year. The study found that the rates of the primary and key secondary efficacy endpoints, which were varying composites of fatal and nonfatal CVD-related events, were significantly reduced by icosapent ethyl compared to placebo. Notably, the use of icosapent ethyl led to a 28% reduction in the secondary endpoint of fatal and nonfatal strokes (HR, 0.72; 95% CI, 0.55–0.93) [28].

3.2.3 Recommendations for Management

1. The selection of cholesterol-lowering therapy for stroke prevention depends on various patient characteristics, which include age, baseline LDL-C levels, presence or absence of clinical CVD, presence or absence of diabetes, and overall 10-year ASCVD risk. The 2018 AHA/ACC Multisociety Guideline on the Management of Blood Cholesterol details the indications for cholesterol-lowering therapies based on individual risk profile [16].
2. Statin therapy is the first-line agent for treatment of hyperlipidemia, with choice of a moderate-intensity or high-intensity statin based on individual risk profile [16].
3. It is reasonable to add ezetimibe to maximally tolerated statin therapy if LDL-C remains above the goal established based on the individual risk profile (typically LDL-C greater than or equal to 70 or 100 mg/dL depending on their ASCVD risk) [16].
4. It is reasonable to add PCSK9 inhibitors to maximally tolerated statin and ezetimibe if LDL-C remains above the goal established based on individual risk profile (typically LDL-C greater than or equal to 70 or 100 mg/dL depending on their ASCVD risk) [16].
5. Based on the 2019 National Lipid Association Scientific Statement, the use of icosapent ethyl is recommended for the lowering of ASCVD risk in patients aged ≥45 years with clinical ASCVD or aged ≥50 years with diabetes that require medication plus ≥1 additional risk factor and with fasting triglycerides 135–499 mg/dL while on high-intensity or maximally tolerated statin therapy [29].
6. Refer to Sects. 3.5 and 3.6 for nonpharmacologic interventions to reduce high cholesterol.

3.3 Diabetes Mellitus

3.3.1 Definition and Epidemiology

The global prevalence of diabetes is on the rise. According to most recent estimates, approximately 422 million adults have diabetes worldwide [1]. Uncontrolled diabetes can lead to several vascular complications, such as myocardial infarction, stroke, blindness, kidney failure, and poor wound healing with resultant limb amputation. The population-attributable risk of ischemic stroke from diabetes is 7.5% [11]. Elevated blood glucose contributes to endothelial damage and accelerated atherosclerosis by a variety of direct and indirect mechanisms [30]. Therefore, effective stroke prevention measures in diabetic patients should focus on glycemic control and aggressive management of coexistent vascular risk factors.

3.3.2 What Is the Evidence?

Previous epidemiological studies have shown a direct relationship between degree of sustained hyperglycemia and the occurrence of cardiovascular events in patients with type 2 diabetes [31–33]. However, randomized controlled trials have not shown a definite benefit of tight glycemic control over good glycemic control in the prevention of these events. In the ACCORD trial, 10,251 diabetic patients with established cardiovascular disease or additional cardiovascular risk factors were randomly assigned to receive either intensive therapy (targeting a glycated hemoglobin [HbA1c] level below 6.0%) or standard therapy (targeting a level from 7.0% to 7.9%). The average HbA1c was 8.1% prior to randomization. The primary outcome was a composite of fatal and nonfatal CVD-related events. At 1 year, the average HbA1c was 6.4% in the intensive-therapy group and 7.5% in the standard-therapy group. No significant difference was observed in the rate of primary outcome between the two groups during follow-up (HR, 0.90; 95% CI, 0.78–1.04; $P = 0.16$). The rate of nonfatal stroke, a secondary outcome, was also similar between the two groups (HR, 1.06; 95% CI, 0.75–1.50; $P = 0.74$). On the other hand, an increase in mortality was seen in the intensive-therapy group compared to standard therapy (HR, 1.22; 95% CI, 1.01–1.46; $P = 0.04$), suggesting a potential harm with the use of a tighter blood glucose target [34]. The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial was a similar study that looked at whether intensive glycemic control (HbA1c $\leq$ 6.5%), compared to standard glycemic control, conferred any benefit in reducing the frequency of major macrovascular and microvascular events. In this study, major macrovascular events included death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, and major microvascular events included new or worsening nephropathy or retinopathy. After 5 years of follow-up, the average HbA1c was 6.5% in the intensive-therapy group and 7.3% in the standard-therapy group. While intensive glucose control led to a reduction in microvascular outcomes, no significant difference was observed in the rate of macrovascular outcomes, despite the difference in glycemic control between the two groups [35].

Selection of Antihyperglycemic Agents

Metformin remains the first-line therapy for glucose control in patients with type 2 diabetes. However, glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors are effective adjunctive therapies that can help reduce glucose levels further and also lower ASCVD risk. Multiple large randomized controlled trials have shown significant reductions in cardiovascular events among patients with type 2 diabetes who were treated with either GLP-1RAs or SGLT2 inhibitors [36].

GLP-1RAs work predominantly by augmenting insulin secretion and suppressing glucagon release by stimulating GLP-1 receptors. Currently, there have been seven major randomized controlled trials that have evaluated the effect of GLP-1RA on the prevention of stroke in patients with type 2 diabetes. A meta-analysis of these

seven studies showed that the use of GLP-1RA was associated with a 16% reduction in the risk of total stroke ($P = 0.001$), driven by a 15% lower risk of nonfatal strokes ($P = 0.002$) [37]. Only two of the GLP-1RAs – subcutaneous semaglutide and dulaglutide – significantly reduced the risk of stroke in single trials (39% in SUSTAIN-6 and 24% in REWIND, respectively) [38, 39]. This observed benefit of GLP-1RA did not correlate with reductions in HbA1c level or body weight, suggesting that the medication's benefit may be from pleiotropic effects [37].

A recent meta-analysis published in 2019 found that treatment with a SGLT2 inhibitor, a medication that prevents glucose reabsorption at the renal tubule, was not associated with a reduced risk of ischemic stroke in patients with type 2 diabetes (HR, 0.95; 95% CI, 0.85–1.07; $P = 0.42$), despite its proven benefit in reducing overall cardiovascular outcomes [40].

3.3.3 Recommendations for Management

1. Good glycemic control is essential in primary stroke prevention. However, in most cases, it is not necessary to target glucose levels to near-normal physiological parameters; rather, a HbA1c goal of <7% is reasonable in many adults, especially for individuals with long-standing diabetes and/or already established CVD [41].
2. A glucagon-like peptide-1 receptor agonist with demonstrated stroke prevention benefit should be considered as part of the glucose-lowering regimen for patients with type 2 diabetes who have established CVD or are at an elevated ASCVD risk [36].

3.4 Obesity and Metabolic Syndrome

3.4.1 Definition and Epidemiology

The worldwide prevalence of obesity has nearly tripled since 1975. In 2016, 39% of adults were overweight (body mass index [BMI] of ≥25 kg/m^2) and 13% were obese (BMI of ≥30 kg/m^2) [1]. Excess body weight is a risk factor for ischemic stroke, with a population-attributable risk of 20.4% [11]. For every 1 unit increase in BMI from 20 kg/m^2, the risk of ischemic stroke increases linearly by about 5% [42–44]. Obesity increases an individual's risk for cerebrovascular disease by several distinct mechanisms, which include the development of insulin resistance, hypertension, accelerated atherosclerosis, atrial fibrillation, and obstructive sleep apnea. Obesity is closely tied with the metabolic syndrome. The metabolic syndrome is defined as the co-occurrence of interrelated vascular risk factors (abdominal obesity, elevated triglycerides, low HDL, high blood pressure, and hyperglycemia) that, together, significantly increases one's propensity of having CVD-related events. The global prevalence of metabolic syndrome follows closely with that of obesity and type 2 diabetes and is estimated to affect one quarter of the world population [45].

3.4.2 What Is the Evidence?

High blood pressure, high blood glucose, and high cholesterol often run comorbid with obesity. The previous sections have outlined specific recommendations on how hypertension, diabetes, and dyslipidemia should each be treated for the primary prevention of stroke. Unfortunately, no randomized clinical trials have, to date, examined the direct effect of intentional weight loss on stroke risk. However, it is well known that weight loss is associated with improvements in blood pressure, lipid profile, insulin sensitivity, and measures of inflammation. A modest weight loss of 5–10% has been shown to reduce SBPs by 3–6 mmHg, increase HDL-C by 3 mg/dL, and decrease HbA1c by 0.5 absolute percentage points [46, 47]. The amount of change in these numbers is proportional to the amount of weight loss achieved. Weight loss is therefore advised in overweight and obese individuals as a means to modify their concurrent risk factors for stroke.

3.4.3 Recommendations for Management

1. For overweight (BMI = 25–29 kg/m^2) and obese (BMI ≥30 kg/m^2) individuals, weight loss is recommended as a means to modify stroke risk factors. Behavioral counseling interventions should be offered when appropriate [6].

3.5 Physical Inactivity

3.5.1 Definition and Epidemiology

According to WHO, insufficient physical activity is a key risk factor for the development of many noncommunicable diseases, including CVD-related diseases, cancer, and diabetes. Despite this association, one in four adults worldwide is not partaking in enough physical activity [1]. Sufficient physical activity is defined by many health organizations to be at least 150 minutes per week of moderate-intensity or 75 minutes per week of vigorous-intensity aerobic physical activity, or an equivalent combination of the two. A sedentary lifestyle leads to obesity, hypertension, dyslipidemia, and glucose intolerance, all of which have been implicated in the pathogenesis of stroke. Physical inactivity accounts for 33.4% of the global burden of ischemic stroke [11].

3.5.2 What Is the Evidence?

Regular exercise exerts many beneficial effects on the human body; this includes improving endothelial function, enhancing glucose regulation, stimulating elevations in plasma tissue plasminogen activator and HDL concentrations, decreasing fibrinogen and platelet activity, and promoting reductions in total cholesterol,

LDL-C, triglycerides, and total body fat [48]. Consistent engagement in physical activity helps reduce blood pressures and control CVD risk and may also carry an independent protective effect against cerebrovascular events. A meta-analysis of 23 studies concluded that moderate to high levels of physical activity were associated with lower stroke incidence and mortality [49].

A precise recommendation on the exact type, frequency, and intensity of exercise needed to confer a protective effect against cerebrovascular disease is difficult to provide. This is due in part to the nature of existing trials, with definitions for low-, moderate-, and high-intensity physical activity being somewhat variable from study to study. Furthermore, many of these trials relied on individual self-report of their level of activity, which can be fraught with bias and inaccuracies.

There are a few large prospective studies that are worth mentioning. One such study is the Northern Manhattan Study, which found that among a cohort of 3298 older, urban-dwelling, and multiethnic individuals, engaging in moderate- to high-intensity physical activity was associated with a lower risk of ischemic stroke. Interestingly, this effect was seen only in men (adjusted HR 0.37; 95% CI, 0.18–0.78), and the benefit did not translate to those who engaged in light-intensity activity [50]. In contrast, the Nurses' Health Study found that gradated levels of physical activity were associated with a reduced risk of ischemic stroke among a prospective cohort of 72,488 female nurses (the relative risks [RRs] across increasing metabolic equivalent [MET] quintiles were 1.00, 0.87, 0.83, 0.76, and 0.52; $P = 0.003$). Walking was also associated with a reduced risk of stroke (RRs across increasing walking MET quintiles, 1.00, 0.77, 0.75, 0.69, and 0.60; $P = 0.02$), highlighting that even a brisk walking pace conferred greater stroke protection than casual pace [51].

3.5.3 Recommendations for Management

1. There is a lack of robust data to support precise recommendations on the exact type, frequency, and intensity of exercise needed to confer a protective effect against stroke. At least 150 minutes per week of moderate-intensity or 75 minutes per week of vigorous-intensity aerobic physical activity (or an equivalent combination of the two) is generally recommended to reduce ASCVD risk [6].

3.6 Nutrition and Diet

3.6.1 Definition and Epidemiology

Dietary patterns have the capacity to modulate stroke risk through a multitude of mechanisms, including its effects on blood pressure, cholesterol levels, oxidative stress, inflammation, thrombosis, endothelial function, glucose and insulin homeostasis, and body weight [52]. An unhealthy diet characterized by high intake of salt and saturated fats, with low consumption of fruits and vegetables, contributes to poor cardiovascular and cerebrovascular health. While the prevalence of unhealthy dietary

practices is difficult to quantify, such practices are associated with an estimated population-attributable risk for ischemic stroke of 22.4% [11]. Unfortunately, individuals with lower socioeconomic status are often disproportionately affected [53].

Current available evidence supports adherence to the Mediterranean and/or dietary approaches to stop hypertension (DASH) diets as a measure to mitigate the risk of stroke. Both diets emphasize a wide consumption of fruits, vegetables, nuts, legumes, whole grains, and lean proteins, all of which are rich in micronutrients and phenolics, while minimizing intake of sodium, saturated fat, red and processed meats, and refined high-sugar foods. The Mediterranean diet also encourages consumption of fish, which is a source of omega-3 fatty acids, and olive oil, which has a high content of monounsaturated fatty acids [52].

3.6.2 What Is the Evidence?

An original meta-analysis of 12 studies found that high adherence to a Mediterranean diet was associated with reduced stroke risk (RR, 0.71; 95% CI, 0.57–0.89) [54]. This was subsequently confirmed by a second meta-analysis in 2014 (RR, 0.68; 95% CI, 0.58–0.79), which expanded on the first meta-analysis with the inclusion of two additional cohort studies and a randomized controlled trial, the Prevención con Dieta Mediterránea (PREDIMED) trial [55]. The PREDIMED trial was a randomized three-arm clinical trial that assigned 7447 Spanish adults to either a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control group consisting of a reduced-fat diet. While the aim of the study was to examine the effect of the Mediterranean diet on the primary prevention of cardiovascular disease, stroke was included as a secondary endpoint. The hazard ratio of stroke for the Mediterranean diet (both groups merged) as compared with the control diet was 0.61 (95% CI, 0.44–0.86). It is important to note, however, that the publication was later retracted due to identified protocol deviations. The results were revised in 2018, but the conclusions remained the same (HR of stroke, 0.58; 95% CI, 0.42–0.82) [56].

A meta-analysis of observational prospective studies looking at the protective role of the DASH diet against CVD found that adherence to a DASH-like diet significantly reduced the risk of stroke (RR, 0.81; 95% CI, 0.72–0.92) [57]. Since that publication, additional prospective studies conducted among 74,404 healthy Swedish men and women, and another in 33,671 Dutch men and women, showed similar results that were consistently supportive of the DASH diet [58, 59]. This is likely mediated in part by improvements in blood pressure control.

3.6.3 Recommendations for Management

1. Adherence to a Mediterranean or DASH diet, which is characterized by a wide consumption of vegetables, fruits, nuts, whole grains, and lean proteins and reduced intake of sodium, saturated fat, red and processed meats, and refined high-sugar foods, is recommended for stroke prevention [6].

3.7 Tobacco Use

3.7.1 Definition and Epidemiology

Despite the detrimental health consequences associated with tobacco use, an astounding 1.1 billion people continue to smoke worldwide [1]. Smoking is a well-established risk factor for ischemic stroke. It is postulated that tobacco smoke causes early arterial damage, progression of atherosclerosis, reduced cerebral blood flow, and development of a systemic procoagulant state, all of which may serve as a causative mechanism for stroke and cerebrovascular disease [60]. A dose-response relationship between tobacco consumption and stroke risk has been described, such that the more tobacco that the individual uses, the likelihood of stroke occurrence increases. On average, cigarette smoking is associated with an approximate two- to fourfold increase in an individual's risk for ischemic stroke. Environmental (second-hand) exposure to tobacco is also known to confer an elevated risk [60]. If tobacco use is eradicated on a population level, it is estimated that 15.1% of ischemic stroke cases would not occur [11].

3.7.2 What Is the Evidence?

The effect of tobacco use on stroke risk is reversible if smoking is discontinued. Tobacco cessation results in a considerable reduction in stroke risk by 2 years after quitting, and that risk approaches to near-baseline levels within 5 years after their last cigarette use [61]. Therefore, smoking cessation should be encouraged as it eliminates a potent stroke risk factor for the smoker and those exposed to second-hand smoke. Effective measures to quit smoking typically include a combination of counseling as well as pharmacologic therapy, such as nicotine replacement therapy, bupropion, or varenicline.

3.7.3 Recommendations for Management

1. Smoking cessation is advised for individuals who smoke and those who do not smoke should refrain from starting. Readiness to quit should be assessed. When the patient is ready to quit, a combination of counseling and pharmacologic therapy may be utilized [6].

3.8 Alcohol Consumption

3.8.1 Definition and Epidemiology

The relationship between alcohol and health is complex and controversial. It is undisputable that excess use of alcohol is harmful and contributes to more than 200 disease and injury conditions [1]. Habitual heavy drinking can induce hypertension

and cardiac arrhythmias, both of which are known risk factors for stroke. On the other hand, many epidemiological studies have shown a benefit of light-to-moderate alcohol intake on cardiovascular risk reduction [62]. The translation of this benefit to lowering stroke risk is not clear. Overall, alcohol consumption carries a population-attributable risk for ischemic stroke of 4.6% [11].

3.8.2 What Is the Evidence?

Several published studies have explored the relationship of alcohol intake on stroke risk, with a nonlinear, J-shaped association generally observed between the two variables. One meta-analysis published in 2016 showed that compared with non-drinkers, a low level of alcohol consumption was associated with a reduced risk of stroke and a high level was associated with an increased risk. Specifically, the RR of ischemic stroke was 0.90 (95% CI, 0.85–0.95) for less than one drink per day, 0.92 (95% CI, 0.87–0.97) for one to two drinks per day, 1.08 (95% CI, 1.01–1.15) for more than two to four drinks per day, and 1.14 (95% CI, 1.02–1.28) for more than four drinks per day [63]. Data were pooled from 27 cohorts, including the Nurses' Health Study, Physicians' Health Study, Framingham Study, and Atherosclerosis Risk in Communities Study. More recent data suggests that perhaps any level of alcohol use may be associated with an elevated stroke risk, with the relationship being more of a log-linear one rather than J-shaped [64]. No prospective randomized clinical trials exist on this subject as heavy alcohol consumption is a well-recognized major health problem and such trials will be ethically untenable.

3.8.3 Recommendations for Management

1. High alcohol consumption is linked to many health issues, including stroke, and heavy drinkers should be encouraged to reduce or abstain from their alcohol use. Those who do not consume alcohol should not be encouraged to start, as the effect of low alcohol consumption on stroke risk reduction is uncertain.
2. For individuals who choose to drink alcohol, consumption should be minimized to $\leq$2 drinks per day for men and $\leq$1 drink per day for nonpregnant women, in accordance with current AHA guidelines [6].

3.9 Atrial Fibrillation

3.9.1 Definition and Epidemiology

The number of individuals with atrial fibrillation (AF) was estimated to be 33.5 million in 2010 [65]. A more recent estimate of the worldwide prevalence of AF is not currently available. Many of the common cardiovascular risk factors discussed in

preceding sections, such as hypertension, diabetes, obesity, sleep apnea, physical inactivity, and alcohol consumption, can contribute to the development of AF. Moreover, ensuing structural cardiac abnormalities, including heart failure and coronary artery disease, can compromise the conductive system and lead to AF [66]. When the heart is not contracting regularly, stasis-induced thrombus forms in the left atrium and becomes a source of cerebral embolus.

The risk of stroke from AF is not uniform and varies based on the co-occurrence of several independent demographic and clinical factors. The annual rate of ischemic stroke in patients with AF ranges from 1% to 15% and can be approximated by calculating the CHA_2DS_2-VASc score [67]. Of note, the CHA_2DS_2-VASc score assigns one point each to six of eight critical risk factors, i.e., congestive heart failure, hypertension, age 65–74 years, diabetes, vascular disease, and female sex category, and two points each for the other two, i.e., age ≥75 years and prior stroke or transient ischemic attack (TIA). Every accumulated point in the risk stratification score is associated with an increased risk of stroke in the untreated AF patient.

3.9.2 What Is the Evidence?

In the 2014 AF guidelines, a CHA_2DS_2-VASc score of 2 or greater was an indication to consider oral anticoagulant therapy [68]. However, in 2019, the AHA/ACC updated their guidelines to suggest that initiation of oral anticoagulation should be considered in men with CHA_2DS_2-VASc ≥2 and women with CHA_2DS_2-VASc ≥3 [69]. The change in recommendation was based on recent studies that showed that female sex, in the absence of other AF risk factors, carried a low stroke risk comparable to that of males. Female sex appeared to be a risk modifier, rather than a risk factor, influencing stroke risk in the presence of ≥2 non-sex-related stroke risk factors [70].

Selection of Anticoagulant Therapy

The effectiveness of warfarin in reducing the occurrence of ischemic stroke in patients with AF has been long established [71, 72]. In recent years, four large randomized clinical trials were conducted to assess the safety and efficacy of the non-vitamin K oral anticoagulants (NOACs). Each of the trials showed consistent evidence of at least noninferiority, if not superiority, of the NOACs for the reduction of stroke or systemic embolism, when compared to warfarin therapy. More specifically, apixaban and dabigatran at the 150 mg dose were both superior to warfarin at preventing stroke or systemic embolism, and apixaban, edoxaban, and dabigatran at the 110 mg dose had lower rates of major bleeding compared to warfarin. All four NOACs (apixaban, dabigatran, rivaroxaban, and edoxaban) were observed to have lower rates of intracranial hemorrhage [73–76]. Several pooled meta-analyses of these randomized clinical trials found that, compared with warfarin therapy, NOACs

led to an overall 15% greater reduction in stroke and thromboembolic events. It was also associated with an approximate 10% reduction in all-cause mortality and a 50% reduction in intracranial hemorrhage [77–81]. AF in the setting of mechanical valve or moderate-to-severe mitral stenosis was part of the exclusion criteria in these studies. The agents are now recommended by the AHA/ACC over warfarin for those who need anticoagulation for nonvalvular AF [69].

Nonpharmacologic Therapy: Percutaneous Left Atrial Appendage (LAA) Closure

Two randomized controlled trials (PROTECT AF [WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation] and PREVAIL [Evaluation of the WATCHMAN LAA Closure Device in Patients with Atrial Fibrillation Versus Long-Term Warfarin Therapy]) have examined the utility of percutaneous LAA closure for the prevention of stroke in AF patients [82, 83]. A meta-analysis combining data from these two trials and their registries showed that event rates for all-cause stroke and systemic embolism were similar between LAA closure and warfarin (1.75 vs 1.87 events per 100 patient-years [PY]; HR, 1.02; $P = 0.94$). However, while LAA closure with the WATCHMAN device was associated with significantly fewer hemorrhagic strokes compared to warfarin, there were more ischemic strokes seen in the device group (1.6 vs 0.9 events/100 PY; HR, 1.95; $P = 0.05$). If procedure-related strokes were excluded, the difference in ischemic stroke rate was not statistically significant between the two groups [84]. A second meta-analysis looking at the 5-year outcomes from the PROTECT AF and PREVAIL trials showed similar trends. The ischemic stroke and systemic embolism rate remained numerically higher with LAA closure, but the difference was not statistically significant (HR, 1.71; $P = 0.08$) [85]. Of note, patients who underwent LAA closure were also on a short-term antithrombotic regimen to allow for proper endothelialization of the device.

3.9.3 Recommendations for Management

1. For patients with AF and an elevated CHA_2DS_2-VASc score of ≥2 in men or ≥3 in women, initiation of oral anticoagulation is recommended per AHA/ACC guidelines [69].
2. For patients with nonvalvular AF (i.e., AF not associated with mechanical heart valve or moderate-to-severe mitral stenosis), NOACs (apixaban, dabigatran, rivaroxaban, or edoxaban) should be considered over warfarin for ischemic stroke prevention [69].
3. Warfarin remains the anticoagulant of choice for patients with valvular AF [69].
4. For patients with AF who should be on anticoagulation for ischemic stroke prevention but have contraindications to long-term anticoagulation, percutaneous LAA closure may be considered as an alternative to pharmacologic treatment [69].

4 Aspirin for the Primary Prevention of Ischemic Stroke

The benefit of aspirin therapy in preventing recurrent ischemic strokes is well established, but the routine use of aspirin in the primary prevention of stroke is controversial [86]. A meta-analysis from 2016 found no significant reduction in the rate of nonfatal stroke with aspirin use among individuals without a previous history of stroke or TIA (RR, 0.95; 95% CI, 0.85–1.06) [87]. Moreover, low-dose aspirin (≤100 mg daily) was associated with an excess risk of major gastrointestinal bleeding and hemorrhagic stroke of 58% and 27%, respectively [88].

Three large randomized trials published in subsequent years produced similar results. In the ASCEND (A Study of Cardiovascular Events in Diabetes) trial, a total of 15,480 individuals with diabetes were randomized to receive either aspirin or placebo. The use of aspirin did not lead to a reduction in the rate of nonfatal ischemic strokes (RR, 0.88; 95% CI, 0.73–1.06) but rather led to a significant increase in major bleeding events (RR, 1.29; 95% CI, 1.09–1.52; $P = 0.003$) [89]. In the ARRIVE (Aspirin to Reduce Risk of Initial Vascular Events) study, 12,546 patients deemed to be at moderate cardiovascular risk were assigned to receive aspirin or placebo. The study showed that aspirin did not carry a protective effect against stroke (HR, 1.12; 95% CI, 0.80–1.55). The rate of gastrointestinal bleeding was higher in the aspirin arm (HR, 2.11; 95% CI, 1.36–3.28; $P = 0.0007$) [90]. Lastly, in the ASPREE (Aspirin in Reducing Events in the Elderly) trial, healthy individuals who were 70 years of age or older did not benefit from aspirin therapy (HR for fatal or nonfatal ischemic stroke, 0.89; 95% CI, 0.71–1.11). Those who were placed on aspirin were at a higher risk of major hemorrhage (HR, 1.38; 95% CI, 1.18–1.62) [91].

A recent meta-analysis combining data from older primary prevention trials with these three new studies showed that aspirin may still play some role in the primary prevention of stroke, carrying a number needed to treat of 540 to prevent one ischemic stroke. However, the number needed to harm was 210 for a major bleeding event [92]. The incremental benefit of aspirin has likely decreased due to the concurrent use of evidence-based hypertension and cholesterol therapies [6].

4.1 Recommendations for Management

1. The prophylactic use of aspirin for primary stroke prevention should not be routinely considered in individuals who are at low ASCVD risk, as the risk of hemorrhage likely outweighs its protective effects of thromboembolism. It may be considered in individuals with an elevated ASCVD risk or those whose lipid, glucose, or blood pressure targets are not optimally achieved and who are not at an increased bleeding risk [6].

5 Antiplatelet Therapy for the Prevention of Recurrent Noncardioembolic Ischemic Strokes

For patients who have had an ischemic stroke or TIA in the past, the use of antithrombotic therapy is indicated for preventing recurrent ischemic events unless a contraindication exists. The choice of antithrombotic therapy should be an anticoagulant if a cardioembolic source is identified. Otherwise, the choice of antithrombotic therapy is generally an antiplatelet agent [93]. The selection of an antiplatelet medication should be made on the basis of its effectiveness, safety profile, cost, patient characteristics, and individual preferences. Here are a few regimens used in common practice:

- *Aspirin* has been shown to reduce the risk of a recurrent ischemic stroke by 22% [94]. The benefit of aspirin is highest in the immediate weeks following an incident TIA or ischemic stroke. It decreases the risk of a recurrent event by 58% in the first 6 weeks [95]. Aspirin is the most commonly used antiplatelet agent in secondary stroke prevention.
- *Clopidogrel*, a platelet ADP receptor antagonist, may be used instead of aspirin for those who are intolerant of the latter medication. No studies have compared clopidogrel to placebo for the prevention of stroke, but subgroup analyses of the CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events) trial suggest that it is probably as effective as aspirin [96].
- The combination of *aspirin and clopidogrel* may be considered for 90 days in patients who have had a recent ischemic stroke or TIA attributable to severe intracranial stenosis according to results extrapolated from the SAMMPRIS (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis) trial [97]. The primary endpoint of recurrent stroke or death in the medical arm of this trial was much lower than expected when compared to historical controls.
- The use of dual antiplatelet therapy (aspirin and clopidogrel) may be considered for 21 days if initiated within 24 hours after a minor stroke or high-risk TIA according to results of the CHANCE (Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events) and POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke) trials. The rate of recurrent stroke and major ischemic events was lower in the first 90 days when this regimen was used compared to aspirin monotherapy [98, 99].
- The combined long-term use of aspirin and clopidogrel, initiated after a remote stroke, does not offer greater benefit for stroke prevention than either agent alone, with increased rates of bleeding observed [100–102].
- The combination of *aspirin and dipyridamole* is shown to be at least as effective, if not more effective, than aspirin alone for secondary stroke prevention. However, its use is often limited by its side effect profile [93].
- *Cilostazol*, a phosphodiesterase 3 inhibitor, reduces the risk of a recurrent stroke by 42% compared to placebo in the Cilostazol Stroke Prevention Study [103]. This medication has been extensively studied in Japan, but its efficacy in non-Asian populations remains uncertain.

6 Conclusion

Ischemic stroke is generally considered a preventable disease. Risk factor modification includes optimal treatment of coexistent hypertension, hyperlipidemia, and diabetes [9, 16, 41]. It also entails adherence to a regular exercise regimen and healthy diet [6]. Those who smoke should be advised to quit, and those who consume alcohol should be asked to limit their intake to low or moderate amounts [6]. Individuals diagnosed with AF should be assessed for appropriateness to initiate oral anticoagulation [69]. In the absence of AF, routine use of antithrombotic medications is not supported in the context of primary prevention [6]. A strategy that includes a combination of pharmacologic and nonpharmacologic interventions for blood pressure lowering, lipid reduction, and glycemic control helps lower ASCVD risk and decreases the risk of first-ever ischemic stroke (Table 4). It is postulated that hypertensive intracerebral hemorrhages may share the same pathophysiologic mechanism as lacunar infarcts within the continuum of cerebral small-vessel disease [8]. Management of this entity should also include treatment of hypertension and diabetes, as well as smoking cessation [5]. For patients with a known history of ischemic stroke or TIA, an individual assessment to initiate antithrombotic therapy should be undertaken to minimize the risk of further events [93].

Table 4 Overall summary of recommendations for primary stroke prevention

Risk factor	Preventive recommendations
Hypertension	For individuals with clinical CVD or high ASCVD risk ≥10%, maintain long-term blood pressure goal of less than 130/80 [9] For individuals with no clinical CVD and low ASCVD risk <10%, maintain long-term blood pressure goal of less than 140/90 [9]
Dyslipidemia	Statins are the first-line agents for treatment of hyperlipidemia [16] Consider adding ezetimibe if LDL-C is not at goal while on maximally tolerated statins [16] Consider adding PCSK9 inhibitors if LDL-C is not at goal while on maximally tolerated statins and ezetimibe [16] Optimal LDL-C goal is based on individual risk profile [16] Icosapent ethyl may be used in statin-treated patients with elevated triglycerides and high ASCVD risk [29]
Diabetes mellitus	A HbA1c goal of <7% is reasonable for many adults [41] GLP-1RAs may be considered as part of the glucose-lowering regimen for patients with established CVD or high ASCVD risk [36]
Obesity	Weight loss is advised as a means to modify stroke risk factors [6]
Physical inactivity	Adults should engage in at least 150 minutes per week of moderate-intensity or 75 minutes per week of vigorous-intensity aerobic physical activity (or an equivalent combination of the two) [6]
Nutrition and diet	Individuals should adhere to the Mediterranean or DASH diet [6]
Tobacco use	Individuals should quit smoking [6]
Alcohol consumption	For individuals who choose to drink alcohol, consumption should be minimized to ≤2 drinks per day for men and ≤1 drink per day for nonpregnant women [6]
Atrial fibrillation	Oral anticoagulation should be initiated in patients with AF and an elevated CHA_2DS_2-VASc score of ≥2 in men or ≥3 in women [69] NOACs are preferred over warfarin for nonvalvular AF [69]

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Prevention of Cardiovascular Disease in Patients with Chronic Kidney Disease

Robin H. Lo and Richard J. Glassock

Summary

- Chronic kidney disease (CKD) is conventionally defined, graded, and diagnosed using glomerular filtration rate (GFR) and albuminuria (or other features of kidney injury), along with persistence for 3 months or more.
- CKD, so defined, is common, particularly in the elderly with comorbidities such as diabetes. Estimates of its global prevalence vary.
- The etiopathogenesis of CKD is extremely varied. Major subdivisions are diabetes- and nondiabetes-related CKD.
- Cardiovascular disease (CVD), in its many forms, commonly accompanies CKD, particularly in moderate to severe grades of CKD (GFR <45 mL/min/1.73 m^2) in older adults. The pathophysiology underlying CVD in CKD is complex and shares many features of CVD occurring in patients without CKD.
- Left ventricular hypertrophy and myocardial fibrosis are common with advancing grades of CKD contributing to risks of heart failure (HFrEF and HFpEF) and arrhythmias.
- Risk stratification for CVD in CKD is complex and still evolving. Most CVD risk equations do not include CKD as a risk variable. Many experts regard CKD as a coronary disease risk equivalent, like some define diabetes.

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- Primary prevention of CKD (and thereby reducing CVD risk) is possible but difficult to prove without long-term randomized clinical trials. Screening of asymptomatic persons at risk for CKD may allow for early detection of CKD and better success for secondary prevention.
- Secondary prevention of progression of CKD to higher grades will likely prevent CVD (in a primary or secondary way). Several successful strategies for secondary prevention of progressive CKD have also been shown to prevent CVD and its complications in randomized clinical trials.

1 Introduction

Chronic kidney disease (CKD) is most commonly defined in adults by a matrix of estimations or measurement of glomerular filtration rate (GFR) and signs of kidney injury (abnormalities of urinary albumin or protein excretion, urinalysis, imaging, or kidney biopsy) which persists for at least 3 months (see Fig. 1) [1]. The severity (and prognosis) of CKD is judged by categories of GFR and albuminuria. As such, CKD can be present with normal levels of GFR, but with increased albuminuria, and an abnormally low GFR can define CKD even in the absence of signs of kidney injury. So defined, CKD is relatively common (particularly in older adults), affects both genders and many ethnicities (preferentially racial minorities), and can in some cases progress to advanced kidney failure requiring dialysis or kidney transplantation. CKD is also associated with excess mortality and morbidity (especially that related to cardiovascular disease, CVD). It is crucial to recognize and appreciate that CKD is a "generic" term representing many individual diseases, often divided into diabetes-related and nondiabetic forms. Obviously, the nature of the disease underlying CKD has an important effect on the risks for and the kinds of CVD that develops before, concomitantly, or after development of CKD. The prognosis for "generic" CKD, illustrated by the colored "heat map" in Fig. 1, has been derived from large epidemiological studies that provide an "average" risk, which can vary considerably from specific disease to disease. For example, the risk of CVD for a given patient with type 2 diabetes or lupus nephritis with grade 3B CKD may not be the same, even after adjusting for age and other comorbidities as in a patient with the same grade of CKD due to IgA nephropathy or tubulointerstitial nephritis. It is not possible to structure this chapter around the specific diseases causing CKD, many of which are not preventable, so we will rely on the "generic" CKD concept, with full recognition of its limitations.

The cardiovascular diseases present in or developing after the recognition of "generic" CKD, so defined, are diverse and include coronary artery disease (CAD, also known as ischemic heart disease), congestive heart failure (either of the reduced or preserved ejection fraction varieties [HFrEF or HFpEF, respectively]), strokes

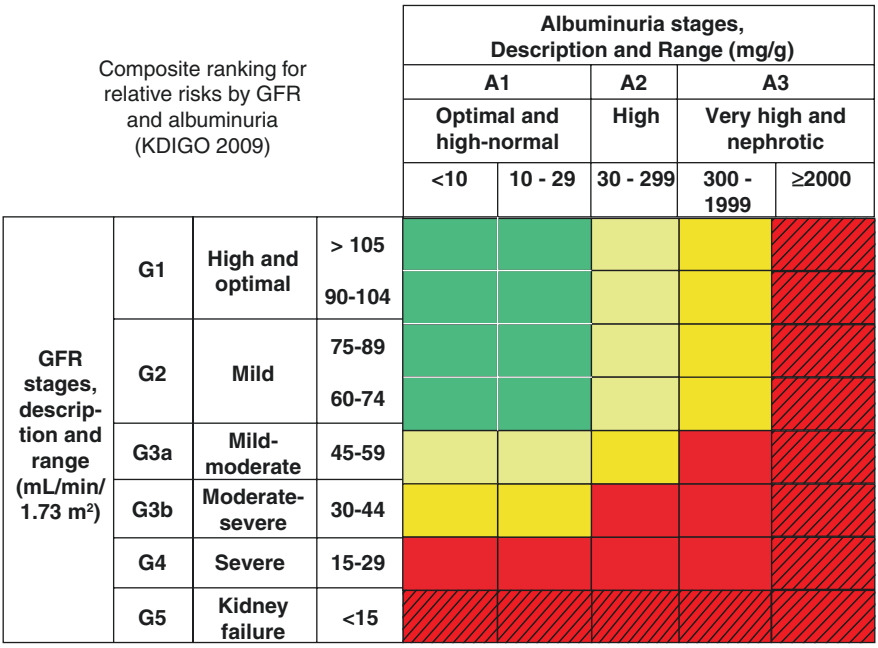

Fig. 1 The categorization of CKD and its prognosis using a 2 × 2 matrix of glomerular filtration rate (GFR – measured or estimated) and albuminuria (uACR – urine albumin-to-creatinine ratio). Green, no CKD; yellow, orange, and red, increasing levels of risk for adverse events, including CVD. (Reprinted from Summary of Recommendations Statements [`]. With permission from Elsevier)

Table 1 Prevalence of cardiovascular morbidities in patients with CKD vs. without CKD

Cardiovascular morbidity	With CKD (%)	Without CKD (%)
Any CVD	64.5	32.4
Coronary artery disease (CAD)	37.9	15.6
Acute myocardial infarction (AMI)	9.3	2.3
Heart failure (HF)	25.9	6.1
Valvular heart disease (VHD)	12.8	5.1
Cerebrovascular accident/transient ischemic attack (CVA/TIA)	16.1	6.7
Peripheral artery disease (PAD)	25.2	9.7
Atrial fibrillation (AF)	23.8	9.8
Sudden cardiac arrest/ventricular arrhythmias (SCA/VA)	4.1	1.4

US Renal Data System [8] - Medicare data

(hemorrhagic, thrombotic, or embolic), peripheral artery disease, valvular heart disease, and arrhythmias (sudden cardiac death and non-valvular atrial fibrillation) (see Table 1) [2]. The general topic of coronary artery disease in CKD has been of great interest for decades. A state-of-the-art review commissioned by the Kidney Disease: Improving Global Outcomes (KDIDO) was recently published [3] and is an

excellent source for contemporary information, unresolved issues, areas of controversy, and future research priorities.

The CVD events associated with CKD (co-incidentally or causally) can also be broadly divided into atherosclerotic and non-atherosclerotic forms. Death from CVD is a common event in patients with CKD, especially in the elderly, and commonly supervenes before CKD has progressed to an advanced stage requiring dialysis or transplantation for survival [4]. Cardiovascular mortality attributed to reduced GFR outnumbers deaths due to kidney failure (ESKD) globally [5].

The pathophysiology underlying the connections between CKD and CVD is complex and only partially understood [6]. Aging is one non-modifiable factor that underlies both CKD and CVD. The CKD-CVD connection involves accelerated atherogenesis, chronic extracellular volume expansion, intravascular pressure disturbances, dyslipidemia, accumulation of "uremic" toxins, hyper-homocysteinemia, hyperuricemia, disordered endocrine and hematological functions, and others. It is likely that CKD itself promotes CVD and CVD can be a cause of CKD; disentangling this "two-way street" in individual patients can be difficult and challenging, particularly among the elderly. Observational data showing an association between these two disease categories are confounded by this phenomenon. Nevertheless, opportunities exist for both primary and secondary prevention of CVD and its morbidity and mortality in patients with established CKD having a propensity for progression to ESKD.

This chapter will summarize the present state of these opportunities, with a focus on patients with mild to moderate CKD rather than very advanced CKD, requiring dialysis or transplantation. This chapter is not intended to be comprehensive but rather a pragmatic discussion of the topic.

2 Epidemiology of CKD and Its Association with CVD

2.1 General CKD and CV Mortality

In the 2019 US Medicare population (mostly over age 65 years), the prevalence of chronic kidney disease (CKD), using the Kidney Disease Improving Global Outcomes (KDIGO) definition specified above, was found to be 14.5%. In this same population, 67.5% of these CKD patients also shared a comorbidity of cardiovascular disease (CVD). In comparison, 35.5% of non-CKD patients were diagnosed with CVD [7]. The 2018 US Medicare dataset was further broken down into specific cardiovascular comorbidities. Coronary artery disease/acute myocardial infarction (CAD/AMI; 47.2%) was the most common CVD morbidity found among these CKD patients, followed by heart failure (HF; 25.9%), peripheral artery disease (PAD; 25.2%), atrial fibrillation (AF; 23.8%), cerebrovascular accident/transient ischemic attack (CVA/TIA; 16.1%), valvular heart disease (VHD; 12.8%), and then sudden cardiac arrest/ventricular arrhythmias (SCA/VA; 4.1%) (see Table 1) [8].

Worldwide, the prevalence of CKD in adults in a meta-analysis performed in 2016 by Hill et al. was found to be 13.4% (95% CI 11.7–15.1%), the majority of which was grade 3 CKD (7.6%; 95% CI 6.4–8.9%) [9]. One study estimates the global burden of cardiovascular disease attributable to impaired kidney function to be 25.3 million disability-adjusted life years [10]. Grade 3 CKD is found in about 0.7% in those 20–39 years of age and rises to 38% in those >70 years of age according to a national survey in the USA conducted in 1999–2004 [11]. (Note the definitions of CKD used in this survey may overestimate the prevalence of CKD in the elderly adult) [12].

Most recently, the Global Burden of Disease-CKD Collaboration has indicated a global prevalence of CKD in adults (all ages) to be about 9.1% or about 700,000,000 persons and the change of age-standardized prevalence over the past 27 years (1990–2017) to be about +2.8% – essentially unchanged. However, the prevalence of CKD varies quite widely from country to country. The global prevalence of end-stage kidney disease treated by dialysis or transplantation continues to rise, largely due to improved access to such treatment in less developed countries [9, 10].

Of note, several factors make the true prevalence of CKD difficult to ascertain in such epidemiological studies. Mild to moderate CKD is likely underestimated due to the asymptomatic nature of the disease, in studies examining volunteers or health records. This ascertainment bias is much less likely when population-based studies are used to estimate prevalence. Furthermore, estimates of prevalence are affected by choices and accuracy of biomarkers and formulas used to estimate glomerular filtration rate (GFR) or assess urinary albumin excretion rate. Using estimated rather than measured GFR itself, inter-assay reliability, failure to fully assess disease duration versus "one-off" testing, and using an absolute rather than age-adjusted threshold to diagnosis CKD all tend to overestimate CKD prevalence in the elderly (the same individuals who are at increased risk for CVD) and underestimate the prevalence of CKD in younger adults [12–14]. Thus, the true global prevalence of non-dialysis-treated CKD may be overestimated, perhaps by a factor of 2.

In summary, CKD is a common disorder, particularly in the older adult, and its age-standardized prevalence in the population of the world is relatively stable but variable between countries. As currently defined, CKD is also commonly associated with CVD, predominantly because of the shared predilection of both CKD and CVD to affect older and elder adults. Nevertheless, CVD is a significant contributor to overall causes of morbidity and mortality in CKD patients. CVD and cancer comprise the majority of the etiologies for death in overall CKD patients, at 30.2% and 31.9%, respectively. Among those with a GFR <60 mL/min/1.73 m^2 and grade 3 CKD patients specifically, CVD was the leading cause of mortality and only behind cancer and infection in grade 1–2 CKD patients [15]. The risk of cardiovascular events increases directly with albuminuria and inversely to GFR, with both albuminuria and GFR conferring independent risk to CV death relative to each other as well as to other traditional risk factors [16, 17]. In grade 3 CKD patients, CVD mortality was found to be about twice as high compared to individuals with normal kidney function (Tables 2 and 3) [16]. A further breakdown of CVD mortality

Table 2 Adjusted hazard ratio for death from any cause, cardiovascular events, and hospitalization according to the estimated GFR

	Adjusted hazard ratio (95% confidence interval) by estimated GFR (mL/min/1.73 m^2)				
Endpoint	≥60	45–59	30–44	15–29	<15
Death from any cause	1.00	1.2 (1.1–1.2)	1.8 (1.7–1.9)	3.2 (3.1–3.4)	5.9 (5.4–6.5)
Any cardiovascular event	1.00	1.4 (1.4–1.5)	2.0 (1.9–2.1)	2.8 (2.6–2.9)	3.4 (3.1–3.8)
Any hospitalization	1.00	1.1 (1.1–1.3)	1.5 (1.5–1.5)	2.1 (2.0–2.2)	3.1 (3.0–3.3)

Based on data from Ref. [17]
Adjusted for age, sex, income, education, use or nonuse of dialysis, and presence or absence of coronary heart disease, prior chronic heart failure, prior ischemic stroke or transient ischemic attack, prior peripheral arterial disease, diabetes mellitus, hypertension, dyslipidemia, cancer, a serum albumin level of 3.5 g per deciliter or less, dementia, cirrhosis or chronic liver disease, chronic lung disease, documented proteinuria, and prior hospitalizations

Table 3 Pooled adjusted hazard ratios for cardiovascular mortality according to estimated GFR from a meta-analysis

Estimated GFR (mL/min/1.73 m^2)	Hazard ratio	95% CI
120	1.00	0.90–1.11
105	0.86	0.77–0.96
90	1.08	1.02–1.14
75	1.01	0.88–1.15
60	1.40	1.25–1.57
45	1.99	1.73–2.28
15	2.66	2.04–3.46

Based on data from Ref. [16]
Adjusted for age, sex, ethnic origin, history of cardiovascular disease, systolic blood pressure, diabetes, smoking, and total cholesterol

showed ischemic heart disease to be leading cause of mortality, followed by strokes, heart failure, valvular heart disease, and then arrhythmia in descending order. Stroke mortality was more prevalent among mild stages of CKD, whereas HF and valvular heart disease mortality increased with more severe stages of CKD [15]. Sudden cardiac death is the leading cause of mortality in patients with dialysis-treated ESKD [18].

2.2 CKD and Coronary Artery Disease (CAD)

Several clinical studies have found reduced kidney function to be independently associated with an increased risk of CAD. In fact, the risk of myocardial infarction in patients with advanced CKD is similar to or greater than the risk in patients with

diabetes, such that some authors suggest CKD should also be considered a CAD risk equivalent [19, 20].

The Atherosclerosis Risk in Communities (ARIC) study examined a population of 14,971 men and women in the USA with grade 1–3 CKD over 12 years for de novo and recurrent events of coronary heart disease defined as myocardial infarction or coronary revascularization procedures. People with GFR equivalent to grade 3 CKD compared to no CKD had hazard ratios of 1.26 and 1.30 for de novo and *recurrent* events of coronary heart disease, respectively, and a hazard ratio of 2.4 for CAD mortality. Notably, the concurrence of anemia with grade 3 CKD greatly increased the risk for recurrent coronary heart disease up to a hazard ratio of 8.01 [21].

The Chronic Renal Insufficiency Cohort (CRIC) study examined a population of 1123 men and women in the USA with mild to moderate CKD (GFR 20–70 mL/min/1.73 m^2) for coronary artery calcification using electron beam or multi-detector computed tomography and found that 25.1% of patients had de novo calcification and 18.0% of patients had progression of calcification at the end of an average of 3.3-year follow-up [22]. The Assessing Diagnostic Value of Noninvasive Computerized Tomography-Derived Fractional Flow Reserve (FFRCT) in Coronary Care (ADVANCE) study also found differences in presentation of acute coronary syndrome in CKD patients, with those individuals with lower GFR tending to present more often with acute myocardial infarction than with stable angina (especially GFR < 45 mL/min/1.73 m^2, HR 3.82, CI 1.55–9.46) [23].

2.3 CKD and Congestive Heart Failure (CHF)

CKD and CHF are intimately related chronic disease epidemics, and determining which disease is primary versus secondary can often be difficult. The Atherosclerosis Risk in Communities study found the incidence rate of de novo HF in their CKD population to be 17–21%, with increasing incidence correlating with increasingly severe CKD [24]. An analysis of the Chronic Renal Insufficiency Cohort population demonstrated similar findings, although the correlation of CHF incidence and CKD was stronger using urine albuminuria and cystatin C-based GFR rather than creatinine-based GFR [25]. Multiple studies have found that reduced renal function is independently associated with increased overall mortality, cardiovascular mortality, and hospitalization in patients with CHF, regardless of preserved versus reduced ejection fraction status [26, 27].

2.4 CKD and Valvular Heart Disease

Valvular heart disease is more prevalent in the CKD population versus the general population, with mitral regurgitation being the most prevalent (43% vs. 24%), followed by aortic stenosis (9.5% vs. 3.5%), aortic regurgitation (19% vs. 10%),

and then mitral stenosis (2% vs. 1%). CKD patients demonstrated greater degrees of left atrial/ventricular dilation, left ventricular hypertrophy, and right ventricular systolic pressures on echocardiogram compared to the general population [28, 29]. Several studies have shown an independent association with increasing aortic valve calcification and decreasing GFR [28, 30, 31]; however, associations of mitral annular calcification and GFR were only observed with comorbid diabetes [31]. At every level of increasing severity of aortic stenosis and mitral regurgitation, CKD patients suffered greater mortality relative to their non-CKD counterparts [29].

2.5 CKD and Stroke

Kidney function is further inversely related to the incidence of stroke (including both ischemic and hemorrhagic forms), with a 43% higher risk of stroke for eGFR <60 mL/min/1.73 m^2. Hypertension, a crucial modifiable risk factor for stroke, is commonly associated with CKD and worsens with advancing disease, likely compounding the risk for stroke in CKD patients [32]. Among the measures of serum creatinine, cystatin C, and urine albumin for kidney function, increasing urine albumin has been demonstrated by several studies to have the strongest independent relationship with stroke risk [33, 34]. A nearly twofold increase risk of incident stroke has been demonstrated in individuals with moderate albuminuria (urinary albumin-creatinine ratio 30–300 mg/g) [32]. In one meta-analysis, the risk of hemorrhagic stroke was elevated even with small elevations in urinary albumin-creatinine ratio <30 mg/g, although this may not have been sufficiently powered due to the lower incidence of hemorrhagic strokes versus ischemic strokes (81% vs. 12%) [33]. The ARIC study additionally noted a marked increase of stroke risk in CKD patients comorbid with anemia, with a hazard ratio of 5.43 (95% CI 2.04–14.41) compared to CKD patients without anemia [34]. An increased risk of embolic stroke is associated with atrial fibrillation (see below).

2.6 CKD and Peripheral Arterial Disease (PAD)

Prevalence and incidence of PAD are higher in CKD populations compared to the general population. An analysis of the National Health and Nutrition Examination Survey (NHANES) estimated a prevalence of 24% of persons with ankle-brachial index <0.9 among those with creatinine clearance <60 mL/min/1.73 m^2 compared to 3.7% among those with creatinine clearance ≥60 mL/min/1.73 m^2 [35]. Similarly, the ARIC study observed a multivariable adjusted relative risk of 1.56 (95% CI 1.13–2.14) for incident PAD in CKD patients [36]. Women with CKD in particular have been found to have a higher incident risk of PAD compared to men, especially

at younger ages (age <40 years, HR 2.57, 95% CI 1.27–5.20) [37]. Albuminuria itself, independent of decreased GFR, has also been found to be associated with an increased risk of developing PAD [38], although there remains debate as to whether this association holds true for nondiabetic patients [39].

2.7 CKD and Non-valvular Atrial Fibrillation (AF)

Atrial fibrillation is the most common cardiac arrhythmia, constitutes a risk for embolic stroke, and has been shown by several studies to be associated with CKD. The CRIC study estimates that non-valvular AF is prevalent in one-fifth of the CKD population, a number replicated by the US Renal dataset Medicare population and which is about two- to threefold of the prevalence in the general population [40]. Furthermore, two prospective cohort studies further showed that the incidence of AF was independently increased in CKD populations with lower cystatin C-based GFR and higher urine albuminuria [41, 42]. The risk of embolic stroke from AF is further enhanced by the presence of CKD, with one study estimating a nearly 50% increase in the risk of ischemic (embolic) stroke or systemic thromboembolism in AF accompanied by CKD (HR = 1.49; 95% CI = 1.38–1.59) [43]. In addition, another study shows a higher stroke risk in CKD patients that develop incident AF versus CKD patients without AF (HR = 2.00; 95% CI = 1.88–2.14) [44]. The risk of total, ischemic, and hemorrhagic stroke is highest at the lowest eGFR and highest urinary albumin-to-creatinine ratio (uACR) with CKD, and the type of stroke differs by degree of decline in eGFR and uACR [45].

2.8 CKD and Sudden Cardiac Death (SCD)

The risk of SCD, normally defined as an unexpected circulatory arrest occurring within 1 hour of acute change of clinical status or unwitnessed death without an obvious noncardiac cause in a patient known otherwise to be well in the past 24 hours, has been shown to increase with declining kidney function [18, 46]. Sudden cardiac death is the most common cause of mortality in dialysis-treated ESKD, probably linked to a high prevalence of left ventricular hypertrophy in this population [18]. An analysis of the Multicenter Automatic Defibrillator Implantation Trial-II (MADIT-II) study described that for each 10 unit reduction in eGFR, there was an associated increase of risk of SCD by 17%. Interestingly, the study found that a survival benefit conferred by implanted cardioverter defibrillator (ICD) therapy was only demonstrated among patients with eGFR ≥35 mL/min/1.73 m^2, with no such survival benefit among patients with eGFR <35 mL/min/1.73 m^2 despite increased prevalence of SCD, suggesting increased resistance to ICD therapy with declining renal function [47].

3 The Pathophysiology of CVD in CKD

The interrelationships between CVD and CKD are complex and multifactorial. Figure 2 graphically displays the major players. Not all of these will be discussed here. The pathophysiology can be broadly subdivided into proatherogenic factors and non-atherogenic factors, although there is overlap between these two categories (see Table 4). Diabetes, particularly type 2 with obesity or the metabolic syndrome, is a very important cause of the coexistence of CVD and CKD. Heart failure and ischemic heart disease are quite common in patients with CKD due to diabetes.

Dyslipidemia Among the proatherogenic factors, dyslipidemia is very important [48]. Dyslipidemia is quite common in CKD and relates to underlying diabetes in many cases and due to nephrotic syndrome or other nondiabetic forms of CKD in others. The patterns of dyslipidemia seen in patients with CKD depend on grade of disease (as assessed by estimated GFR), the degree of proteinuria (albuminuria) concomitantly present, and the existence of complicating inflammation/malnutrition and the presence or absence of diabetes [49]. In patients with advanced CKD and no or only mild proteinuria, the pattern is one of elevated triglycerides, increased very-low-density lipoprotein (VLDL), increased intermediate-density lipoproteins (IDL), increased oxidized lipids, elevated non-high-density lipoproteins (non-HDL), variable high-density lipoprotein (HDL), and an increase in highly

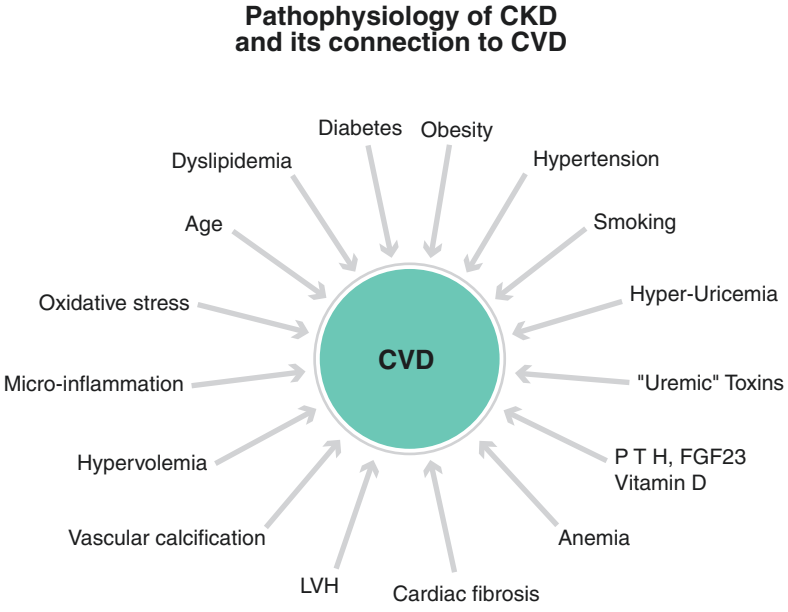

Fig. 2 Factors that operate in the linkage between CKD and CVD. (CKD chronic kidney disease, CVD cardiovascular disease, LV left ventricular hypertrophy, PTH parathyroid hormone, FGF23 fibroblast growth factor-23)

Table 4 Proatherogenic and non-atherogenic factors operating in the association of CVD with CKD

Proatherogenic:
Obesity and diabetes
Dyslipidemia
Hypertension
Micro-inflammation
"Uremic" toxins (ADMA)
Hyperuricemia
Smoking
Diet (high saturated fat, high carbohydrate (fructose), high sodium, low plant sources of protein)
Inactivity
Non-atherogenic:
Chronic volume expansion
Left ventricular hypertrophy and cardiac fibrosis
Anemia
Vascular calcification
Hormonal disorders (PTH, FGF23, Klotho, vitamin D)
Electrolyte disorders (especially potassium and arrhythmias)

atherogenic small dense low-density lipoproteins (LDL) [48–51]. In patients with CKD accompanied by substantial proteinuria (including nephrotic syndrome), the pattern is one of elevated total cholesterol, increased LDL, and variable HDL levels. Hypertriglyceridemia and hyperchylomicronemia can be seen in severe nephrotic syndrome [51, 52]. The molecular and metabolic disturbances underlying these patterns of dyslipidemia in CKD have been extensively reviewed by Moradi and Vaziri [50] and will not be recounted in detail here. However, the dyslipidemia seen in CKD contributes to the excess of atherosclerotic CVD observed in patients with CKD, of diverse etiology. Paradoxically, decrements in non-HDL and non-HDL/HDL ratio in advanced CKD treated by dialysis are associated with an increased CVD mortality rather than the converse seen in the general population [53], perhaps due to complicating malnutrition/inflammation.

Hypertension and Hypervolemia Elevations of systolic (and diastolic) blood pressure and pulse pressure are commonly seen in various forms of progressive CKD (except those characterized by salt-losing states) [54]. A progressive increase in extracellular volume accompanied by incomplete suppression of the renin-angiotensin-aldosterone axis is likely the cause of CKD-associated hypertension [55]. An increase in centrally driven sympathetic nervous system activity also contributes to elevated arterial pressure and peripheral resistance in CKD [56]. Systolic arterial hypertension is also abetted by a decrease in vascular compliance, perhaps related to collagen cross-linking and calcification of the media seen in progressive CKD (see below) [57]. The increased systemic arterial blood pressure and expanded extracellular fluid volume promote both atherogenic CVD (ischemic heart disease,

peripheral arterial disease, and thrombotic stroke) and left ventricular hypertrophy, leading to congestive heart failure with reduced ejection (HFrEF) fraction and arrhythmias, such as atrial fibrillation. Cardiac fibrosis is augmented by prolonged hypervolemia, especially in the presence of poorly suppressed aldosterone, and this can lead to heart failure with a preserved ejection fraction (HFpEF) [58], more commonly seen in CKD than in the general population. Prolonged hypertension in CKD is also responsible for an increase in risk of hemorrhagic stroke. The anemia of advanced CKD also contributes to left ventricular remodeling in CKD [59].

Uremic Toxins and Hormonal Factors A panoply of "uremic toxins" accumulates in advancing CKD, such as asymmetric dimethyl arginine (ADMA), advanced glycation end products (AGEP), trimethylamine N-oxide (TMAO), and others (such as indoxyl sulfate, hyper-homocysteinemia, hyperphosphatemia) [60–62]. These substances can lead to myocardial and vascular injury (endothelial damage). The hormonal profile is altered in CKD, with increases in parathyroid hormone and fibroblast growth factor 23 and reduced α-Klotho generation, which collectively can have adverse direct effects on the myocardium and vessels [63–65]. α-Klotho is a novel glucuronidase transmembrane enzymatic protein with important "anti-aging" properties. It also serves as a cofactor for FGF-23 action. The reduction of serum α-Klotho levels seen in CKD might contribute to "premature aging" and accelerated arteriosclerosis/atherosclerosis. Marinobufagenin levels are increased in CKD and can promote cardiac fibrosis [66]. Disturbances leading to impaired Klotho generation in CKD can promote cardiac TGF-β signaling and cardiac fibrosis [67]. Decreases in active vitamin D (1,25-dihydroxyvitamin D) in CKD can have adverse effects on the coronary circulation and myocardium [68]. Loss of endogenous erythropoietin participates in the development of anemia in CKD, which can have adverse effects on the heart and circulation in general [69]. Hyperuricemia is another factor that can contribute to CVD accompanying CKD (see below).

Vascular Calcification Patients with progressive CKD, particularly its later stages, can be affected by a process of vascular (arterial) calcification, involving large- and medium-sized arteries (including coronary arteries) and heart valves (mitral and aortic) [57]. This process is an active one, involving modifications in arterial smooth muscle biology [57]. It predominantly affects the tunica media (Monckeberg's sclerosis) and leads to impaired relaxation and reduced vascular compliance. In advanced forms, it can produce a calcific uremic arteriopathy with ischemia and necrosis of the skin (calciphylaxis) [70]. The calcific deposits in the media have a chemical composition resembling bone (hydroxyapatite). The calcific deposits in atherosclerotic plaques have a different composition and clinical significance (see below).

Chronic Inflammation and Enhanced Oxidative Stress For poorly understood reasons, most forms of CKD (diabetic and nondiabetic) are associated with features of chronic inflammation (such as manifested by increased C-reactive protein and/or Il-6 serum levels) and increased oxidative stress [71, 72]. The cytokine milieu and/

or uremic toxin burden (e.g., indoxyl sulfate levels) underlying this phenomenon can have profound effects on atherogenesis, by causing proatherogenic changes in blood lipids (such as oxidized LDL and HDL transformation to an atherogenic lipid) [73]. These changes may account in part for the enhanced risk of CVD in CKD.

4 Risk Stratification for CVD in CKD

There is little doubt that CKD is associated with an excess risk of morbidity and mortality from CVD. The factors relevant for risk stratification in CKD are summarized in Table 4. The risk of coronary artery disease (and heart failure) increases as CKD progresses to more advanced grades, despite correction for traditional CVD risk factors [74]. Go and colleagues were among the first to quantify the risk of CVD events (mortality and hospitalization) in a large cohort (1,120,295 subjects; mean age 52 years, 55% women) reported in 2004 [17]. There was a graded increase in CVD risk when eGFR fell below 60 mL/min/1.73 m^2, but the most significant increases in risk were seen when eGFR fell below 45 mL/min/1.73 m^2. Any increase in CVD risk in grade 1 or 2 CKD (and possibly grade 3 CKD) is largely related to proteinuria (albuminuria), not GFR. Subsequently, many other studies showed an excess risk of CVD and all-cause mortality in older adults when eGFR fell below 45 mL/min/1.73 m^2 (see Fig. 3), only a few of which are cited here [75, 76]. This association was particularly evident when albuminuria was present. Brantsma et al. using data from the PREVEND study in the Netherlands found that stage 1 and 2 CKD (characterized chiefly by abnormal albuminuria) have a greater risk of CVD than stage 3 CKD (chiefly characterized by abnormal GFR) [77]. Increased urinary albumin excretion, even close to the high normal range (10–30 mg/day), has been repeatedly shown to augment CVD risk [78]. Prediction of CVD risk in community-dwelling older adults without clinical evidence of CVD using combinations of eGFR and albuminuria was studied by Nerpin et al. in the USLAM study in Sweden [79]. They found that both uAER >8.6 mg/d and an eGFR <45 mL/min/1.73 m^2

eGFR, mL/min/1.73 m^2	Age: <60		Age: 60–70		Age: >70	
	ACR <30 mg/g	ACR ≥30 mg/g	ACR <30 mg/g	ACR ≥30 mg/g	ACR <30 mg/g	ACR ≥30 mg/g
>100	1.20 (0.95–1.52)	2.49 (1.77–3.49)	1.12 (0.97–1.38)	1.78 (1.29–2.45)	0.87 (0.67–1.12)	1.57 (1.07–2.31)
80–100	1.00 (reference)[a]	2.02 (1.36–3.01)	1.00 (reference)[a]	2.28 (1.79–2.91)	1.00 (reference)[a]	1.69 (1.42–2.00)
60–80	1.58 (1.17–2.12)	2.28 (1.40–3.73)	1.12 (0.94–1.34)	1.92 (1.46–2.53)	1.13 (1.01–1.26)	1.88 (1.60–2.12)
45–60	2.11 (1.23–3.61	4.00 (2.13–7.51)	1.47 (1.08–1.99)	3.21 (2.32–4.43)	1.48 (1.28–1.70)	2.38 (2.00–2.84)
<45	2.96 (0.94–9.30)	6.80 (4.08–11.3)	2.59 (1.64–4.08)	7.13 (5.36–9.50)	2.22 (1.84–2.67)	3.71 (3.12–4.42)

[a] Incidence rate ratio; relative to reference group for each age strata.
Color coding for relative risk of all-cause mortality: green, <1.5; yellow, > 1.5 and <2. 5; orange, >2.5 and <4.0; red, >4.0. Color version available online.

Fig. 3 The association of CKD (according to eGFR and albuminuria) and all-cause mortality (predominantly CVD – related to eGFR and albuminuria uACR) in various age groups. Values shown are incidence rate ratios for all-cause mortality. (Green, <1.5; yellow, >1.5 < 2.5; orange, >2.5 < 4.0; red, >4.0). (Reprinted from Warnock et al. [75]. With permission from Karger Publishers)

improved the integrated discrimination index for CVD mortality prediction. Interestingly, the eGFR prediction was only significant when it was based on cystatin C but not creatinine-based formulas [79]. This is most likely due to the impact of micro-inflammation (see above) elevating serum cystatin C levels rather than greater accuracy of eGFR-cystatin C for assessment of true measured GFR [80]. The conclusion is that the presence and magnitude of albuminuria is more important for risk prediction of CVD in CKD and that the risk of CVD events is mostly associated with eGFR creatinine levels below 45 mL/min/1.73 m^2 in older adults. The rate of decline of GFR over time is another factor to consider in risk stratification for CVD in patients with CKD. Monitoring the change in eGFR over time seems to improve CVD prognostication [81].

As stated above, most (but not all) of the excess risk for CVD in CKD is captured by traditional approaches to quantifying risk according to multivariable risk equations (such as Framingham or the ACC/AHA pooled risk scoring formulas) [74]. Indeed, Clase and coworkers found that the addition of uACR or eGFR values to traditional risk scoring led to no meaningful change in the proportion of patients assigned to an intermediate-risk category among a cohort of patients older than 55 years with documented CVD [82]. On the other hand, addition of eGFR and uACR has a profound impact on classification of risk for ESKD [83], irrespective of age, when the competing risk of mortality is taken into consideration. Di Angelantonio et al., in a prospective population-based cohort study (n = 16,958, ages 31–81 years) without known CVD, found that the addition of CKD information to traditional CVD risk assessment had only a modest effect on reclassification of risk [84]. The incremental gain provided by adding CKD to risk assessment was less than that provided by diabetes or smoking status. Importantly, most of the CVD risk prediction algorithms in common use do not include eGFR, albuminuria, or CKD. Only the UK QRISK-2® includes CKD (grades 4 and 5 only; eGFR <45 mL/min/1.72 m^2) [85].

The controllable traditional factors associated with CKD that have a powerful impact on CVD risk (including ASCVD, stroke, heart failure, and arrhythmias) include hypertension, dyslipidemia, obesity (and metabolic syndrome), diabetes (and glycemic control), and smoking. Age, gender, family history, and ancestry also contribute to CVD risk but mostly independent of CKD status. Of course, both CKD and CVD are diseases that preferentially affect older adults, and these traditional risk factors are operative in non-CKD-associated CVD covered by other chapters in this manual.

Nontraditional CVD risk factors observed in subjects with CKD include high-sensitivity C-reactive protein (hsCRP) and interleukin 6 levels (as a feature of chronic inflammation), volume overload, anemia, vascular calcification, vitamin D deficiency, hyper-homocysteinemia, hyperuricemia, vitamin K deficiency, oxidative stress, uremic toxins (such as ADMA and TMAO levels), parathyroid hormone (PTH), fibroblast growth factor-23 (FGF-23) levels, and Klotho deficiency [63, 86–89]. These toxins and other molecules may bias the results of estimating GFR [86]. Paradoxically, some reports suggest that an increase in eGFR, seen in early diabetes and in excessive protein intake, may be associated with increased risk of

CKD/CVD [89], but the mechanisms underlying this association are unclear. Cardiac biomarkers, such as cardiac troponin-T and NT-proBNP, may have application for better risk classification in patients with CKD [90]. Many of these nontraditional risk factors for CVD in CKD are the subject of ongoing research aimed at improving the accuracy of prediction of CVD risk in CKD. Some of these may have obvious preventative strategic importance in the future.

Coronary artery calcification (CAC) is common in CKD and increased in frequency and severity as CKD progresses [91]. Patients on long-term dialysis (survivors) tend to show progressively increasing degrees of CAC, which, paradoxically, might suggest a "protective effect" of such calcification [92]. Assessment of the coronary arterial calcium (CAC) score may play a useful role in assessing overall CVD risk in selected patients with CKD, perhaps in helping to inform on decisions for certain therapies (e.g., statins) [93], but it is unknown if treatments designed to prevent or cause regression of vascular calcification are beneficial, and there are no guidelines recommending repeating CAC scoring to evaluate the effects of therapy. Other nontraditional risk factors for CVD have not been adequately studied prospectively in CKD.

Left ventricular hypertrophy (LVH) is common in CKD and tends to increase in frequency and severity as CKD progress, mediated by volume expansion and poorly controlled hypertension [94, 95]. Such LVH increases the risk of heart failure, sudden cardiac death, and atrial fibrillation. Assessment of LVH by cardiac ultrasound or MRI can be a useful tool in evaluating non-atherogenic CVD risk [94]. Standard EKG assessment of LVH may be too insensitive for this purpose but is required for accurate diagnosis of atrial fibrillation and embolic stroke risk assessment.

5 Strategies for Prevention of CVD in Non-dialysis CKD

Primary Prevention of CKD In an ideal world, the best strategy to reduce the burden of CVD associated with CKD is to prevent the development of CKD in the first place (primary prevention). This is easier said than done. It seems reasonable to postulate that a reduction in the prevalence of visceral obesity and the incidence of type 2 diabetes mellitus as well as earlier detection and better management of hypertension and diabetes in the general population will ultimately reduce the incidence and prevalence of CKD.

Moderate exercise, caloric moderation, lower salt intake, smoking cessation, and perhaps a diet rich in plants and fiber might accomplish this goal, but this requires a commitment of society to move away from Western diets, high in processed foods, refined sugars, salt, and animal-based protein, particularly processed or unprocessed red meat [96, 97]. Avoidance of high protein intake might have salutary effects on the incidence of CKD, particularly in individuals born with a nephron deficiency consequent to low birth weight, due to fetal dysmaturity, or who have congenital or acquired single kidneys (see also below) [98]. The frequency of low birth weight and nephron deficiency varies widely, largely due to differences in prenatal care and

maternal nutrition. The impact of long-term high protein intake on incident CKD is controversial (see above) [99]. Unfortunately, long-term randomized trials have seldom been conducted with incident CKD as an endpoint, so prevention of CKD by means of lifestyle changes, while challenging, should not be dismissed. Elimination of smoking would also likely have a beneficial impact on both CVD and CKD [100].

Detection and control of elevated blood pressure is commonly touted as a tool for reducing the incidence of CKD and its progression to kidney failure [101, 102]. This proposal assumes that increased BP above some arbitrary threshold is causally related to the development of CKD. While this may be true for a subset of patients with very severe ("malignant") hypertension, evidence exists to support the notion that CKD, often in subtle difficult-to-detect forms, causally underlies most forms of primary hypertension. Hypertension and its control appears to be an important player in the progression of established CKD, although it is difficult to tease apart the direct (non-antihypertensive) effects from the blood pressure-lowering effects of commonly used antihypertensive drugs on progression of CKD. Nevertheless, blood pressure above the normal range is an important causal factor in the generation of ASCVD and heart failure, with or without CKD [102].

The Systolic Blood Pressure Intervention Trial (SPRINT) of hypertension treatment in older, nondiabetic adults at moderate to high CVD risk is quite informative [103]. Intensive systolic blood pressure control (to <120 mmHg) did not prevent incident CKD (according to new-onset eGFR <60 mL/min/1.73 m^2 or new-onset albuminuria); instead, it was associated with acute reductions in eGFR that were largely reversible upon discontinuation of therapy. Unfortunately, the follow-up was short (only 3.26 years), and severe hypertension (systolic blood pressure > 180 mmHg) was an exclusion criterion. The benefits of intensive blood pressure control on CVD were attenuated in those subjects with CKD at baseline, which comprised 28% of the randomized subjects and was usually grade 3 or less. Abnormal albuminuria was modest or absent in the patients randomized (uACR = 44 ± 160 mg/gm). The HR for the primary outcome in patients with CKD at baseline was 0.82 (95% CI = 0.63–1.07), however, demonstrating the benefit of intensive BP control in such patients for reducing CVD events. Additionally, recent very large observational epidemiological studies have shown that higher systolic blood pressure (>130 mmHg) are associated with (but not necessarily causal for) a higher risk of incident grade 3–5 CKD [104].

In summary, many CVD benefits (largely due to the avoidance of the primary outcomes of stroke and heart failure) accrue when blood pressure is strictly controlled in the absence of overt CKD, but whether control of hypertension per se will reduce incident CKD remains uncertain. The impact of aggressive blood pressure control on CVD in CKD remains controversial, but reduced stroke burden is one possible favorable outcome. The exact target blood pressure appropriate for patients with CKD for secondary prevention of CVD is not fully agreed upon, but a systolic pressure somewhere between 120 and 130 mmHg systolic seems reasonable [101, 105–107]. The selected values may depend on the method of measuring blood pressure (office, home, ambulatory monitoring) [101, 107]. The J-shaped relationship of blood pressure and CV morbidity and mortality seen in CKD patients (particularly

in advanced grades of CKD) is in part explained by the concomitant malnutrition/micro-inflammation commonly observed in CKD [104, 106].

Angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB), also known as renin-angiotensin system inhibition (RASi), are effective in slowing progression of established CKD, when abnormal albuminuria is present [108, 109], especially in diabetic subjects, but their effectiveness in primary prevention of CKD is unknown.

Many forms of nondiabetic CKD have a low potential for primary prevention, particularly when genetic mutations or autoimmunity is the underlying cause. Forms of CKD due to environmental factors, such as nephrotoxins or infections, are potentially preventable. Avoidance, treatment, or prophylaxis of infections known to induce CKD and avoidance of nephrotoxins (like adulterants in herbal medicines, toxic pesticides, air pollution, drugs, cigarette smoke) that can injure the kidneys [97–100, 110–112] can be an important feature of CKD prevention. These precepts are especially true in the neonate and infant and in the elderly population. The issues surrounding prevention and control of CKD are different for developed nations compared to low- to medium-income countries [111, 112]. Adequate maternal health and nutrition are commonly overlooked aspects of CKD prevention [111]. Poor maternal health and nutrition can be a cause of fetal dysmaturity leading to low birth weight and prematurity, both of which predispose to low nephron endowment (congenital nephropenia) (see above) [111]. Nephropenia at birth is an important and under-appreciated preventable cause of the later development of CKD. Improved prenatal care and adequate maternal nutrition can reduce the prevalence of low birth weight and prematurity and thus avoid congenital nephropenia and its expected adverse effect on CKD later in life. Acute kidney injury (AKI) can be an antecedent to incident CKD, so avoidance of all kinds of AKI, such as by minimization of nephrotoxins, and meticulous postoperative management will likely have a salutary effect on new-onset CKD [113]. A healthy lifestyle in general can have potential for reducing the rate of incident CKD [100].

Screening for CKD By definition, screening for CKD in the general (apparently healthy) population by assessment of eGFR and/or albuminuria will have no *impact* on primary prevention of CKD; however, it might have a beneficial impact on secondary prevention of CKD progression or primary/secondary prevention of CVD, if early detection can be translated into effective treatment for CKD that delays its progression or leads to effective or even curative treatment [114] for underlying CKD that decreases morbidity and mortality directly related to CVD. Screening for disorders that increase risk of developing CKD, such as diabetes and obesity, might help in the primary prevention of CKD (and thereby CVS), but unfortunately we lack the long-term randomized controlled data to evaluate the utility of such population-based screening. Thus, most preventative disease organizations do not currently recommend population-based screening for CKD [115, 116]. Targeted screening of those at highest risk for CKD (diabetes, obesity, hypertension, and family history of kidney diseases) is presently advocated by many kidney disease organizations, but formal proof of the long-term benefits and lack of harms of such

targeted screening is still lacking [115, 116]. Early detection and increased societal awareness of CKD were prominent themes of the 2020 World Kidney Day, endorsed by numerous nephrology organizations.

Secondary Prevention of Progression in established CKD As described previously, patients with established diabetic or nondiabetic CKD have a tendency to progress to kidney failure (grade 5 CKD; previously known as ESKD) at variable rates, and they may present with no obvious clinical features of underlying CVD, atherosclerotic or non-atherosclerotic. There is great potential for both secondary prevention of progressive CKD and primary/secondary prevention of CVD in such patients [4]. Since advanced forms of CKD are often regarded as a "coronary artery disease risk equivalent" [117, 118] like certain people with diabetes, the characterization of interventions directed at CVD as primary or secondary in nature is often blurred (see Table 5 for a summary of the status of pharmacological interventions in patients with CKD designed to prevent CVD).

Table 5 Pharmacologic interventions for prevention of CVD and its complications in patients with CKD

Established:
Renin-angiotensin system inhibition (RASi; angiotensin-converting enzyme inhibitors or angiotensin receptor blockers – especially in type 1 and type 2 diabetes with abnormal albuminuria)
Beta-blockers for HFrEF with eGFR <30 mL/min/1.73 m^2
Sodium-glucose cotransporter-2 (SGLT2i; empagliflozin, dapagliflozin, canagliflozin), in type 2 diabetes with overt albuminuria, or possibly nondiabetic CKD with overt proteinuria (other than ADPKD or vasculitis) and/or HFrEF with eGFR >30 mL/min/1.73 m^2
Statins (with or without ezetimibe): in diabetes- or nondiabetes-associated CKD not requiring dialysis
Glycemic control (with metformin or glucagon-like peptide receptor 2 agonist; GLP-1) or thiazolidinedione agents (pioglitazone) in type 2 diabetes, but not intensive (HbA 1C of 6.5–7%)
Hypertension control (especially with RASi); target blood pressure 130/80 mmHg
Anticoagulants (warfarin, novel oral anticoagulants) – for non-valvular atrial fibrillation – in patients with mild to moderate CKD, but bleeding risk and calciphylaxis (with warfarin) of concern
Not yet fully established:
Anti-thrombotic agents (aspirin, clopidogrel) – bleeding risk
Hypouricemic agents (allopurinol, febuxostat)
Anemia management (iron or erythropoietin)
Fibric acid derivatives (gemfibrozil, fenofibrate)
Omega-3 fatty acids (eicosapentaenoic acid)
Pro-protein convertase subtilisin/kexin type 9 inhibitors (PCSK9i; evolocumab, alirocumab)
Novel hypolipidemic agents (bempedoic acid, apabetalone)
SGLT2i (in nondiabetic CKD)
Anticoagulants in non-valvular atrial fibrillation and prevention of stroke in dialysis-dependent kidney failure

In general, strategies that slow or prevent the progression of CKD to higher grades or kidney failure also lower morbidity and mortality of CVD. The following paragraphs summarize the current status of pharmacologic and non-pharmacologic interventions in patients with established CKD to slow progression and/or reduce the risk of CVD morbidity or mortality.

5.1 Interventions in Established CKD That Slow Progression or Reduce CVD Risk or Both

RAS Inhibition As a result of the Captopril, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL), and Irbesartan in Diabetic Nephropathy (IDNT) Trials, among others, we are quite confident that intervention with RASi in established diabetic CKD (both type 1 and type 2 diabetes) can both slow progression of CKD (decreasing the rate of doubling of serum creatinine or developing kidney failure) and reduce CVD complications [108, 109, 119, 120]. Similar data that exist for nondiabetic CKD are also present, but the impact of RASi on progression of CKD may be disease dependent and highly variable [109]. Importantly, the extent of benefit is related both to *persistent* lowering of blood pressure and independently to the *persistent* reduction of albuminuria. The use of these agents for "reno-protection" and "cardio-protection" may also be applicable to many cases of nondiabetic CKD, when moderate to severe proteinuria (albuminuria) is present but the controlled trial evidence is much weaker.

In the SPRINT trial [103] mentioned above (where most patients were given RASi for blood pressure control), there were no reno-protective effects of intensive blood pressure control in patents with CKD at baseline, and, as stated previously, the cardio-protective effects of intensive blood pressure management were blunted considerably in patients with CKD at baseline. Combinations of RASi with dihydropyridine calcium channel blockers (CCB) are particularly effective and well tolerated for slowing CKD progression and reducing CVD incident events as shown by the ACCOMPLISH trial, despite a paradoxical tendency for increased urinary albumin excretion with such regimens [121, 122]. Direct renin inhibitors may have safety issues, such as hyperkalemia [123]. The safety profile of ACEi and ARB is quite favorable, but patients may initially manifest a decrement of GFR which is an expected consequence of their hemodynamic effects. Hyperkalemia may become an issue in more advanced CKD, but this can often be managed by concomitant oral administration of potassium-binding resins such as kayexalate [124]. A rise in serum creatinine levels (up to about 15% from baseline) can frequently be seen during the early phases of treatment with RASi. This is a reversible hemodynamic effect that usually indicates a favorable long-term response to treatment with this class of agents.

The combination of a neprilysin inhibitor (sacubitril) to an angiotensin receptor blocker (valsartan) has been shown to have clinical efficacy (compared to valsartan

alone) in NYHA class II–IV heart failure for secondary prevention of heart failure events in HFrEF but not in HFpEF [125, 126]. About 36% of the subjects randomized to the HFrEF trial had preexisting CKD, and worsening of eGFR occurred less commonly with the sacubitril-valsartan combinations than valsartan alone. A preliminary analysis of this data shows that the sacubitril-valsartan combination slows the rate of progression of CKD compared to valsartan alone (presented at ASN meeting in 2019). The effects of the combination agent on heart failure-related events were not different in those with or without CKD at baseline. Thus, this combination may have beneficial effects on "progression" of CKD, but this has not yet been formally tested in a prospectively designed trial with "hard" CKD endpoints (doubling of serum creatinine or kidney failure). The effects of the sacubitril-valsartan combination on albuminuria needs further study. The combination of sacubitril and valsartan had no different effects on albuminuria compared to irbesartan [127]. To date, there have been no "head-to-head" trials of the sacubitril-valsartan combination versus SGLT2 inhibitors in patients with CKD with or without diabetes.

The target blood pressure associated with maximum benefit (all-cause mortality and/or reduction in CVD events) and safety in patients with established CKD is not well understood. Aggarwal and coworkers conducted a systematic analysis of pooled data from four randomized clinical trials (AASK, ACCORD, SPRINT, and MDRD) that included subjects with CKD (diabetic or nondiabetic). An intensive target of <130 mmHg systolic was associated with a reduction in all-cause mortality when compared to a target of <140 mmHg but only in those with grade 3 or greater CKD who were not undergoing intensive glycemic control as an aspect of management of comorbid type 2 diabetes [128]. However, the ACC/AHA blood pressure guidelines call for a target BP of <130/80 mmHg in persons with CKD [129].

Beta-Blockers for Congestive Heart Failure Moderate to severely reduced GFRs are commonly found in patients with congestive heart failure, both HFrEF and HFpEF types. A comprehensive meta-analysis of RCTs examining beta-blockers for HFrEF (with normal sinus rhythm) has shown a benefit of these agents in terms of improved mortality rates in subjects with eGFRs of 30–59 mL/min/1.73 m^2 [130]. Too few subjects with eGFR <30 mL/min/1.73 m^2 were enrolled in the included trials for analysis. Mortality was not affected by the use of beta-blockers in HFrEF when atrial fibrillation was present, regardless of the level of eGFR (see below).

Statins and Other Hypolipidemic Agents Statins generally have little or no impact on rates of progression of established CKD, although some studies with atorvastatin have shown some improvement in the rate of decline in eGFR [131]. Statin therapy is useful for prevention of ASCVD in non-dialysis-dependent CKD [132–134]. Statin therapy, when begun after dialysis therapy is required for ESKD, has no beneficial effects on CVD, despite substantial (35–40%) decline in LDL cholesterol (LDL-C) levels from baseline as shown by the 4D (atorvastatin) and AURORA (rosuvastatin) trials [135, 136]. The reason for the failure of stains to modify risk of ASCVD in kidney failure treated by dialysis is unknown but might have been due to

the unique nature of the dyslipidemia in advanced CKD [134] or to the requirement for much lower levels of LDL-C to show a benefit [137]. In addition, vascular calcification in the media in CKD rather than atherosclerosis per se might be a partial explanation for the limited efficacy of statins in more advanced CKD, including ESKD (see "Pathophysiology" above).

However, the Study of Heart and Renal Protection (SHARP) trial involving 3023 subjects with dialysis-dependent CKD and 6247 with non-dialysis-dependent CKD (all with eGFR <60 mL/min/1.73 m^2) allocated to a placebo or a simvastatin-ezetimibe combination showed beneficial effects on a composite CVD endpoint after a follow-up of 4 years [138]. The serum LDL cholesterol level decreased from 109 to 70 mg/dL in the active treatment group (a 36% decrease). The relative risk of a composite of major nonfatal ASCVD events decreased by 17% in the active compared to the placebo group overall, but no benefits were seen in the dialysis-dependent group. There was a (nonsignificant) trend toward greater benefit with higher eGFR and/or albuminuria at baseline. No benefits were seen in CVD or all-cause mortality. The treatment was generally well tolerated. The main benefits were a reduction in nonhemorrhagic stroke (risk ratio = 0.71; 95% CI = 0.57–0.92) and in coronary revascularization procedures (risk ratio = 0.71; 95% CI = 0.59–0.90). There was no evidence of a slower rate of CKD progression in the actively treated group. This and other studies have led to the general recommendation, further endorsed by the ACC/AHA 2018 cholesterol management guideline [139] that patients with non-dialysis CKD may receive statin therapy, regardless of the level of plasma LDL-C. The consensus is that patients receiving dialysis should not start statins, but if they are receiving statins, they may be continued, if tolerated. The specific question of whether adding a statin in patients with kidney failure (ESKD) who experience a new acute myocardial infarction or nonhemorrhagic or embolic stroke would lead to clinically meaningful benefits was not addressed by the SHARP trial. This requires further study, but many experienced clinicians would begin statin therapy in these circumstances, even in subjects on dialysis.

The impact of other hypolipidemic agents on CVD in patients with pro-protein convertase subtilisin/kexin 9 (PCSK9) inhibitors, omega-3 fatty acids, fibric acid derivatives, and novel lipid-lowering agents (bempedoic acid, lomitapide, apabetalone) has not been sufficiently studied in large well-powered RCTs of long duration in patients with CKD [140–143]. The ability of PCSK9 inhibitors to lower LDL-C levels needs further study in CKD, but the results from the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial are highly encouraging [144]. Fibric acid derivatives (such as fenofibrate) can increase PCSK9 production and can also cause a dose-dependent, but reversible, decrease in GFR by a direct effect on the kidney. However, in diabetic patients, fenofibrate may reduce total CV events (mainly fewer nonfatal myocardial infarctions), reduce albuminuria, decrease retinopathy, and possibly slow progression of CKD [145, 146]. The effects on proteinuria and progression of CKD have not been adequately studied in nondiabetic CKD.

Sodium-Glucose Transporter 2 Inhibitors The dramatic emergence of sodium-glucose transporter 2 inhibitors (SGLT2i), causing an acquired form of renal glycosuria, as effective and reasonably safe agents for slowing progression of established CKD (eGFR 30–59 mL/minj/1.73 m^2) and avoiding hospitalization for heart failure (mainly HFrEF) in patients with type 2 diabetes mellitus (and perhaps nondiabetic kidney disease as well) has altered the landscape of secondary prevention of CKD and also primary and secondary prevention of CVD in T2DM [147–153]. Data from large randomized controlled trials (such as Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Patients [EMPA-REG], Canagliflozin Cardiovascular Assessment Program [CANVAS], Canagliflozin and Renal Endpoint Diabetes with Established Nephropathy Clinical trial [CREDENCE], and Dapagliflozin Effect on Cardiovascular Event Trial [DECLARE-TIMI 58]) (see [145–151] for reviews) have very convincingly shown efficacy for slowing progression of CKD (in type 2 diabetes) and for reduction of CVD events, primarily heart failure. Most of the subjects randomized in these trials had overt CVD prior to randomization. However, only canagliflozin is approved by the FDA for slowing progression of CKD (in patients with diabetic kidney disease and albuminuria of >300 mg/day) and reducing the risk of hospitalization for CHF (usually HFrEF), largely the result of the CANVAS and CREDENCE trials. A meta-analysis of these trials involving 38,723 subjects followed for a mean of 2.9 years with 20% having established CKD (grades 1–3B) and 59% with known CVD, including HF, Showed that the use of SGLT2i (usually added to stable doses of RASi) reduced the HR of a composite of major adverse CV events (MACE) to 0.88 (95% CI = 0.82–0.94) and significantly reduced the occurrence of hospitalization for CHF (HR = 0.66; 95% CI = 0.60–0.76), CV death (HR = 0.83; 95%CI = 0.75–0.92), and all-cause death (HR = 0.85; 95% CI = 0.79–0.92) [147]. There was no overall benefit on stroke. These benefits were observed irrespective of CKD status (except for stroke which was decreased only in those with CKD at baseline). The rate of progression of CKD was reduced (HR 0.66; 95 CI = 0.53–0.81) often in association with a reduction in albuminuria in the CREDENCE trial [148]. The beneficial effect on slowing rates of progression in CKD is much greater in those subjects with higher degrees of baseline albuminuria, especially if >300 mg/day. The beneficial effects on MACE were seen largely when these agents were used for primary prevention. Additional systematic reviews and meta-analyses have shown that SGLT2i are primarily effective for secondary prevention of CVD in diabetic patients, mostly for reducing hospitalization for HFrEF and slowing progressions of CKD, with less robust effects on ASCVD. The extent of benefit varies with baseline eGFR – greater benefit for HFrEF and lesser benefit for CKD progression in patients with more severe grades of CKD [153].

These beneficial cardio- and reno-protective effects of SGLT2i cannot be easily explained by the modest reduction in HbA1c and systolic blood pressure, so they seem to be manifestations of direct effects on the heart and kidney or systemic effects independent of glycemia and blood pressure control. The mechanism of action of these agents upon these outcomes is not presently fully understood and

may not be a class effect but one that varies between agents within the class. Afferent arteriolar constriction reducing maladaptive glomerular capillary pressure seems to be involved in reno-protection with all agents in the class [152]. An augmentation of tubulo-glomerular feedback is a popular hypothesis [154]. Basically, this hypothesis advances the idea that increased delivery of NaCl to the distal nephron (by virtue of a proximal nephron reduction of both glucose and NaCl reabsorption) activates a process located at the macula densa and juxtaglomerular axis of the same nephron to constrict the afferent arteriole and thus reduce glomerular capillary pressure (and single nephron GFR). However, these agents also affect volume excess (via natriuresis), reduce inflammation, lower body weight, lower plasma uric acid levels, reduce oxidative stress, impair fibrosis, and impact Na:H+ exchange in myocardium, among other effects [152, 154]. These pleiotropic effects of SGLT2i beyond their rather mild hypoglycemic effect (absent in patients with more advanced CKD) make these agents attractive candidates for treating patients with nondiabetic CKD with or without CVD (such as is being studied in Dapagliflozin in CKD trial [DAPA-CKD]). The preliminary results of this latter trial seem to indicate a favorable effect on CKD progression and CHF, even in subjects without diabetes [151, 155, 156]. An increase in serum ketone bodies and their influence on organ bioenergetics and inflammatory mediators might provide a potential unifying mechanism for the salutary effects of SGLT2i on the heart and kidney [157]. In addition, an exploratory analysis of the DAPA-HF trial has demonstrated a beneficial effect on worsening heart failure and CV mortality when dapagliflozin is added to recommended therapy in both diabetic and nondiabetic patients [158].

While these agents appear to have a reasonable safety profile, non-hyperglycemic ketoacidosis, acute kidney injury, severe perineal infections (Fournier's gangrene), and in some studies (mainly CANVAS) an excess of lower limb amputations have been observed so caution and close surveillance is indicated.

The aforementioned trials limited randomization to those subjects with an eGFR >30 mL/min/1.73 m^2. The safety and efficacy of these agents in more advanced CKD is not yet known. Most patients studied so far have utilized SGLT2i added to a baseline of optimal RASi, so we are not yet sure of the effect of these agents when used as monotherapy, but there are important interactions between SGLT2i and RASi in diabetic subjects, particularly in relation to volume control [159, 160]. The effect of these agents on HFrEF (see also Reference [159] for update on heart failure in CKD) is very impressive. The effect of SGLT2i on HFpEF is under study (e.g., PRESERVED-HF, EMPEROR-Preserved, EMPERIAL-Preserved). The beneficial effects of sacubitril-valsartan combinations have not yet been directly compared to SGLT2i in CKD with HFrEF.

Because of their weak hypoglycemic effects (especially in CKD with reduced eGFR), they are best combined with other hypoglycemic agents, especially metformin or a glucagon-like peptide 1 receptor agonist (GLP1), in T2DM to maintain HBA1c within recommended ranges (see below) [161–163]. Hypoglycemia is rare with these agents. Concomitant use of diuretics is not contraindicated, but such patients need careful follow-up to avoid iatrogenic volume depletion and acute kidney injury. Patients with CHF in T2DM are good candidates for SGLT2 inhibitor

therapy, even without CKD. SGLT2 inhibitors have now become "standard of care" for patients with CKD (grades 1–3B) and T2DM, especially if HFrEF is present. SGLT2 inhibitors might also reduce major atherosclerotic events, if HBA1c is decreased.

Glycemic Control (in Patients with Diabetes and CKD) Adequate standard glycemic control is a well-established goal in prevention of microvascular disease (diabetic nephropathy and retinopathy) and macrovascular ASCVD in patients with T1DM and T2DM [161, 163]. In T2DM patients with CKD, with or without overt CVD, the use of metformin (only if the eGFR is >30 mL/min/1.73 m^2), GLP1 receptor agonists (such as dulaglutide, exenatide, lixisenatide, liraglutide, semaglutide), and/or SGLT2i (if eGFR is >30 mL/min/1.73 m^2) is preferred in patients with CKD or without CHF or overt ASCVD [164–166]. Very recently, a comprehensive decision algorithm for prescribing SGLT2 inhibitors and GLKP-1 receptor agonists for diabetic kidney disease has been published [167]. This is a very useful approach for CVD and kidney failure risk stratification. Sulfonylureas and dipeptidyl-peptidase 4 inhibitors (DPP-4i, gliptins) have little if any beneficial effects on CVD in T2DM [162]. Insulin therapy is necessary in many T1DM and some T2DM patients, but it should be avoided in moderately advanced CKD if possible due to an enhanced risk for hypoglycemia. A goal of achieving a HbA1c of 6.5–8.0% is reasonable, depending on the grade of CKD (see [162, 163]).

Whether intensive glycemic control has any advantage in patients with CKD is doubtful. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) targeted a HbA1c of <6.5% reduced risk for nonfatal myocardial infarction but increased all-cause mortality (mostly due to CV event) [168], especially in those with mild to moderate CKD [169]. Older, frail subjects and those with advanced kidney disease are likely to fare poorly with intensive programs of glycemia control [170]. The Veterans Affairs Diabetes Trial (VADT) showed some benefits on CVD events of intensive glycemia control over the first 5.6 years of follow-up, but this effect was not sustained on prolonged follow-up totaling 15 years (active treatment + posttrial observation) [171]. No legacy effect of intensive treatment on CV event rate was observed. However, after 11 years of follow-up (with 5.6 years of intensive glycemic control), the patients in the intensive therapy group had a 34% higher odds of maintaining an eGFR of >60 mL/min/1.73 m^2 compared to the standard therapy group, suggesting that a legacy effect is seen with CKD outcomes [172].

Peroxisome proliferator-activated receptor gamma agonists (thiazolidinediones/glitazones such as pioglitazone) can improve glycemic control in T2DM and may slow progression of kidney disease, reduce proteinuria, and improve secondary CV outcomes [173–175]. But CHF can be aggravated, and they can cause edema, somewhat limiting their overall usefulness for secondary prevention of CVD in CKD.

Volume Control While not extensively studied, the use of salt restriction and diuretics is commonly advised in CKD to minimize the effect of chronic volume expansion on hypertension and LVH and the undesirable effects in CVD including CHF. In the initial stages of CKD, thiazide diuretics may be effective, but in later

stages (eGFR <30 mL/min/1.73 m^2) they lose their natriuretic efficacy, even though they may retain some antihypertensive effect [176]. Loop-acting diuretics (furosemide, bumetanide, torsemide) may be preferred in such patients. Mineralocorticoid receptor antagonists (MRA: spironolactone, eplerenone, finerenone) can be used to improve blood pressure control in CKD when hypertension is resistant to two or more agents, and such treatment may have additional CV benefits such as improving CHF [177, 178]. However, hyperkalemia is a risk, particularly when patients with advanced CKD are concomitantly receiving RASi. This risk can be attenuated by coadministration of a potassium-binding resin such a patiromer or sodium zirconium cyclosilicate [124]. Mineralocorticoid receptor antagonism might improve outcomes in advanced dialysis-requiring kidney failure with an acceptable margin of safety, but this will only be proven by ongoing clinical trials [178, 179].

Diet and Other Non-pharmacologic Approaches The use of dietary intervention for prevention of progression of CKD and for primary or secondary prevention of CVD in patients with established CVD has a long and checkered history. The difficult in doing rigorously controlled, well-powered RCTs has limited the development of evidence-based recommendations. Population-wide observational studies have suggested that a "healthy" eating style, in addition to avoiding obesity, smoking, and obtaining moderate exercise, can lower risk of CVD. However, this benefit of primary prevention of CKD has never been confirmed in an RCT. A large body of observational data support a beneficial effect of a low-protein diet on progression of CKD (secondary prevention), but this has also not been unequivocally confirmed in an RCT [180, 181]. Whether such low-protein diets are also beneficial for CVD prevention in such CKD patients remains uncertain. Also, it remains uncertain if high-protein diet causes CKD or accelerates its progression [96, 97], but consumption of increased amounts of processed or unprocessed red meat may have deleterious effects on CVD risk in CKD [96, 97].

A diet rich in plant-based foods, a Mediterranean style diet, and/or a DASH-type diet rich in fruits and vegetables and low in salt and red meat [182, 183] seem to have cardio-protective properties and perhaps a reno-protective effect [183, 184], perhaps via better control of ideal weight, blood pressure, avoidance of excess sodium salt, and improvement in potassium intake. A prudent, healthy style diet of a DASH, Mediterranean, or plant-based forms and avoiding saturated fat by replacing it with poly- or monounsaturated fats and vegetable sources of protein should be advised for all patients with CKD, with or without CVD. Avoiding sources of dietary cholesterol does not seem to be necessary in patients with CKD, with or without CVD. The value of prebiotics and/or probiotics for primary or secondary prevention of CVD in CKD remains largely unknown [185].

Anemia Management Moderate to severe anemia (hemoglobin of 9–10 gm/dL) is fairly common in more advanced CKD (eGFR <45 mL/min/1.73 m^2). This is due to a combination of relative iron deficiency and inadequate endogenous erythropoietin production. Anemia of this degree can contribute to LV remodeling and LVH [83]. Treatment of iron deficiency by oral or parenteral iron is indicated. Treatment with

exogenous erythropoietin is not advised in pre-ESKD forms of CKD as these agents may promote CVD, especially stroke [186]. Patients with CKD and a history of stroke should avoid exogenous erythropoietin unless the anemia is severe (hemoglobin <9 gm/dL and nonresponsive to iron repletion therapy).

Vascular Calcification Only very limited information is available concerning interventions to reduce vascular CAC for secondary prevention of CVD in CKD. Very recently, denosumab (a monoclonal antibody inhibitor of the bone resorption mediator – RANKL) has been shown to slow or stop progressive CAC artery calcification in advanced dialysis-dependent kidney failure, but whether this has any effect on CVD events is unknown [187]. Non-calcium-containing phosphate binders in patients with moderate non-dialysis-requiring CKD may actually increase the frequency of CAC [188]. The use of cinacalcet to reduce PTH levels has not been shown to reduce the risk of ASCVD events in kidney failure treated by dialysis [189]. A role of oral vitamin K supplementation or sodium thiosulfate for prevention or treatment of vascular calcification is unknown but is being studied.

Antiplatelet Treatment for Prevention of CVD in Patients with CKD Antiplatelet therapy using aspirin or other agents appears to reduce the risk of CVD events in patients with CKD while having no effect on progression of CKD [190]. The risk of adverse bleeding events from these agents is increased in CKD. One systematic review and meta-analysis of RCTs involving 27,773 patients with CKD showed that for every 1000 patients with CKD treated for 12 months with antiplatelet agents, 23 major CVD events will be prevented and 9 major bleeding events will occur [190]. Another study using propensity matching came to opposite conclusions, with increased risks of ASCVD events and progression of CKD with the use of low-dose aspirin [191]. Aspirin, if it is used at all in CKD, is not effective for primary prevention (if you believe that CKD is a coronary risk equivalent), but it may be useful for secondary prevention of ASCVD but with some level of bleeding risk.

Anticoagulants for Atrial Fibrillation Non-valvular atrial fibrillation (NVAFib) is common in CKD (see above), thought to be due to LVH, underlying HFpEF or HFrEF, and an enlarged left atrium. Such patients are at risk for embolic stroke. Prophylactic anticoagulation using warfarin or a novel oral anticoagulant (NOAC; apixaban, rivaroxaban, dabigatran, edoxaban) may be indicated [192]. The bleeding risk is increased in advanced CKD, so the balance between efficacy and safety is altered in CKD. In addition, warfarin and the vitamin K deficiency it produces can have unfavorable effects on vascular calcification in CKD, including calciphylaxis [193]. In addition, anticoagulation in CKD may predispose to anticoagulant-related nephropathy, as the cause of AKI superimposed on CKD, probably due to large amounts of hemoglobin in the tubular lumina provoking oxidant-induced cellular injury [194]. At present, only limited trials of prophylaxis of embolic stroke in CKD with have been conducted, as advanced CKD has been an exclusion factor in many trials. A recent systematic review and meta-analysis [195] have shown that warfarin is largely ineffective in prevention of ischemic stroke in patients with kidney failure

(grade 5 CKD, ESKD). The risk of hemorrhagic stroke was increased (HR = 1.49; 95% CI = 1.03–1.94), but there was no added risk of major bleeding or increased mortality. Apixaban appears to be preferred in moderately advanced kidney failure because of its favorable pharmacokinetic profile in patients with reduced eGFR [196]. As stated previously, treatment of HFrEF in patients with NVAF using beta-blockers does not appear to reduce mortality in patients with CKD regardless of the extent of renal impairment [130].

Hypouricemic Agents Asymptomatic hyperuricemia (plasma uric acid levels usually between 7 and 9 mg/dL) is fairly common in CKD, mainly in those with grade 3–5 CKD. A large body of observational and experimental data strongly suggests that this hyperuricemia in an independent risk factor for CVD and for progression of CVD, mainly ASCVD [197–199]. Cutoff values for serum uric acid levels identifying risk for acute myocardial infarction have been established in women but not in men [198]. Controlled trials of hypouricemic agents (mainly allopurinol) have had mixed results both for reno- and cardio-protection [197]. Due to a well-known but uncommon propensity for allopurinol to produce devastating side effects (exfoliative dermatitis, vasculitis) which are hard to predict in individual patients and uncertainty concerning its beneficial effects, it is not generally recommended for treatment of asymptomatic hyperuricemia in CKD. This is a very controversial area, and many experts do not recommend the use of hypouricemic agents in asymptomatic hyperuricemia for the purpose of slowing the rate of progression of CKD [200]. In the view of some, febuxostat is not recommended for this indication, as it has been associated with an increased risk for CVD [201]. However, the association of febuxostat with enhanced CVD risk has been challenged by recent observations, including the febuxostat for Cerebral and Cardiovascular Events Prevention Study from Japan [202]. This open label RCT including 1070 patients with or at risk of cerebral, CV, or renal disease showed that febuxostat reduced serum uric acid and decreased the primary composite event rate of cerebral, CV, and renal events (HR = 0.75; 95% CI = −0.59–0.95). There was no increase in CVD events in the febuxostat-treated group, and renal impairment was marginally less in the febuxostat group (HR = 0.745; 95% CI = 0.56–0.99). Clearly, this field is in a dynamic state, and further studies may help to clarify the uncertainties that exist concerning the risk/benefit ratio for the use of either allopurinol or febuxostat for cardio-renal protection in CKD with asymptomatic hyperuricemia. These agents have a clear and unequivocal role for treatment of symptomatic gout with or without CKD or CVD.

Revascularization Procedures A comprehensive discussion of this complex topic is beyond the scope of this chapter. Such procedures are generally used to treat underlying, overt, often acute, ischemic heart disease. They may not be indicated in patients with stable angina, including patients with advanced CKD, as studied in the ISCHEMIA-CKD trial [203, 204].

Implantable Defibrillators This topic is also beyond the scope of this discussion. Implantable electrical defibrillators are used to prevent a recurrence of ventricular

fibrillation (VF) in patients who survive an episode of VF and "sudden cardiac death" or in patients deemed to be at high risk for fatal ventricular arrhythmias (such as patients with HFrEF and EF <35%) [205]. The benefits conferred by implantable electrical defibrillators measured in terms of prolonged survival appear to be limited in patients with CKD, especially those with advanced CKD or ESRD treated by dialysis.

6 Conclusions

Chronic kidney disease is a common problem that is frequently accompanied by covert or overt cardiovascular disease that takes many forms, both atherosclerotic and non-atherosclerotic in origin. The association of CKD and CVD is at least in part due to risk factors held in common, such as advancing. Age, diabetes, obesity, hypertension, and dyslipidemia but CVD-promoting factors unique to CKD also contribute. The added burden of CVD seen in CKD contributes to a very great extent to the morbidity and mortality of CKD. At least to some extent, these adverse consequences are preventable. Primary prevention of CKD is at least feasible, though not proven, by better control of high blood pressure, avoidance of obesity and diabetes, minimizing exposure to nephrotoxic agents (including drugs, pesticides, air pollution, and cigarette smoking), and better maternal health, thus reducing the prevalence of low birth weight and congenital nephropenia. But secondary prevention of progression of CKD to ESKD and management of overt or covert CVD using strategies to minimize the adverse consequences of dyslipidemia, reducing chronic volume expansion, improving glycemic control (in diabetics), improving nutrition, safely treating anemia, controlling the accumulation of "uremic" toxins, inhibiting vascular calcification, preventing heart failure and left ventricular hypertrophy, and reducing the prevalence of cardiac arrhythmias are all part of CVD prevention in CKD. Many gaps exist in our knowledge of how best to safely and effectively prevent CVD in patients with CKD, in part because of limitations for entry of patients with overt CKD into CVD prevention trials. Nevertheless, the recent upsurge of RCTs examining the effects of novel agents (e.g., SGLT2 inhibitors, hypouricemic agents, hypolipidemic agents, drugs for optimal glycemic control) in patients with both CKD and overt or covert CVD augurs a favorable future for this important objective.

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Primary Prevention of Cardiovascular Disease Guidelines

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Summary

- Healthy lifestyle modification is at the center of primary prevention efforts.
- Shared decision-making is recommended when tailoring primary prevention efforts
- Accurately estimating cardiovascular risk is the first step in guiding prevention efforts.
- Estimation of ASCVD risk starts with calculating the 10-year ASCVD risk using the Pooled Cohorts Equations. If uncertainty exists regarding the accuracy of risk estimation, determining the presence of risk-enhancing factors is helpful.
- Coronary artery calcium measurement is the *best tie-breaker* when risk estimation remains unclear.
- Low-dose aspirin is reasonable when ASCVD is high and bleeding risk is low.
- >150 minutes per week of moderate intensity or >75 minutes per week of high-intensity exercise is recommended.
- Smoking cessation significantly lowers CV risk and the use of pharmacotherapies and behavioral therapies enhances quitting success.
- Controlling blood pressure with lifestyle changes and then pharmacotherapy if needed, significantly reduces CV risk.

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1 Introduction

Cardiovascular disease (CVD) remains the leading cause of death in the western world, with one in three Americans having atherosclerotic cardiovascular disease (ASCVD) and the estimated proportion may reach one half by 2030 [1]. With better lifestyle choices, nearly 80% of all cardiovascular disease can be prevented [2, 3]. The overall longitudinal effects of hyperlipidemia, blood pressure, obesity, smoking, poor diet, and diabetes are overwhelming. Although advances in prevention have played a critical role in reducing cardiovascular mortality, with the CVD death rate decreasing by 18.6% from 2006 to 2016, the rate of reduction has plateaued due to obesity and diabetes epidemics [4].

Pursuing a healthy lifestyle is at the center of primary prevention. To facilitate cardiovascular health and ASCVD risk factor control, the American Heart association (AHA) identified severe metrics of ideal cardiovascular health, collectively called "Life's Simple 7™". These metrics include healthy weight, adequate physical activity, a balanced healthy diet, not smoking, as well as achieving target values for blood pressure, cholesterol, and blood glucose. Only 17% of US adults have ≥5 of these metrics at ideal levels, which highlights a significant health gap in primary prevention.

The AHA/American College of Cardiology (ACC) released new comprehensive guidelines for primary prevention in March 2019 with emphasis on promoting a healthy lifestyle throughout the entire lifespan [5]. The new guidelines also focus on (1) adopting a team-based approach to ASCVD risk factor modification (2) shared decision-making between patient and clinician, and (3) attention to the social determinants of health.

Here we discuss the 2019 ACC/AHA Guideline of Primary Prevention of CVD in a simple, ABCDE-structured approach. The goal is to help clinicians implement best practices of primary prevention using this simple framework (Fig. 1).

2 Assessment of Risk

Accurate assessment of ASCVD risk is the first step in initiating a clinician-patient discussion about ASCVD prevention. Appropriate risk assessment allows for the identification of patients at elevated risk of ASCVD who may benefit from lifestyle and pharmacotherapy options. For adults 40–75 years of age, estimation of the 10-year ASCVD risk using the race- and sex-specific Pooled Cohort Equations (PCE) is recommended as the first step. However, the new guidelines also emphasize the significant limitations of the PCE in assessing risk in certain populations. These limitations primarily arise from the fact that the PCE do not reflect all known ASCVD risk factors and that the PCE were initially validated in non-Hispanic whites and non-Hispanic blacks.

The PCE may underestimate risk in HIV or rheumatoid arthritis patients or those with low socioeconomic status. Therefore, estimated ASCVD risk should be interpreted within the context of the individual patient's circumstances. To refine risk estimation for

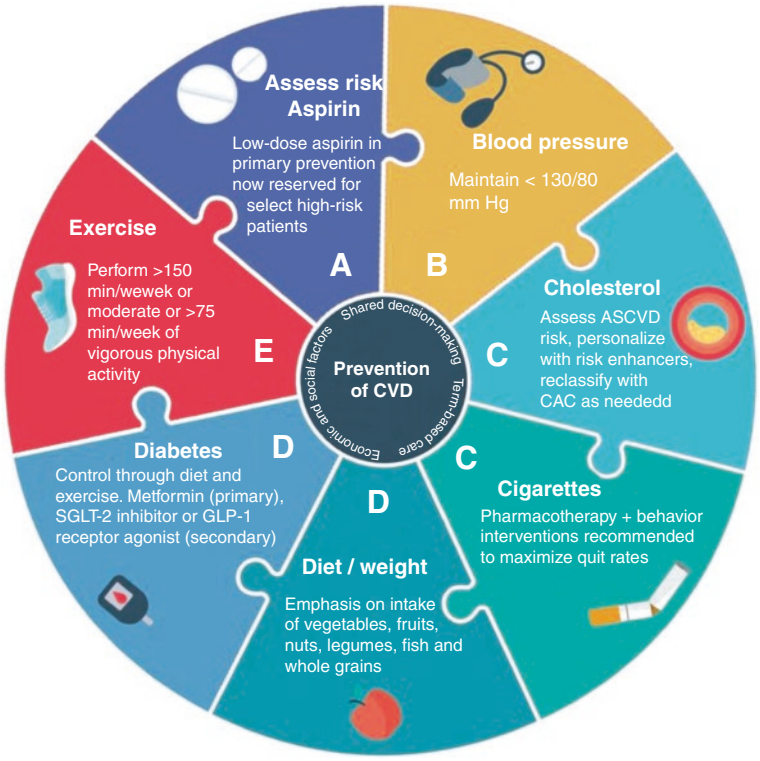

Fig. 1 ABCDE of primary prevention: lifestyle changes and team-based care

individuals with borderline (5% to <7.5%) or intermediate (≥7.5% to <20%) 10-year ASCVD risk, three strategies are acceptable (Fig. 2): (1) estimating lifetime risk, (2) determining whether additional risk-enhancing factors are present, and the selective use of a (3) a coronary artery calcium score. Table 1 lists ASCVD risk-enhancing factors which should be ascertained in patients in whom the validity of the PCE risk estimation is questionable or still unclear to the patient and/or clinician. The presence of multiple risk-enhancing factors may prompt reclassification to a higher ASCVD risk group or simply indicate that the patient has a high 30-year ASCVD risk.

If physicians still have doubts about the accuracy and validity of risk estimation in individuals with intermediate risk or selected patients with borderline risk, the guidelines now recommend the selective use of coronary artery calcium (CAC) as the best tie-breaker (Fig. 3). CAC is far superior to other subclinical imaging markers or blood-based biomarkers and has well-established discrimination and risk reclassification properties [6, 7]. A CAC ≥100 Agatston units reliably reclassifies risk upwards and a CAC of zero accurately reclassifies risk downwards by 60–70%. A CAC score is very useful in refining ASCVD risk estimates in all ethnic groups [8]. A recent study from MESA showed that in patients with intermediate ASCVD estimated risk, even when three or more risk-enhancing factors are present, the presence of a CAC of 0 is found in about 43% of individuals [9].

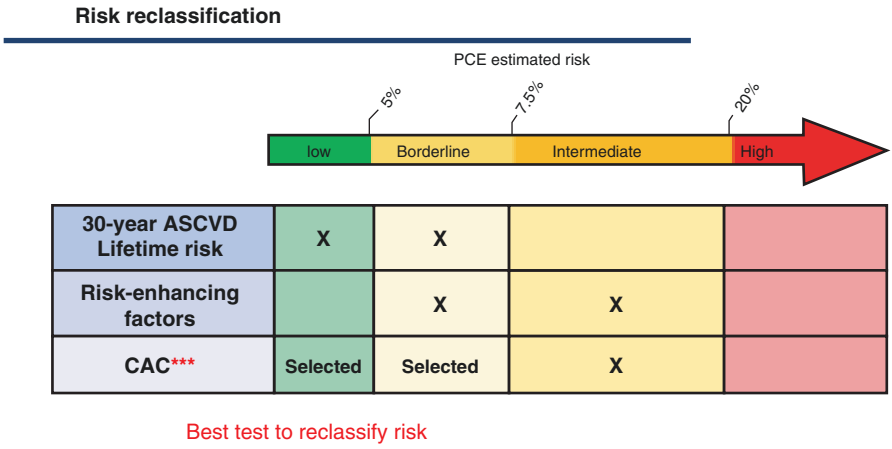

Fig. 2 Tools used in risk reclassification according to estimated 10-year ASCVD risk using the PCE

Table 1 ASCVD risk enhancers

ASCVD risk enhancers
Family history of premature ASCVD
Primary hypercholesterolemia
Chronic kidney disease
Metabolic syndrome
Conditions specific to women (e.g., preeclampsia, premature menopause)
Chronic inflammatory conditions (especially rheumatoid arthritis, psoriasis, HIV)
Ethnicity (e.g., south Asian ancestry)
Lipid/biomarkers:
Persistently elevated nonfasting triglycerides (≥175 mg/dL)
In selected individuals if measured:
hsCRP ≥2 mg/L
Lp(a) levels ≥50 mg/dL or ≥ 125 nmol/L
ApoB levels ≥130 mg/dL
Ankle-brachial index <0.9

3 Aspirin

With its long history and low cost, aspirin is the most commonly used medication in primary prevention, with an estimated 40% of US adults aged >50 years using aspirin for primary prevention in the prior decade [10]. However, with randomized controlled trials such as the Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE)

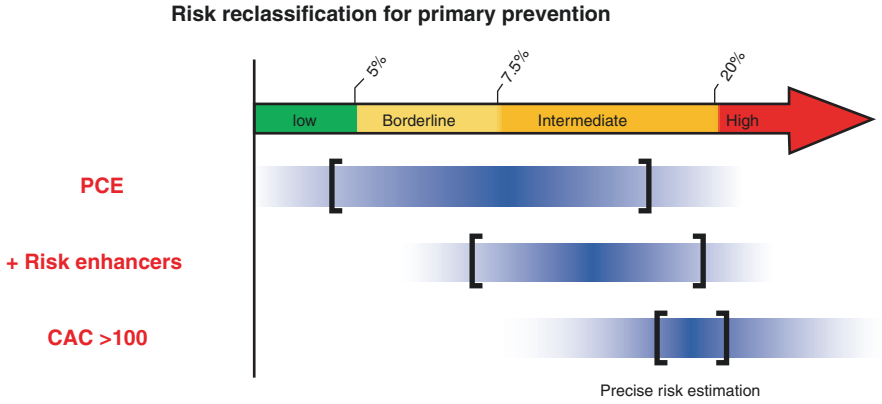

Fig. 3 Example of how risk-enhancing factors and coronary artery calcium help refine ASCVD risk estimation

[11], A Study of Cardiovascular Events In Diabetes (ASCEND) [12], and Aspirin in Reducing Events in the Elderly (ASPREE) [13] studies, the role of aspirin has been recently questioned in primary prevention. In patients with moderate CV-risk without diabetes, the ARRIVE trial showed that 100 mg of aspirin daily in a moderate CV-risk population increased the risk of bleeding without any benefit on the incidence of major CV events [11].

In diabetics with no prior history of CVD, the ASCEND trial showed that 100 mg of aspirin led to a 12% relative risk reduction in major adverse CV events vs placebo, but the absolute benefits was counter-balanced by a significant increase in bleeding events [12]. There was no reduction of colorectal cancer risk. The ASPREE trial examined the use of 100 mg of aspirin daily in individuals age 70 or older without heart disease, dementia, or disability, and found no disability-free survival benefit. In fact, the all-cause mortality in the group who took aspirin was slightly higher [13].

Prescribing aspirin for primary ASCVD prevention is no longer based solely on a threshold of estimated ASCVD risk. Rather, a tailored decision to start aspirin should be based on the overall ASCVD risk estimate (inclusive of PCE risk estimate and risk-enhancing factors) weighed against the risk of bleeding (Fig. 4). It is reasonable to start aspirin in adults 40–70 years of age with high overall ASCVD risk estimate ≥20% (with risk-enhancing factors) or at least moderate coronary artery calcium and low risk of bleeding (IIb, A). However, aspirin is not recommended for primary ASCVD prevention if the risk of bleeding is moderately high (III, C-LD). Similarly, aspirin should not be routinely administered for primary ASCVD prevention to individuals >70 years of age given risk of bleeding that outweighs protective benefit in this age group.

Despite this, major clinical guidelines offer conflicting advice. European guidelines recommend against using aspirin for primary prevention because of risk of bleeding. USPSTF recommends aspirin for primary prevention of CVD and

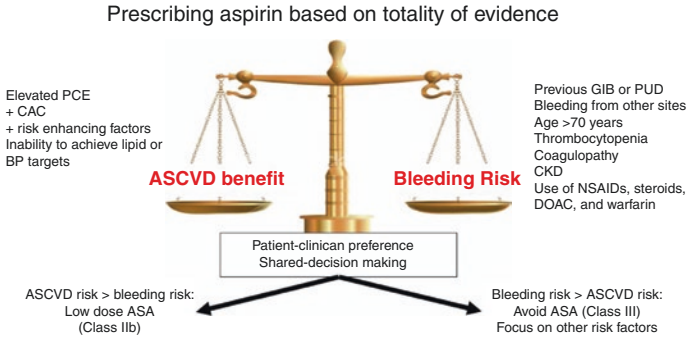

Fig. 4 A tailored decision to start aspirin should be based on the overall ASCVD risk estimate (inclusive of PCE risk estimate and risk enhancing factors) weighed against the risk of bleeding

colorectal cancer in those aged 50–59 years who have a low risk of bleeding and a 10-year ASCVD risk of 10% and an individual decision for those aged 60–69 who meet the risk threshold. The American Diabetes Association suggests that in diabetics with increased cardiovascular risk, aspirin therapy (75–162 md/day) may be considered for primary prevention after a comprehensive discussion with the patient on the benefits versus the comparable increased risk of bleeding [14].

4 Blood Pressure

Hypertension is the number one cause of disability-adjusted life-years worldwide. Poor blood pressure (BP) control is the most common risk factor for CVD, stroke, CAD, heart failure, and PAD. Evidence from epidemiological studies show that hypertension across all ages provides an incremental association with risk of stroke, ischemic heart disease, and heart failure. Despite decades of public health campaigns and guidelines, hypertension remains undertreated. Approximately half of the U.S. adult population, 103 million persons, has high blood pressure.

With the 2017 ACC/AHA Hypertension Guideline, all individuals with a BP ≥130/80 mm Hg have hypertension [15]. This lower threshold to treat hypertension is partially based on the landmark Systolic Blood Pressure Intervention Trial (SPRINT), which showed significant improvement in CV mortality in hypertensive patients with intensive blood pressure control (<120 mmHg) compared to standard target of <140 mmHg, with a benefit-to-harm ratio of approximately 2.5 in high-risk patients [16]. Even in individuals with <10% ASCVD risk, there was a benefit-to-harm ratio of approximately 1.2, indicating favorable outcomes across all levels of CVD risk. A 20 mmHg increase in SBP and 10 mmHg increase in DBP are associated with double the risk of death from vascular disease.

The 2017 ACC/AHA Blood Pressure Guideline stirred much controversy in the redefining of hypertension. Although there is an obvious dose-response between

incremental increases in BP and CV outcomes, this raises questions on the effect of redefining hypertension and generalizability of intensive blood pressure targets in intermediate risk patients. With this new lower cutoff, the adult prevalence of hypertension jumped from 32% to 46% overnight. One question is not whether we should focus on early high blood pressure, but rather is this definition suitable and realistic?

The ESC/ESH guideline has a higher target for blood pressure, defining hypertension as BP ≥140/90, and recommending a BP target of <130/70–79 mm Hg for only high-risk conditions (diabetes, stroke, coronary artery disease) [17]. Even within the USA, various societies have adopted different cutoffs with net benefit and cost efficacy in mind. However, the new guideline represents a population-based strategy aimed to achieve a more dramatic reduction in BP with emphasis on early weight loss, a heart-healthy diet, sodium restriction, and exercise.

Currently, the guideline recommends lifestyle changes in low-risk adults with BP <140/90 mmHg [15]. In higher risk adults, with BP ≥140/90 mmHg and/or a 10-year estimated ASCVD risk >10%, lifestyle *and* medication are recommended. The best proven lifestyle interventions for hypertension are the DASH diet (BP reduction ~11 mmHg), weight loss, sodium restriction, and aerobic exercise [18]. Dietary modifications should be an important component of hypertension management and prevention. Dietary patterns greatly affect blood pressure. The DASH diet, along with Mediterranean diet, and a diet with less saturated fat and alcohol consumption all lower blood pressure. Other dietary factors, such as increased fiber intake and plant-based foods also reduce blood pressure [19].

There are multifactorial barriers in improving BP control, including social determinants of health, cultural norms, inadequate dispersal of health education by health care practitioners, lack of reimbursement for health education, lack of access for healthy foods and safe sites for exercise, and higher cost of foods that are lower in sodium and calories. Hypertension is more prevalent in African Americans than in Caucasians and increases the risk of stroke and end-stage renal disease disproportionately in African Americans. Moreover, people living in lower socioeconomic areas have greater odds of having high BP. There is a strong association between area of residence, such as the Southeastern USA and prevalence of hypertension [20]. Having a regular source of care is strongly associated with better BP control [21]. Challenges to prevention, detection, awareness, and management of hypertension demand a timely multidisciplinary approach directed not only to high-risk patients, but also to workplaces, schools, government, policymakers, and the food industry [22].

5 Cholesterol

There is a direct relationship between low-density lipoprotein cholesterol (LDL-C) levels and ASCVD risk. In the Atherosclerosis Risk in Communities (ARIC) study, every 39 mg/dL increase in LDL-C increased the risk of a coronary event by 40% [23]. The Framingham Heart Study showed that individuals were more than 1.5

times more likely to develop significant coronary disease if LDL-C was greater than 160 mg/dL compared to if LDL-C was less than 130 mg/dL [24]. Moreover, there is a 20–25% relative reduction in ASCVD risk per unit of LDL-C reduction (mmol/L) [25]. With the 2018 cholesterol guidelines, there is a recommendation for more intense reductions in LDL-C and addition of proven non-statin therapy in patients at high risk [26]. These changes were driven by data collected from clinical studies demonstrating a direct relationship between extent of LDL-C reduction and CV event reduction [27, 28].

The 2019 ACC/AHA Primary Prevention Guideline emphasizes starting lifestyle interventions early and recommends shared decision-making before considering the initiation of statin therapy [26]. This process should include a discussion of the patient's risk factors and estimated lifetime risk. The ASCVD calculator provides risk estimation in adults 40–75 years of age who do not have diabetes and whose LDL is greater than 70 but less than 190 mg/dL. By calculating 10-year ASCVD risk with the PCE, patients can be categorized as low (5%), borderline (5–7.5%), intermediate (7.5–20%), or high (>20%) risk. For those at low risk, lifestyle changes are often sufficient. For adults with intermediate (≥7.5% to <20%) or high (≥20%) 10-year ASCVD risk, a moderate-intensity statin is recommended after a clinician-patient risk discussion. Reducing LDL-C by at least 30% or more is recommended. For optimal risk reduction, especially for those with high risk, up-titration of statin therapy to achieve an LDL-C reduction of at least 50% is recommended. Maximally tolerated statins are recommended for individuals with severe primary hypercholesterolemia [29, 30].

In adults age 40–75 with type 2 diabetes, the recent guidelines recommend initiation of a moderate-intensity statin. In those with diabetes and multiple ASCVD risk factors, it is reasonable to consider a high-intensity statin with the aim of lowering LDL-C by 50% or more. Lastly, the following diabetes-specific risk enhancers warrant consideration of high-intensity statin therapy: long diabetes duration (at least 10 years for type 2 diabetes, at least 20 years for type 1 diabetes), albuminuria greater than 30 mcg/mg creatinine, estimated glomerular filtration rate less than 60 mL/min/1.73 m^2, retinopathy, neuropathy, and an ankle-brachial index <0.9.

5.1 Shared Decision-Making: CAC and Risk-Enhancing Factors as Tie-Breakers

Estimating the 10-year ASCVD risk with the PCE is the first step in starting the conversation about statin therapy for primary ASCVD prevention. However, the PCE either significantly overestimates or underestimates risk in about half of individuals in the 5–20% ASCVD risk range. Therefore, a hallmark of the recent guidelines is improved risk stratification for borderline (5–7.4%) and intermediate-risk (7.5–20%) adults. Determining the presence of risk-enhancing factors (Table 1) may help reclassify patients into a higher risk category that warrants statin therapy. Selective use of CAC for risk stratification in intermediate-risk patients is

recommended if the decision to start a statin remains unclear or if the patient is reluctant to start statin therapy. Compared to risk-enhancing factors, measuring CAC provides the best method to reclassify patients into a higher or lower risk category.

Data from the MESA and Framingham cohorts have shown CAC testing in intermediate-risk groups significantly improves risk stratification and provide helpful guidance on therapy decisions. In patients at borderline risk, with risk-enhancing factors and/or substantial coronary artery calcification (CAC), moderate-intensity statin therapy should be strongly considered. Statin therapy is strongly recommended if CAC is 100 or higher or in individuals in the 75th percentile or higher for their age, sex, and race. They may also be considered in individuals with CAC scores 1–99 and aged 55 years or older. A CAC score of 0 is associated with a very low rate of ASCVD events over the next decade, and statins should be deferred (except in patients with active tobacco use. Diabetes, positive family history, or familial hypercholesterolemia).

The dose response and tolerance to statin therapy should be assessed in about 6–8 weeks. If LDL-C reduction is sufficient (≥30% reduction with intermediate- and 50% with high-intensity statins), routine assessment of risk factors and compliance with medication are necessary to determine effect in about 6–12 months.

5.2 LDL-C Assessment

There are multiple methods for LDL-C assessment, but the Friedewald equation (total cholesterol- HDL-C – triglycerides/5) has been the standard since the 1970s. The equation uses a fixed ratio of 5:1 between triglycerides and VLDL-C. It can be inaccurate at low LDL-C and high triglycerides levels, clinical scenarios that are becoming more common as a result of obesity epidemics and new LDL-lowering therapies. The 2018 Cholesterol Guideline acknowledged the importance of accurate LDL-C estimation and provided a Class II recommendation in measuring direct LDL-C or using an alternative method of estimation, such as the Martin/Hopkins equation, when LDL-C is below 70 mg/dL [29]. The Martin/Hopkins LDL-C equation is a validated method that can be used to estimate LDL-C by applying an adjustable factor for the ratio of triglycerides to VLDL cholesterol.

6 Cigarettes

Tobacco use is the leading preventable cause of disease and death in the USA. Almost one-third of ASCVD deaths in adults are related to smoking and secondhand smoke. Smoking is strongly associated with the risk of atherosclerotic disease. There is strong evidence for smoking-related vascular damage, endothelial dysfunction, and immunological derangement from a wide variety of clinical and basic science

studies [31]. While smoking is a well-known risk factor for CHD and stroke, its effect on peripheral arterial disease (PAD) may be overlooked. However, the risk for PAD remains high, up to 30 years, after smoking cessation. In a recent study, the association between pack-years and vascular disease was greatest for PAD compared to CHD and stroke [32].

Use of electronic cigarettes and hookah have also increased recently (now an estimated 1 out of 20 Americans). E-cigarettes, also known as "vapes" or "electronic nicotine delivery systems" are battery-operated, handheld devices that resemble traditional cigarettes. They work by heating an e-liquid, which may contain nicotine and a combination of various carriers and flavors, to create a "vapor". E-cigarettes have been shown to almost double the risk for MI.

Quitting smoking at any age substantially decreases both ASCVD and total mortality risk. The risk of ASCVD has been reported to decline after smoking cessation within 5 years. Moreover, there is a clear dose-response relationship between length of smoking cessation and risk. Although reducing smoking consumption correlates in approximately a linear fashion with risk of lung cancer, the dose-response for CVD is steep at low cigarette use and then levels off [33, 34]. It has been shown that the substantial risk for CHD and stroke remains even when smoking a few cigarettes, including one cigarette a day [33].

Tobacco use should be assessed at every health care encounter for patients who smoke. It is imperative that clinicians discuss smoking cessation at every encounter. This involves assertive encouragement, frequent follow-up, and gentle persistence. A combination of behavioral and pharmacotherapy to assist quitting should be recommended. The benefit of behavioral and/or pharmacotherapy is well established. Figure 5 includes seven medications approved by the FDA for smoking cessation, including five forms of nicotine replacement. For bupropion and varenicline, the black box warnings for neuropsychiatric events have been removed by the FDA. This has been highlighted in the new 2019 ACC/AHA guidelines to encourage the use of either of these two agents when appropriate [26]. In pregnant women, the benefit of tobacco cessation is substantial. However, the safety profile of agents used for smoking cessation is still lacking in pregnant women.

Electronic Nicotine Delivery Systems such as e-cigarettes are not recommended since the safety profile and evidence of benefit are not yet clear. Since tobacco use dependence is a chronic disease, it requires long-term management. Training health care workers in tobacco treatment increases success in helping their patients quit. Training individual staff dedicated to tobacco treatment have better smoking cessation rates.

Tobacco treatment specialists are highly qualified professionals who have the skills, knowledge, and training to provide evidence-based interventions to smokers. Having a tobacco treatment specialist at every health care system is reasonable. A thorough history to identify exposure to tobacco products smoking is useful since secondhand smoke is harmful. Physicians should advise patients to avoid smoking (including Electronic Nicotine Delivery Systems).

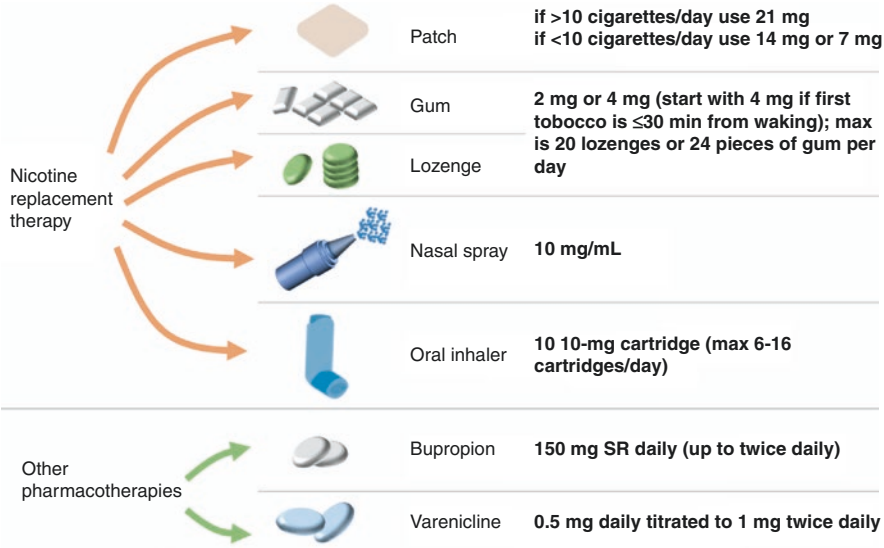

Fig. 5 Nicotine replacement therapy and other pharmacotherapies approved for smoking cessation

7 Diabetes

The obesity epidemic has dramatically increased the prevalence of type 2 diabetes (T2D) in the USA. Over 35 million US adults have diabetes and an additional 92 million have prediabetes. T2D is associated with double the mortality risk and ten-fold increase in hospitalizations for CHD [4, 35]. The 2019 guidelines for primary prevention emphasize nutrition, physical exercise, and appropriate diabetic therapy (metformin, SGLT-2 inhibitor, GLP-1 agonist) in individuals with diabetes [26].

7.1 Diet and Exercise

All persons with diabetes should eat a heart-healthy diet and aim for at least 150 min of moderate intensity or 75 min of vigorous-intensity exercise per week. A heart-healthy diet has been shown to significantly improve glycemic control and potentially relieve insulin resistance enough to induce the remission of diabetes. The Mediterranean diet and vegetarian diets have demonstrated significant weight loss and improved glycemic control in studies compared to control diets [36, 37]. Often, establishing a comprehensive nutritional plan requires a team approach and assistance from a registered dietitian-nutritionist or diabetes education program.

Aerobic and resistance exercises reduce blood glucose, with the combination being most effective – lowering A1c by ~1% [38]. A 1% decrease in A1c level has

been associated with 15–20% decrease in major CV events [38, 39]. Data from the Nurses' Health Study also demonstrates a dose-dependent decrease in CV events with increased physical activity among female nurses with diabetes [40]. A combination of aerobic and resistance training is better than either alone.

7.2 Diabetes Medications

Metformin remains first-line therapy along with lifestyle changes in improving glycemic control and ASCVD risk [26]. Recently several diabetes trials with SGLT2 inhibitors and GLP-1 receptor agonists (GLP-1 RAs) have demonstrated a clear improvement in CVD outcomes.

SGLT-2 inhibitors work by decreasing reabsorption of sodium and glucose in the renal tubules resulting in greater diuresis and reduction in serum glucose. Three drugs (empagliflozin, canagliflozin, and dapagliflozin) in this class have been studied and found to improve outcomes for CVD and heart failure endpoints. GLP-1 receptor agonists (RAs) reduce glucose by stimulating insulin secretion and suppressing glucagon when glucose is elevated. Five agents (lixisenatide, exenatide, dulaglutide, liraglutide, and semaglutide) have been shown to safely lower glucose, with the latter three demonstrating a significant reduction in a composite endpoint of CV death, MI, and stroke.

Recently, the REWIND trial showed that adding dulaglutide in a large primary prevention cohort reduced CV outcomes, suggesting that the CV benefits of this class apply to a larger population than shown before. These benefits were noted across individuals with both prior CVD and no prior CVD, across various BMIs, and A1c levels [41]. Compared to SGLT-2 inhibitors, GLP-1 RAs improved CV outcomes mainly by decreasing atherosclerotic events and promoting weight loss. SGLT2 inhibitors, on the other hand, had greater reduction in heart failure and renal impairment-related events.

These therapies are shaping a new paradigm of improving CV risk beyond. Further research is needed on investigating additional mechanisms at play, such as inflammatory pathways and the cardio-metabolic-renal axis, in understanding these agents' effects as well as their use in primary prevention populations.

8 Diet and Weight

There is tremendous controversy surrounding the ideal diet for CV health. The current dietary recommendations that support healthy eating are based on maintaining caloric balance and focusing on food composition and quality. The Mediterranean-type and plant-based diets have been shown as superior in improving CV health and helping with weight loss.

The Mediterranean diet consists of (1) high intake of extra virgin olive oil, fresh vegetables (especially leafy greens), fruits, whole grains, nuts, and pulses (edible seed from a legume) /legumes; (2) moderate intake of fish, lean meats, low-fat dairy, poultry, wine; and (3) low intake of red meats and sweets. Adults who consume a plant-based or Mediterranean diet have a lower mortality risk compared with adults eating a standard Western diet [42]. Diets rich in sugar, refined carbohydrates, trans- and saturated-fat diets, sodium, carbohydrates and processed meats (hamburgers, hot dogs, deli meats) are associated with increased CV risk [43]. Current evidence supports the protective benefits of nuts, olive oil, and other mono- and poly unsaturated liquid vegetable oils, plant-based diets, and antioxidant-rich foods. The Mediterranean diet has been shown to reduce CVD by 30% relative risk reduction compared with control diet [44]. In the PREDIMED study, individuals at high CV risk had a lower incidence of CV events when assigned to a Mediterranean diet with extra-virgin olive oil or nuts compared to those assigned to a low-fat diet [45].

The DASH diet is similar, with the emphasis being low sodium intake, low saturated and *trans*-fat intake, and consuming a potassium, calcium, magnesium, fiber, and protein-rich diet. It lowers blood pressure and LDL-C. Sodium and lipid control are strongly tied to simple substitutions and the selection of fats, respectively. This could be particularly important in ethnic/native diets where these substitutions can greatly reduce their health risks while maintaining the culture of the food. Vegetarian and vegan diets maintain the same principles, but substitutes plant-based protein sources (soy, legumes, nuts, and whole grains) in place of meat and seafood.

In the EVADE CAD (Effects of a Vegan Versus the American Heart Association-Recommended Diet in Coronary Artery Disease) trial, a vegan diet lowered inflammation more than the AHA diet [46]. The vegan diet in this study provided similar benefit as the AHA diet for weight loss, glycemic control, and dyslipidemia. There is some evidence that plant-based diets may work to alter the microbiome and reduce ASCVD risk. Lastly, fiber has been consistently shown to lower CVD risk in both observational and dietary intervention studies. A 7 g/day increase in fiber intake was associated with a 9% decrease in CHD incidence and shown to reduce all-cause mortality among MI survivors.

Low-carbohydrate, high-protein/fat (LCHF) diets have grown more popular over the past two decades. They have been associated with weight loss and increased insulin sensitivity, but also increased LDL-C levels and increased all-cause mortality when used for extended periods. Yet, caloric restriction and carbohydrate reduction, especially in patients with diabetes, remain mainstays of weight loss. As part of a comprehensive lifestyle program, overweight individuals are recommended to lose 3–10% of body weight by caloric restriction and increased physical activity. This includes monitoring BMI annually or more frequently, along with considering measuring waist-to-hip circumference, a better marker of visceral adipose tissue. Given the nutritional and fiber deficiencies associated with the LCHF diet as well as lack of long-term data on its efficacy and safety, a low saturated fat, low simple carbohydrate diet is still recommended over LCHF for weight loss [47]. Ultimately, the best diet is the one the patient can implement and sustain.

The way and pace at which we eat has evolved greatly over the past century. Processed and fast-foods have become more prevalent as well as eating frequency has increased. There is a growing consumption of starchy foods and sugar-sweetened beverages. In the USA, over 75% of processed food has some form of added sugar. There has been a reported nearly 20% increase in CHD risk in the highest category of sugary beverage consumption compared to the lowest consumption [48]. Food that was traditionally dispersed through local markets has become a mass marketed, industrialized production. The government heavily subsidizes these processed poor-quality foods. More than half of our population's calories come from subsidized foods, and calories from these foods are associated with greater cardio-metabolic risks [49]. This demands national agricultural and nutritional policy attention.

Healthy eating habits are created over a lifetime and influenced by economic, social, and psychological factors. Lack of education, nutrition knowledge, access to healthy foods, and abundance of "food deserts" contribute to poor diet. Price and time scarcity have also been shown to encourage poor food choice. Lastly, branding, marketing, and culture are extremely powerful influences on eating norms.

9 Exercise

Only about 20% of US adults are meeting the overall physical exercise recommendations (CDC). There is a strong inverse relationship between the amount of physical activity and ASCVD events and mortality. Adults should engage in at least 150 minutes per week of moderate-intensity or 75 minutes per week of vigorous-intensity exercise. Compared to no regular exercise, any type of exercise has been shown to protect against CVD risk. Exercise duration and intensity have also been shown to be directly related to improved mortality (Fig. 6). Blood pressure has been shown to improve with regular aerobic exercise and with resistance training. Systolic and diastolic pressure may decrease to 15 and 9 mm Hg, respectively, in patients with mild essential hypertension [50, 51]. Exercise reduces the risk of stroke, improve glycemic control, and prevent metabolic syndrome, various cancers, osteoporosis, and dementia.

Physical activity works to reduce systemic inflammation and consequently ASCVD risk. In one study, atherogenic cytokine production decreased by 58% and production of athero-protective cytokines increased by 36% [52]. Furthermore, recent studies have indicated an association between ASCVD and psychosocial/stress factors. The adoption of a routine exercise regimen has been implicated in improvements in stress, depression, and other CV parameters such as heart rate variability, baroreflex reactivity, and autonomic balance. Epidemiological studies show a dose-response relationship between growing number of psychosocial factors and CHD. More data also shows that positive psychosocial interactions improve health; however, there has been limited translation of these findings into clinical practice. Meditation, tai chi, and mindfulness remain to be explored in future ASCVD primary risk reduction research.

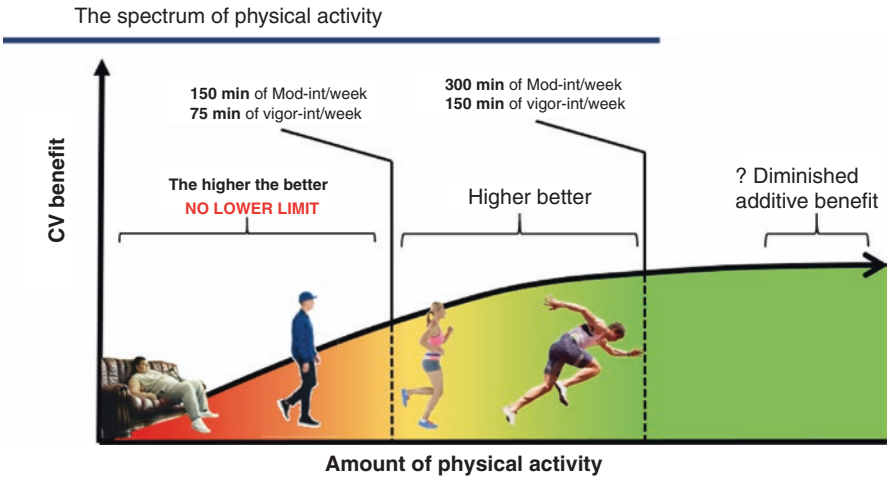

Fig. 6 The spectrum of physical activity and cardiovascular (CV) benefit

10 Economic and Social Factors

The World Health Organization defines social determinants of health as "the circumstances in which people are born, grow, live, work, and age, and the systems put in place to deal with illness." This definition suggests health and illness are linked directly to social, economic, cultural, and environmental factors. About 80–90% of our health is influenced by social determinants of health, while only 10–20% is determined by the health care we receive [53]. Low-income populations have a higher risk of heart disease. More evidence shows that addressing social needs improves health outcomes. The Centers for Medicare & Medicaid Services has developed a 5-domain screening tool, including housing instability, food insecurity, transportation difficulties, utility assistance needs, and interpersonal safety, to address this gap in our care system.

The 2015 Scientific Statement from the AHA on social determinants of risk and outcomes for CVD catalogs socioeconomic position (including income, education, employment status), race, ethnicity, social support, culture, access to medical care, and residential environments as contributory players, along with psychological and behavioral mechanisms [54]. In the Eight Americas study, authors found a 14-year difference in life expectancy between the highest (Asian Americans) and lowest (blacks in poor urban areas) groups [55]. African Americans are 2–3 times more likely to die of heart disease compared to Caucasians [56]. Moreover, neighborhoods have been linked to CVD outcomes.

In an ARIC substudy, where authors examined census-derived indicators of socioeconomic characteristics over a longitudinal follow-up, living in a disadvantaged neighborhood was associated with a 70–90% higher risk of CHD in whites and 30–40% higher risk in blacks independent of other factors (income, education, and occupation) [57]. Lastly, psychological and behavioral mechanisms have been implicated by which social conditions contribute to CVD. Poor environments

expose individuals to more daily stressors, crime, and limitations to physical activity. These factors may potentiate autonomic dysregulation (reduced heart rate variability), increased inflammatory response, hypothalamic-pituitary axis dysfunction, more adiposity, insulin resistance, and encourage poor behaviors.

11 Omega-3 Fatty Acids

Despite the wide uptake of statin therapy for primary prevention, many patients still have significant residual cardiovascular risk. Therefore, therapies to reduce residual risk have been investigated. Omega-3 fatty acids are long chain poly-unsaturated fatty acids found in diet such as fatty fish. Eicosapentaenoic (EPA) is a poly-unsaturated fatty acid that received recent attention in reducing residual risk in patients with elevated triglycerides while on statin therapy. The Japan EPA lipid intervention study (JELIS) randomized 18,645 patients to 1800 mg of EPA in an open label design [58]. All patients received a statin (10 mg of pravastatin or 5 of simvastatin). The study found a 19% reduction in major coronary events compared to statin alone. This benefit was independent of TG reduction.

Several trials tried to replicate this finding without success likely due to lower omega-3 fatty acids or type of omega-3 fatty acid used or short trial follow up durations. The Reduction of Cardiovascular Events with Icosapent Ethyl Intervention Trial (REDUCE-IT) randomized patients with triglycerides ≥150 mg/dL and high cardiovascular risk to high-dose EPA, in the form of icosapent ethyl, or placebo [59]. One third of patients enrolled in this trial had no prior cardiovascular disease but were at high cardiovascular risk due to diabetes combined with additional cardiovascular risk factors.

After a median follow-up of 4.9 years, EPA therapy was associated with a 25% reduction in cardiac events compared to placebo with no significant heterogeneity of effect in the secondary or primary prevention groups. The benefit of EPA therapy was consistent in those with and without established cardiovascular disease and similar in diabetics and nondiabetics as well as across levels of triglycerides at baseline or at follow-up. The Food and Drug Administration recently approved in December 2019 icosapent ethyl for reduction of cardiovascular events in patients with triglycerides of 150 mg/dL or more on statin therapy who also have either ASCVD or diabetes and two or more additional risk factors for cardiovascular disease.

12 Conclusions

The prevalence of CVD has been projected to rise 10% between 2010 and 2030 in the USA. Improvements in prevention have not been shared equally across populations in the USA, with significant disparities among economic, racial, and ethnic

groups. National policy changes are needed to reflect these guidelines into healthy practice. It is our responsibility as clinicians to implement these recommendations in our primary prevention practices and to engage patients to become partners in this lifelong process.

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Secondary Prevention and Cardiac Rehabilitation

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Summary

- Cardiovascular diseases are the leading cause of mortality worldwide.
- The rise of comorbidities such as obesity and type 2 diabetes exacerbate CVD prevalence.
- Effective secondary prevention strategies are needed to combat this issue.
- Lifestyle and behavioral interventions such as increasing physical activity and improving nutrition are effective at reducing CVD risk.
- Integrating these interventions into structured programs such as cardiac rehabilitation have been effective.
- There is a need to raise awareness of these programs among patients and providers in order to connect at-risk patients with these evidence-based therapies.

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1 Introduction

1.1 Burden of Cardiovascular Diseases

Cardiovascular disease (CVD) is the main cause of morbidity and mortality worldwide, accounting for nearly a third of deaths in 2016 (17.9 million of the 56.9 million deaths) [1–4]. Well over half of those deaths are due to coronary heart disease (CHD)—the most common type of CVD and the world's biggest killer [1]. CVD deaths are predicted to increase to over 23.6 million by 2030 due to aging populations and a high prevalence of risk factors for atherosclerosis, such as high blood pressure, type 2 diabetes mellitus (T2DM), obesity, high levels of atherogenic lipids, inadequate diet, low physical activity, and smoking [2, 4–6].

The links between CVD, obesity, T2DM, and physical inactivity are well established and are the main reason for the risk of CVD-related death being almost three times greater in high-income countries than low-income countries [4, 7–10]. In the USA alone, where less than 23% of adults report participating in adequate leisure-time aerobic and muscle-strengthening activities to meet the recommended amount [4–6], the annual cost of CVD is over $200 billion [6]. With CVD risk factors rapidly increasing in prevalence and going unchecked in many adults, developing effective prevention programs have gained considerable interest over the years [7–11]. While there has been an overall increase in CHD burden in high-income countries, mortality rates have declined since the 1980s due to preventive interventions, modern treatments for acute cardiovascular events, and rehabilitation programs, all of which have been shown to prolong survival [2, 4, 5, 12, 13]. In many countries, CHD rates are now less than half what they were in the early 1980s, mainly due to preventive lifestyle interventions including the success of smoking legislation [4, 5].

As CVD morbidity continues to rise, with a growing number of survivors of myocardial infarction (MI) and an associated number of patients with chronic heart failure (HF), so does the burden on the medical and economic infrastructure [4, 14]. People with CHD, including post-MI survivors, and people with chronic HF experience marked reductions in their exercise capacity, which has detrimental effects on their activities of daily living, health-related quality of life, hospital admission rate, and mortality.

The combination of population growth and aging, and increasing exposure to behavioral and metabolic risks continues to drive the increasing trends in CVD at the global level and the number of adverse outcomes in individuals with established CVD including survivors post-acute cardiovascular (CV) events [2, 4]. The growing body of evidence confirms that secondary prevention modalities such as optimal pharmacotherapy and aggressive, comprehensive risk factor management improves survival, reduces recurrent events and the need for interventional procedures, and improves quality of life for these patients [15]. Evidence-based data provide the basis for the formulation of guidelines that include a number of general recommendations on the management of patients with established CVD which are aimed to prevent the progression or recurrence of the disease [5, 13, 16–21]. Secondary

prevention modalities include behavioral interventions such as changes in nutrition, body weight control, and physical activity as well as smoking cessation and pharmacotherapy-based prevention strategies, which address lipid disorders, T2DM, platelet aggregation, and arterial hypertension (see Table 1).

CVD prevention consists of a coordinated set of actions, at the population level or targeted at an individual, which are aimed at eliminating or minimizing the impact of CVD and their related disabilities [5]. Although therapeutic targeting of CVD and traditional risk factors for atherosclerosis has reduced mortality rates, this effect is not sufficient and has not prevented an increase in CVD morbidity [1, 2, 4, 14]. Much of this problem is attributable to suboptimal implementation of prevention strategies and uncontrolled risk factors in individuals with established CVD [6]. Structured cardiac rehabilitation (CR) programs offer a means to address this problem.

According to national and international guidelines, participation in a center- or home-based CR program is recommended in patients post-hospitalization for systolic HF, acute coronary syndrome, chronic stable angina, cardiac surgery, or revascularization procedure to improve patient outcomes and reduce disease recurrence [13, 16, 18–22]. CR is a comprehensive exercise, education, and behavior modification program designed to improve the physical and emotional condition of patients with CVD through a combination of activities, in particular, exercise training alongside educational and psychological support [23]. CR programs usually consist of a personal assessment of the patient, advice on physical activity, training exercises, nutritional advice, weight management, lipids and blood pressure control, tobacco cessation, and psychosocial management. Rehabilitation after a CV event can be a lifelong process and is generally divided into three to four phases, which can be categorized as inpatient, outpatient, and maintenance [23].

CR has been consistently shown to improve patient outcomes [24]. An overview of six Cochrane systematic reviews of CR (148 randomized clinical trials [RCTs] with 97,486 subjects) concluded that for low- to moderate-risk patients with HF, or

Table 1 Secondary prevention strategies

Components of secondary prevention [5, 13]
Smoking cessation
Blood pressure control
Lipid management
Physical activity
Nutritional counselling
Weight management
Type 2 diabetes mellitus management
Antiplatelet agents/anticoagulants
Renin-angiotensin-aldosterone system blockers
Beta blockers
Influenza vaccination
Depression screening/treatment
Cardiac rehabilitation

patients who are post-MI or revascularization, exercise-based CR decreased hospital admissions and improved health-related quality of life compared with usual care and may reduce mortality longer term [24]. However, despite national and international guidelines consistently recommending CR as an effective and safe intervention in patients with CHD and HF [13, 16, 18–22], uptake of CR remains at suboptimal levels [23]. In addition, maintaining longer-term adherence to CR is also a key challenge.

Ineffectiveness of current diagnostic and treatment strategies for CVD indicate the need to develop more effective preventive interventions which presents both a public health challenge and opportunity. There is evidence that the primary prevention based on lifestyle interventions is effective; the elimination of health risk behaviors can potentially prevent at least 80% of CVD [25]. Further improvements in secondary prevention strategies are also expected to lead to additional significant benefits in patients with established CVD.

2 Secondary Prevention

2.1 US and European Guidelines

Current guidelines for the secondary prevention of CVD involve intensive therapies specifically targeting management of CV risk factors [13, 16]. The American Heart Association (AHA) and American College of Cardiology (ACC) Class I recommendations typically involve behavioral counseling for appropriate lifestyle modifications including smoking cessation, dietary changes, and physical activity goals coupled with pharmacologic therapies. Similarly, the European Society of Cardiology (ESC) focuses on optimizing medical therapy and emphasizes lifestyle modification through patient education in order to reduce CHD risk factors [16]. This chapter will focus on specific behavioral strategies including physical activity, exercise, nutrition, and psychosocial factors. Table 2 reviews the US and European guidelines for behavioral treatments for HF and CHD.

2.2 Pharmacotherapy Optimization

The patients' care team must closely monitor medication prescriptions and adherence to specific practice guidelines [16, 27, 28], especially as patients age and comorbidities increase. Polypharmacy (commonly defined as ≥5 medications) [29] can be a risk factor in itself, with the compounding of various medications producing undesirable, or even dangerous, side effects such as poor adherence, drug interactions, frailty, hospitalizations, cognitive impairments, and medical errors, to name a few [30, 31]. A prospective cohort study following 4000 adults over 14 years

Table 2 US and European behavioral guidelines for secondary prevention

Condition	Heart failure		Coronary heart disease	
Regional recommendations	USA [19, 26]	Europe [5, 21]	USA [13, 20]	Europe [5, 16]
Physical activity	Regular physical activity	Regular physical activity	30–60 minutes of moderate aerobic activity at least 5 days a week (preferably 7 days a week) and increase daily lifestyle activities	30–60 minutes of moderate aerobic activity at least 5 days a week but even irregular activity and leisure-time activity are beneficial
Exercise training	Exercise training to improve functional status in those who are able Refer to cardiac rehabilitation program in clinically stable HF patients *Note: Those with New York Heart Association functional class IV are at higher risk for exercise training*	Regular aerobic exercise to provoke mild to moderate breathlessness for improving functional capacity and symptoms, and reducing the risk of HF hospitalization Resistance training may be appropriate Refer to exercise-based cardiac rehabilitation program as needed	All eligible patients diagnosed with acute coronary syndrome, coronary artery bypass surgery, percutaneous intervention, chronic angina, and/or peripheral artery disease within the past year should be referred to a cardiac rehabilitation program	Exercise-based cardiac rehabilitation programs are recommended in patients with coronary heart disease, including patients hospitalized for an acute coronary event or revascularization, and patients with HF

(continued)

Table 2 (continued)

Condition	Heart failure		Coronary heart disease	
Regional recommendations	USA [19, 26]	Europe [5, 21]	USA [13, 20]	Europe [5, 16]
Nutrition and diet	Adjust fluid intake based on weight and weather conditions. Limit to 2 L/d for hospitalized/advanced HF patients Reduce sodium intake to 1500 mg/d in Stage A and B heart failure, <3 g/d in Stage C and D heart failure	Adjust fluid intake based on weight, presence of hypovolemia and acute decompensation, and weather conditions. Consider reducing to 1.5-2 L/d in patients with severe HF Lower sodium intake to <6 g/d Healthy diet Reduce alcohol consumption	Increase fresh fruits, vegetables, and low-fat dairy products in diet Reduce intake of saturated fats (<7% of total calories), trans fatty acids (<1% of total calories), and cholesterol (<200 mg/d) Moderate alcohol consumption Reduce sodium intake	Increase consumption of fruit, vegetables, and wholegrains. Eat fish (1–2 servings/week) and nuts (30 g/d) in moderation Limit lean meat, low-fat dairy products, and liquid vegetable oils Restrict saturated fat (<10% of total energy intake) and trans unsaturated fats (<1% of total energy intake); replace with polyunsaturated fats Reduce alcohol to <100 g/week or 15 g/d Lower sodium intake to <6 g/d Avoid energy-dense foods (e.g., sugar-sweetened drinks)
Psychosocial factors	Increase social support	Provide psychosocial support to patients, families, and/or caregivers	Screen for depression in patients with recent coronary artery bypass surgery or myocardial infarction Refer to mental health specialist as needed	Assess for psychosocial risk factors Refer to mental health specialist as needed

found that among adults with polypharmacy, those exhibiting intermediate to favorable healthy lifestyle behaviors had a marked reduction in all-cause and CVD mortality (up to 54% and 60% respectively) [32]. They calculated that replacing one medication with one healthy lifestyle habit could theoretically reduce risk by about 30%, both for all-cause and CVD death [32]. Reducing the pharmacotherapeutic burden on patients is becoming part of routine CV care as providers prioritize reducing medication prescriptions while still optimizing for effectiveness and adherence [33].

2.3 Physical Activity

An integral component of secondary prevention is the incorporation of physical activity (PA) in the daily routine, particularly when trying to mobilize sedentary patients after a Major Adverse Cardiovascular Event (MACE). This entails sustained moderate aerobic activity outside of a clinical setting which includes familiar exertive work such as gardening, household chores, and walks [13]. The ESC recommends that all individuals accumulate at least 30 min/day, 5 days/week of moderate-intensity PA (i.e., 150 min/week) or 15 min/day, 5 days/week of vigorous intensity PA (75 min/week), or a combination of both, performed in sessions with a duration of at least 10 min [5]. For lipid control or body weight management, longer durations of PA, 40 and 60–90 min/day, respectively, have been proposed. The current recommendation for PA in stable coronary artery disease (CAD) patients is 30–60 minutes of moderate-intensity aerobic PA at least 5 days of the week, to elicit a heart rate 60–85% of maximum [13, 16]. In building endurance through PA, those with a history of CAD and MI can better perform physical tasks before reaching their anginal threshold [34]. A decline in the event of myocardial ischemia is seen with sustained aerobic exercise due to a decrease in myocardial oxygen demands for the same amount of physical work [5, 35]. Highly controlled modes of PA include brisk walking, running, cycling, or swimming that involves large muscle groups which can increase peak aerobic capacity and are inversely related to all-cause mortality in patients with CAD [36]. Even leisure-time PA lower than what the ESC recommends decreases mortality risk among previously sedentary patients [37], and increasing levels of activity is associated with lower CV mortality [38].

2.4 Exercise Training

Exercise training (ET) has actively been a core component of secondary prevention programs (SPP) and early models of CR [34]. ET is structured, goal oriented, and often includes physiological monitoring and takes place in an exercise-training facility or even a clinical setting. According to the European Association for Cardiovascular Prevention & Rehabilitation (EACPR), exercise training models

should be well-planned, repeated bodily movements meant to maintain or improve physical health over a set period of time [39].

Moderate aerobic activity is the foundation of many exercise training models. These aerobic exercises can be performed in sustained intervals as short as 10 minutes, and should be repeated multiple times throughout the week for a minimum total of 2.5 hours. ET should incorporate submaximal endurance training, sustained aerobic exercises (which can be evaluated based on VO2max), weight and resistance training when appropriate [40]. After completion of an exercise-training program the patient should present a 5–10% improvement in CV fitness, strength, and flexibility [41]. In addition to CV and strength exercises, resistance training has also been found to be valuable in improving muscular strength by at least 25% in both men and women [42]. It was also found that strength and resistance training over a span of only 12 weeks led to a 38% improvement in submaximal walking time. These data suggest that increased muscle strength plays an important role in building endurance in patients that moderate aerobic exercise alone cannot provide [43]. Resistance exercises maintain muscle mass, strength, and function and, with aerobic activity, have benefits regarding insulin sensitivity and control of lipids and blood pressure [16].

Exercise enhances oxygen delivery to the myocardium, improves angina, and increases exercise capacity, which is an independent predictor of increased survival among patients with chronic coronary syndrome [16]. Every 1 mL/kg/min increase in exercise peak oxygen consumption was associated with a 14–17% reduction of risk for CV and all-cause death [36]. Exercise-based CR reduces CV mortality and hospitalizations in patients with CHD compared with no exercise controls [44, 45].

Several systematic reviews and meta-analyses have demonstrated that ET improves exercise tolerance, quality of life, and HF hospitalization rates [21], and reduces all-cause mortality in subjects with HF [46]. A single large RCT showed a reduction in the primary composite outcome of all-cause mortality or all-cause hospitalization [47]. The most recent Cochrane review including 44 trials with 5783 patients with HF (predominantly HF with reduced ejection fraction, HFrEF) showed that exercise-based CR has no impact on mortality but reduces the risk of all-cause hospital admissions and may reduce HF-specific hospitalizations in the short-term follow-up (up to 12 months) [48]. Regular exercise sufficient to provoke mild or moderate breathlessness is recommended in patients with chronic HF (independently from left ventricular ejection fraction) to improve functional capacity and symptoms [21]. Regular aerobic exercise is recommended in stable patients with HFrEF to reduce the risk of HF hospitalization [21]. ET (or regular PA) is recommended as safe and effective for patients with HF who are able to participate to improve functional status [19].

The ideal "dose" of endurance ET is debatable—since there is the possibility that too much exercise training may have ill effects [49]. Running or walking decreases CVD mortality risk progressively at most levels of exercise in patients after a cardiac event, but the benefit of exercise on CVD mortality and CHD-related deaths is attenuated at the highest levels of exercise (running: above 7.1 km/d or walking briskly: 10.7 km/d).

MI, and to a lesser degree sudden cardiac death, appears to occur more frequently in patients with CVD than in healthy individuals while exercising [50]. Intense

physical exertion precedes anywhere from 4% to 20% of MIs and more than doubles the risk of sudden cardiac arrest in sedentary males than in active males [51]. Participation in low-impact, continually monitored ECG exercises are at the lowest risk of event occurrence. The occurrence of MACE in patients that happen during supervised ET ranges from 1 in 50,000 to 120,000 hours of exercise [34]. Furthermore, for every 1.5 million patient-hours of exercise there are only 2 fatalities reported on average [52].

2.5 Nutrition

The role of a cardioprotective diet is generally acknowledged to play a significant role in a healthy lifestyle [53]; data collected over the past 60 years from observing and studying dietary patterns around the world has shined a light on the correlation between dietary content and the incidence of CVD [54, 55]. For example, since the first observation connecting dietary fat intake with serum cholesterol levels and CHD in the Seven Countries Study, researchers have further stratified types of fat into those that are more beneficial for us to consume for their cardioprotective benefits from more healthful polyunsaturated fats to more harmful saturated and trans fatty acids [56–58]. Considering such data, the AHA has made diet recommendations increasing consumption foods such as fish, walnuts, flaxseeds, soybean oil, and corn oil which are high in polyunsaturated fats [59]. These provide a healthier alternative to the harmful aforementioned fats that can be commonly found in butter, lamb, beef, fried foods, pastries, and processed oils [60]. In the USA, the most consumed calorically dense foods are burgers, sandwiches and tacos, sweet snacks, and sugar-sweetened beverages, and there is a glaring need to replace these highly processed and artificially sweetened foods with nutrient-dense alternatives [53]. It is not uncommon for patients to be entrenched in their unhealthy eating patterns, and it is important to acknowledge the many personal and economic barriers that may be preventing people from changing how and what they eat.

Unhealthy diets are major factors that increase the risk of CHD and its progression [61]. The contribution of hypercholesterolemia, diabetes, obesity, and high blood pressure to the progression of CHD is well documented [62–64], but modifiable. Implementation of healthy diet and eating patterns in CHD patients have resulted in a reduction in mortality and CV events. For example, the risk of CHD is reduced by 2–3% when 1% of energy intake from saturated fatty acids is replaced by polyunsaturated fatty acids [16]. Saturated fatty acid intake should be reduced to a maximum of 10% of energy intake by replacing it with polyunsaturated fatty acids. A meta-analysis of prospective cohort studies has shown that, on average, a 2% increase in energy intake from trans fatty acids increases CHD risk by 23% [5]. It is recommended to use *trans* fatty acids as little as possible: preferably no intake from processed food and <1% of total energy intake from natural origins [5]. Even considered independently from traditional risk factors for CVD, dietary patterns that are high in protein and fat and low in carbohydrates, also known as the "Western diet," have been shown to promote more extensive atherosclerosis and decrease the

number of endothelial progenitor cells (EPCs), albeit in animal models [65]. In clinical studies, a greater number of circulating EPCs are correlated with improved vascular function and reduced mortality, occurrence of a first major CV event, rate of revascularization, and hospitalization from CV causes [66, 67].

Certain dietary patterns, such as the Mediterranean Diet (MD), the Dietary Approaches to Stop Hypertension (DASH) diet, and the Vegetarian diet, have been shown to reduce CVD risk factors in patients with established CHD or at high risk for developing CHD [68–76]. A summary of these different types of diets can be found in Table 3. Though there are many versions of the MD, it is characterized by its focus on high intake of olive oil, whole grains, fresh fruit and vegetables and low intake of red meat and processed foods. The MD has been extensively studied in cardiac patients and is widely prescribed by physicians as part of guideline-directed care [16, 77, 78]. The Lyon Diet Heart Study was a randomized secondary prevention trial which showed that a MD reduced the rate of CV events during follow-up lasting up to 4 years after a first MI [71]. More adherent subscribers to the MD dietary pattern are at lower risk of CHD by two-thirds and stroke by one-half based on data from multiple large-scale epidemiological and interventional studies [53]. A meta-analysis of prospective cohort studies has demonstrated that greater adherence to a MD is associated with a 10%

Table 3 Components of popular diets for managing CV risk and their components

Dietary pattern	Fat	Carbohydrate	Protein	Dairy	Alcohol
Mediterranean [84]	High monounsaturated to saturated fat ratio, olive oil and tree nuts emphasized	High intake of plant-based foods, i.e., fruit, vegetables, and legumes	Reduce red meat consumption to a minimum and increase fish and seafood	Moderate consumption of milk and other dairy products	Low to moderate red wine consumption
DASH [85]	Primary source of fat from proteins and dairy	Grains and grain products (include at least 3 whole grain foods each day), fruit, vegetables, nuts, seeds, and legumes	Lean meats, fish, or poultry	Mostly low-fat or non-fat dairy foods	Allowed in moderation
Vegetarian [86]	Plant-based oils allowed, typically low in saturated fats	Vegetables, fruits, grains	Nuts, seeds, and legumes. No intake of animal meats, but may consume animal products.	Usually allowed	No restrictions noted

reduction in CVD incidence or CV mortality and an 8% reduction in all-cause mortality [79]. A primary prevention RCT in high-risk individuals suggested that following a MD over a 5-year period, compared with a control diet, was related to a 29% lower risk of CVD [68]. The DASH diet was developed to treat and prevent high blood pressure without medication and is complementary to the MD with a focus on lowering the daily intake of sodium [80]. It has since evolved into different versions that more closely resemble the MD with more plant-based proteins and unsaturated fat, which has proved effective in controlling the progression of more CV risk factors [81]. There are similarly many variations of the vegetarian diet, but it is characterized by excluding the consumption of animal meats including fish and poultry. In 1999, an analysis of more than 76,000 people followed for an average of 10.6 years demonstrated death from ischemic heart disease was 24% lower in vegetarians versus nonvegetarians. Furthermore, compared to regular meat eaters, occasional meat eaters had a 20% lower mortality from CVD and people who ate fish, but not other types of meat, had a 34% lower mortality from CVD [82]. In a meta-analysis of 11 RCTs, the vegetarian diet significantly lowered lipid levels except for triglycerides [83].

2.6 Psychosocial Factors

While CVD remains the leading cause of mortality in the United States, accounting for about 25% of deaths each year [4, 87], there were approximately two million more office visits to psychiatrists than cardiologists in 2016 [88]. Past reviews have identified five major psychosocial contributors to CVD risk: depression, anxiety, personality factors and character traits (i.e. anger and hostility), social isolation, and chronic life stress [89]. While more recent results from observational studies have shown mixed results linking anxiety and personality factors to CVD incidence and deserve deeper study [90, 91], the other psychosocial contributors have shown more consistent supporting data. These psychological factors are twofold in that they can influence patients' susceptibility to developing CVD through both pathophysiological and behavioral mechanisms. Over stimulation of the sympathetic nervous system [92, 93], hypercortisolemia [94, 95], enhanced platelet reactivity [96], and impaired vagal control [97] in patients exhibiting these symptoms may confer increased risk of atherogenesis and arrhythmogenesis via biological pathways. Higher incidence of smoking, poor diet, and increased alcohol consumption are common comorbid conditions in these populations as well [98–100].

Since 1990, depressive disorders have been in the top five Level 3 causes of global years lived with disability (YLDs) in women and men combined, featuring in females more prominently [14]. The same report supports past observations that psychosocial stresses tend to cluster together. This may have additive effects that contribute to higher risk of CV events. As observed in the Psychosocial Factors Outcome Study [101], depression and social isolation predicted mortality

in HF patients independently from demographics, clinical predictors, and treatment.

Depression is particularly important to consider in the secondary prevention population as depressed mood has been associated with poor medication compliance. According to a meta-analysis on over 18,000 participants, depressed patients are more than 1.5 times less likely to be adherent to their medications than their nondepressed counterparts [102]. Poor medication adherence and depressive symptoms had a negative synergistic effect in HF patients on cardiac event-free survival rate (hazard ratio (HR) = 4.949) compared to those who exhibited only one risk factor (HR = 1.366 and 1.41) or no risk factors (HR = 1.0) [103].

Higher rated chronic stress is associated with higher incidence of primary CV events [104, 105] and may increase CV mortality in patients with stable CHD [106]. Mindfulness meditation has been shown to reduce depressive and anxious symptoms, blood pressure, and body mass index (BMI) in CHD patients [107]. Other techniques such as yoga are associated with positive effects on reducing systemic inflammation, stress, and cardiometabolic risk factors when combined with other prevention programs, such as cardiac rehabilitation [108]. A recent study found significant benefit of yoga on endothelial function, arterial stiffness, and blood pressure over a brisk-walking intervention in an elderly population [109]. RCTs investigating other meditative practices such as Chinese Qi Gong and Transcendental Meditation have shown improved physiologic markers and in one case even demonstrated regression of atherosclerosis [110, 111]. While more research needs to be conducted in this field, these techniques present a great opportunity for widely implementable low-risk and low-cost therapies [112].

Similarly, there is a need for more investigation into the connections between social support and CVD [113]. While data has not shown much causal significance of perceived social support on incidence of CHD [114, 115], several epidemiologic studies have observed a positive correlation between increased social support with improved prognosis post-MI and better functional status post-stroke [116–120]. In fact, social support networks appear to be just as important in predicting 1-year mortality after acute myocardial infarction as traditional CV risk factors [121].

3 Cardiac Rehabilitation

Traditionally, CR was developed to safely transition patients back to daily physical activities after an adverse CV event. However, CR has substantially evolved along with our understanding of the importance of secondary prevention strategies, and now also incorporates risk-factor reduction and healthy habit formation to a varying degree (see Fig. 1) [122]. There is now a comprehensive set of criteria that any SPP must meet in order to be nationally certified by the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) (http://www.aacvpr.org/certification/). The core components of CR and SPP put forth by the AHA/AACVPR are summarized in comparison to the criteria required by Medicare to qualify for reimbursement in Table 4. CR is a multidisciplinary effort which consists of a core

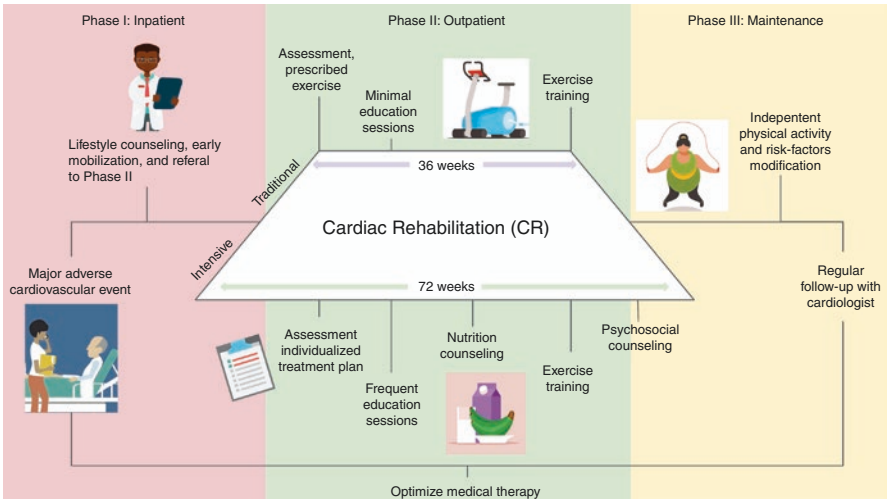

Fig. 1 Cardiac rehabilitation at a glance

Table 4 Core components of SPP and CR

Core components of CR/SPP	
AHA/AACVPR Guidelines [122]	*Medicare Guidelines* [123]
Patient assessment	Psychosocial assessment
	Outcomes assessment
Weight management	Cardiac risk factor modification, including education, counseling, and behavioral intervention tailored to the patients' individual need An individualized treatment plan detailing how components are utilized for each patient. The individualized treatment plan must be established, reviewed, and signed by a physician every 30 days
Blood pressure management	
Lipid management	
Diabetes management	
Tobacco cessation	
Psychosocial management	
Physical activity counselling	
Nutritional counselling	
Exercise training	Physician-prescribed exercise each day cardiac rehabilitation items and services are furnished.

team of a cardiologist, nurse, physical therapist, dietitian, and psychologist with other professional consultants as appropriate [41].

3.1 US and European Guidelines

Referral to a comprehensive outpatient CR program is a Class I recommendation for all eligible patients within 1 year of a diagnosis of acute coronary syndrome, coronary artery bypass graft (CABG) or percutaneous coronary interventions (PCI), chronic

angina, and peripheral artery disease. For patients who undergo CABG or PCI, referrals should be placed prior to hospital discharge or at their first follow-up clinic visit. Lower-risk or stable patients should also consider participating in some sort of outpatient CR and wellness activity, such as a home-based or exercise-based program [13].

The ESC and EACPR have published guidelines on referring acute cardiac patients to exercise-based CR programs prior to hospital discharge and encourage more development in home-based and telerehabilitation models [5]. Following the ESC guidelines, exercise-based CR is recommended as an effective means for patients with chronic coronary syndromes to achieve a healthy lifestyle and manage risk factors [16]. Also, all patients with acute MI should participate in exercise-based CR programs, taking into account their age, pre-infarction level of activity, and physical limitations [124]. This CR program preferably includes exercise training, risk factor modification, education, stress management, and psychological support. CR can also be useful in clinically stable patients with HF to improve functional capacity, exercise duration, quality of life, and mortality [19].

3.2 Phase I

After an acute cardiac event, patients may begin Phase I CR in the hospital as soon as they have reached a stable condition. Programs vary across institutions and have become less formal as hospital stays trend shorter, but typically focus on patient support, education, and early mobilization. Based on their clinical situation, patients receive an exercise prescription and work on regaining their confidence in performing daily activities and limiting the side effects of bed rest. Before discharge, patients should receive an initial exercise assessment, comprehensive discharge plan, and referral to an outpatient program [40, 41].

3.3 Phase II

Phase II medically supervised outpatient CR provides monitored exercise, education and counselling. Ideally, these should be graduated sessions, equipping patients to self-monitor their exercise response and adhere to heathy lifestyle practices so that they can confidently transition to the last phase.

3.3.1 Standard CR

Most standard CR (SCR) programs follow a 36-session model, in which patients participate in supervised exercise for 1 hour, 3 days a week, sustained over a 12-week interval [122] with minimal education on CVD and risk factors, as well as independent exercise [125].

The goal of the workout is daily sustained, low-impact aerobic activity that can be increased over time. Exercises may entail long-distance and long-duration walking and should be tailored to the individual based on health assessments and severity of the MACE in order to maintain minimal risk of physical and musculoskeletal injury [122]. A substantial benefit of participating in a SCR program includes supervised exercise via electrocardiographic (ECG) blood pressure and heart rate/arrhythmia monitoring as a means to surveille and revise exercise prescriptions, ensuring that patients are exerting themselves safely [126, 125].

The majority of SCR programs are exercise-focused, with some patient education on other risk factor modifications such as smoking cessation, recommended dietary guidelines, and stress management [127]. The bare-boned model of CR, although seemingly effective short term, may be too minimal considering a study in 2012 revealed that 45.4% of cardiometabolic deaths were associated with poor nutritional intake [128].

3.3.2 Intensive Phase II Programs

Intensive CR (ICR) programs are more rigorous and robust, requiring twice as many sessions as SCR to formally incorporate interventions such as mindfulness activities, group support, and nutrition counselling in addition to the standard exercise program. Up to 6 of the 72 sessions can be used per day and all sessions must be used within 18 weeks [129]. Three programs are currently approved for reimbursement by Centers for Medicaid and Medicare Services (CMS): The Ornish Reversal Program (Ornish), Pritikin Program (Pritikin), and the Benson-Henry Institute for Mind Body Medicine and Massachusetts General Hospital's Cardiac Wellness Program (MGH/BHI) [130–132].

Notably, these programs have passed thorough review by CMS to qualify as an ICR program eligible for reimbursement. Each of the programs have effectively demonstrated positive effects on halting the progression of CHD, reduces the need for CABG, and/or reduces the need for PCI [129]. In peer-reviewed, published research, patients enrolled in these programs have statistically significant reductions in five or more of the following measures: low-density lipoprotein, triglycerides, BMI, systolic blood pressure, diastolic blood pressure, and/or the need for cholesterol, blood pressure, and diabetes medications [129]. SCR programs do not undergo this approval process. See Table 5 for the breakdown between CR programs.

3.4 Phase III

In phase III CR, patients independently continue their exercise conditioning and lifestyle changes at home with regular office visits with their physician. However, an increasing number of CR centers offer maintenance programs which allow phase II graduates to exercise in their facility without the same intensive supervision.

Table 5 Overview of SCR versus ICR

	Standard cardiac rehab	Intensive cardiac rehab
Modalities offered	Outpatient	Outpatient
Visits covered by Medicare	36 sessions over 12 weeks (+ 36 sessions if deemed medically necessary)	72 sessions over 18 weeks
Emphasis	Exercise Patient education of CV risk factor modification	Exercise Patient education of CV risk factor modification Diet and nutrition counselling Psychosocial therapy and support
Format	CR programs in the USA follow AACVPR Guidelines and are not branded like the ICR programs	Ornish Program Pritikin Program Benson-Henry Institute Cardiac Wellness Program *Note: Must be supported by peer-reviewed, published literature to be eligible for CMS reimbursement*
Indications	An acute myocardial infarction within the preceding 12 months A coronary artery bypass surgery Current stable angina pectoris Heart valve repair or replacement Percutaneous transluminal coronary angioplasty or coronary stenting A heart or heart-lung transplant Stable, chronic heart failure defined as patients with left ventricular ejection fraction of 35% or less and New York Heart Association (NYHA) Class II to IV symptoms despite being on optimal heart failure therapy for at least 6 weeks Peripheral arterial disease Diabetes mellitus (EACPR only) [27] Metabolic syndrome (EACPR only) [27]	
Contraindications (delineated only for the exercise component of CR)	Unstable angina Acute decompensated congestive heart failure Complex ventricular arrhythmias Severe pulmonary hypertension (right ventricular systolic pressure >60 mm Hg) Intracavitary thrombus Recent thrombophlebitis with or without pulmonary embolism Severe obstructive cardiomyopathies Severe or symptomatic aortic stenosis Uncontrolled inflammatory or infectious pathology Any musculoskeletal condition that prevents adequate participation in exercise	

Sustaining these preventive and rehabilitative changes at this stage are essential for reducing risk of recurrent CV events [23]. As there are no uniform guidelines on phase I and III CR, the more structured and well-studied phase II will be the main focus as discussed below.

3.5 Supporting Clinical Data

According to recent data from the AHA, patients with CVD who complete a CR program have a 31% lower hospital readmission rate, improvement in performing daily activities, exercise performance, and psychosocial symptoms [133]. Participation in an exercise-based CR program led to a 20% decrease in total and CV mortality in post-MI patients at 1-year follow-up compared to those who did not participate in a CR program [134]. In one trial, 27 HF patients who were put through a CR program with intense aerobic interval-training three times a week for 12 weeks exhibited a 35% improvement in left ventricular ejection fraction and a 40% decrease in pro B-type natriuretic peptide when compared with control groups and exercise groups that simply focused on endurance-training [135]. Post-PCI patients participating in CR exhibit a 39–47% reduction in all-cause mortality compared to those who opted not to participate in a CR program [136, 137]. This difference is sustained up to 10 years later in patients who completed CR versus those who did not as indicated by their 46% lower mortality [136].

Outcomes of long-term CR participation were evaluated in the Global Secondary Prevention Strategies to Limit Event Recurrence After MI (GOSPEL) trial involving over 3000 patients from Italian CR centers [138]. After completing a standard CR program, participants were randomized to either the 3-year intensive CR program involving behavioral counselling and aerobic exercise or to the standard-of-care group. The intervention group had significantly better diet, exercise, and stress management habits as well as decreased several combined endpoints, such as CV mortality plus nonfatal MI and stroke by 33%, cardiac death plus nonfatal MI by 36%, and nonfatal MI by 48% [138].

Dr. Dean Ornish's Lifestyle Heart Trial was a seminal study published 30 years ago that systematically studied the effects of combining multiple therapeutic modalities of diet, exercise, stress management training, and smoking cessation versus treatment as usual in patients with established CAD [139]. After 1 year, 18 out of 22 patients in the experimental group experienced regression of their coronary artery lesions, while 10 out of 19 of those in the control group had progression of their lesions as evaluated by coronary angiography [139]. Approximately three quarters of patients in both groups completed a follow-up 5 years after the original study and reportedly maintained their relative lifestyle changes. In the experimental group,

coronary plaque continued to improve while the control group had nearly a 30% relative worsening from baseline [140]. At both these time points, those who were most adherent to the lifestyle changes exhibited the most plaque regression, suggesting a causal relationship. Within the same 5-year period, the control group had more than twice as many cardiac events than the treatment group.

Long-term adherence to the Pritikin program has also demonstrated benefit. In a cohort of 64 patients who participated in a 26-day residency program, improvements in angina were sustained over 5 years [141]. In the short term, participation in the Pritikin program appears to reduce many CV risk factors including serum lipids and blood pressure, reducing the need for pharmacological therapy [142–144]. No data have been published on longer-term outcomes, however.

These two programs, the Ornish program and the Pritikin program, recommend their patients follow primarily plant-based, low-fat diets. The Ornish program implements a vegetarian diet that allows egg whites and non-fat dairy [145]. All fat is naturally occurring from plants and make up less than 10% of calories in this diet. Similarly, the Pritikin program substantially limits fat intake to 1 teaspoon of oil per 1000 calories consumed, which translates to around 10% of calories consumed. However, it does allow for fish, white meats, and lean proteins [146]. Both programs emphasize consuming foods high in omega-3 fatty acids, a type of polyunsaturated fat which are found in plant and fish oils, of which higher consumption is associated with lower rates of sudden cardiac death, a leading cause of death in CHD patients [147].

The MGH/BHI program shares similar targeted core strategies as the other ICR programs, but tends to be slightly more lenient than its peers. Generally, patients in this program meet less frequently (3 hours/week), and are counselled to follow the AHA's dietary guidelines for heart health which align more closely with the MD than the Ornish and Pritikin eating patterns (<30% fat versus <10% fat in diet) [148]. In a Medicare-backed study to demonstrate the effectiveness of Ornish and MGH/BHI ICR programs, both arms showed statistically significant changes in risk factors such as lower blood pressure, low-density lipoprotein cholesterol, and better cardiac functional capacity. These benefits were sustained after 12 and 24 months in patients who continued to adhere to the lifestyle modifications learned in the program [149].

In a recent study following post-CABG patients going through SCR who received dietary counselling that followed current AHA guidelines found that there was no significant change in their dietary content from baseline to 3 months post-CR [150]. Contrast this to the Ornish ICR program, with its comprehensive recipes, cooking demonstrations and group meals, which have shown 100% adherence 1 and 5 years post-CR to a low-fat, vegetarian diet in a cohort of 20 people [140]. A 5-year follow-up on 50 patients who underwent a Pritikin ICR program revealed over 85% of participants reported a 50% or greater adherence to the low-fat, high-fiber, and high-complex carbohydrate diet, which was correlated with a reduction in serum cholesterol and triglycerides as well [141].

In a retrospective cohort study of 5908 patients in two SCR programs in Australia, moderate to severe depression, stress, and anxiety were prevalent in 18%, 13%, and

28% respectively, of this group upon program entry. These patients were significantly more likely to drop out compared to their peers who exhibited normal to mild symptoms [151]. They were also significantly more likely ($p < 0.001$) to be current smokers, live a sedentary lifestyle, have diabetes, and have a lower baseline MET level. Despite this population being at higher risk for depression and social isolation, most CR programs still lack an effective psychological health component. Indeed, though the Pritikin program offers educational classes on topics including stress management, it does not offer group and targeted therapy as the Ornish program does.

As research progresses and new fields such as behavioral cardiology emerge [152], incorporating evidence-based stress management techniques into CR programs is becoming more widespread. RCTs are currently underway testing novel yoga-centered CR programs [153]. ICR programs have a unique therapeutic opportunity to deliver dedicated psychosocial treatment to their patients both in the form of individual stress-management counselling and group support network development.

3.6 Referrals, Attendance, and Adherence

While the benefits of participation in CR programs reducing hospital readmission rates and CV mortality are clear [28, 154], recent data shows that only about two-thirds of eligible acute MI patients are referred to CR upon hospital discharge and only a third of those actually attend, despite it being a guideline-recommended therapy for these patients [155]. This is a glaring shortcoming, and hospital systems implementing automatic referral see a substantial increase in eligible patients receiving CR referrals [156]. Though referral rates have been steadily rising since 2007, they still remain notoriously low, especially for women, ethnic minorities, and elderly patients [34], and are inferiorly prescribed compared to medication and lifestyle counselling on discharge [157].

As difficult as it is to refer the right patients to CR, an even smaller proportion of patients attend and complete the full 36 sessions of SCR [158]. Gaining Medicare coverage for CMS-approved indications of these programs in the last 10 years has substantially lessened the cost for many patients, more so for ICR patients because the consolidated sessions lower the co-pay burden. Even then, obstacles such as transportation and scheduling have an additive effect in patients' determination to attend CR. Participation rates range from 20% to 30%, with even the most effective programs reaching only about 60% of eligible patients [159]. Lower rates are seen in patients with depression, higher BMIs, and tobacco abuse, who may benefit the most from these programs [160]. This is concerning as the effect of CR on long-term risk is dose dependent with more sessions attended associated with lower risk of death and MI after 4 years [161]. A retrospective review calculated that patients who completed all sessions of SCR had nearly a 50% decrease in risk of death and 30% decrease in risk of MI compared to those who only attend 1 session, and a 14%

and 12% risk reduction, respectively, in those who completed 24 sessions. Long-term adherence is equally disappointing, with a reported 27% of participants adherent to exercise recommendations after a year and a half post-CR [162].

Lifestyle adherence rates tend to be better post-ICR than post-SCR. In an aforementioned study, 98% of 580 patients participating in the Ornish (n = 140) and MGH/BHI (n = 440) programs completed the first 3 months of ICR. After a year, the adherence to the lifestyle modifications was still generally good for both programs (67% and 72% adherence for Ornish and MGH/BHI programs, respectively), though it continued to decline at the 2-year mark (47% and 58%, respectively) [149]. This is still notable as it is nearly double that of SCR programs at the 1–2 year post-CR mark despite the fact that ICR is more rigorous and requires greater lifestyle changes.

Taking patients' perspectives into account can assist with determining where resources should be targeted for improvement of CR programs. Self-reports from patients who completed SCR and maintained their exercise training identify referral structure, group support, and education of health benefits as some of the more important factors in determining CR participation and adherence [163]. Higher self-efficacy, a marker of behavioral persistence, development during the program was associated with better long-term adherence as well [164].

4 Future Directions

The disconnect between patients and CR programs may be alleviated by establishing more community-based CR programs to allow widespread access, which will in turn ideally yield improved attendance and better long-term adherence to programs [165, 166]. With the progression of the technology of wearable and mobile devices, remote continuous monitoring may be the solution to overcoming the entrance barrier to CR programs and resource-intensive in-person CR sessions. Preliminary data has shown some positive effects of integrating digital health technologies into SPPs [167, 168]. At this time, remote CR programs are not eligible for reimbursement by Medicare in the USA, but are covered in countries such as the United Kingdom, Australia, and Canada through their national healthcare policies [169]. As such, remote CR programs are slightly more prevalent in these countries, though more feasibility studies are needed to explore implementability and effectiveness of these types of programs.

5 Conclusions

Exercise, diet, and psychosocial factors all play an important role in maintaining health, but even more so in the prognosis of patients with established CVD. CR programs target these lifestyle factors to varying degrees and participation has

clearly demonstrated benefits in patient outcomes and risk factors. Whether patients are attending an exercise-based program or integrating other lifestyle modifications through an ICR program, stronger adherence to interventions both during and after the program are associated with better results. Exploration into new modalities of delivering CR, including yoga and remote health monitoring, are exciting avenues of research in this field. However, a major barrier that has yet to be effectively addressed is how to bridge the gap between these programs and the people who will benefit the most from them. Though CVD morbidity continues to rise, SPPs such as CR still go largely underutilized. Greater awareness and understanding of the benefits of CR must be reinforced at both the provider and patient level concurrent to developing stronger infrastructure to implement accessible programs to all eligible patients.

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Integrative Approaches for Cardiovascular Disease Prevention

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Summary

- Integrative medicine plays a critical role in addressing the underlying risk factors that play a pivotal role in the prevention and treatment of atherosclerotic cardiovascular disease.
- Evidence-based medicine supports the use of various nutraceuticals, mind-body modalities, and acupuncture as adjunctive therapies for maintaining wellness, mitigating stress, and improving blood pressure, blood glucose, and cholesterol levels, all of which play a role in improving cardiovascular health.
- Lifestyle modifications, such as well-balanced nutrition and physical activity, should be routinely addressed by practitioners and may require a multidisciplinary team-based approach.
- Much of the research within integrative cardiology would benefit from larger, randomized controlled trials.
- Successful integrative cardiology centers incorporate a team of holistic care providers, including but not limited to nutritionists, acupuncturists, and biofeedback, mindfulness, yoga, and tai chi specialists.

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1 Introduction

Integrative medicine encompasses a multidisciplinary, patient-centered approach that tailors medical care to an individual using evidence-based therapies and modalities focusing on body, mind, and spirit. Many different care models have focused on this important interplay of body, mind, and spirit, including Ayurvedic, Chinese, and osteopathic medicine, many of which are incorporated into the integrative approach. Over the years, anecdotes passed down over generations have given way to evidence-based evaluation of integrative treatment approaches. Understanding the connection of intrinsic and extrinsic factors and focusing on the whole person instead of the specific disease has been described as "systems healthcare" [1], including everything from the individual DNA sequencing to microbiome (the body's collection of microorganisms, predominately bacteria, the bulk of which live in the gut) to the epigenome (the chemical alterations to an individual's genome, or DNA, through inheritance, environmental exposures, or others, influencing how their genes are expressed) [2].

This system of healthcare is further defined in the Academic Consortium for Integrative Medicine and Health's description, "Integrative medicine and health reaffirms the importance of the relationship between practitioner and patient, focuses on the whole person, is informed by evidence, and makes use of all appropriate therapeutic and lifestyle approaches, healthcare professionals and disciplines to achieve optimal health and healing" [3]. These tenets directed toward a focus on cardiovascular disease (CVD) prevention and management are translated to integrative cardiology, with a focus on prevention, lifestyle, mind-body therapies, nutraceuticals, and other therapies to individualize each approach.

Patients seek out integrative therapies for many reasons, including guidelines not fitting their personal or spiritual beliefs or because they may experience side effects from recommended therapies. It is important for medical providers to be able to incorporate integrative modalities into our daily practice to meet patient needs. We discuss in this chapter health promoting and disease prevention strategies with a focus on integrative cardiology approaches, including the available evidence for their efficacy and current recommendations.

2 Integrative Approaches to Primary and Secondary Prevention: Definition and Principles

Integrative medicine plays a key role in both primary and secondary prevention of CVD. A large component of the integrative philosophy is lifestyle modification, which is supported by the 2013 and 2019 American College of Cardiology and American Heart Association joint guidelines [4, 5]. Specifically, nutrition, physical activity, tobacco cessation, and stress management are key factors to address for prevention. Cardiovascular risk should be regularly assessed with the atherosclerotic

cardiovascular disease risk calculator, incorporating age; sex; race; blood pressure; cholesterol; history of diabetes, hypertension, and tobacco use; and use of statin and aspirin [6]. The guidelines also provide a list of risk-enhancing factors, such as family history, metabolic syndrome, inflammatory factors, as well as female-specific factors related to pregnancy that can further help inform the treatment decision, as well as coronary calcium scoring when the treatment decision is still uncertain. Coronary calcium score, family history, and high-sensitivity CRP has also been proposed to help further delineate risk through the Astro-CHARM risk calculator [7]. These risk scores can help practitioners navigate guideline-based testing and treatment for at-risk patients. Presence of CVD or risk factors, such as obesity, diabetes, hypertension, and hyperlipidemia, serve as opportunities for individualized, attainable lifestyle modifications. Those with known coronary artery disease, hypertension, and/or dyslipidemia should be on guideline-directed medical therapy [8, 9], to the extent possible.

3 Role of Nutrition and Lifestyle Approaches

The key to primary prevention is attaining and maintaining health through regular physical activity and well-balanced nutrition. There is a dose-response relationship between physical activity and incidence of CVD and cardiovascular mortality, with increasing amounts of physical activity conferring lower risk [10]. Physical activity recommendations include at least 150 minutes of moderate-intensity or 75 minutes of high-intensity aerobic exercise per week [10]. In addition, exercise regimens should incorporate strength training, balance, and stretching in order to improve or maintain physical function and prevent injury [10]. As of 2018, the aerobic physical activity target was not met by approximately 50% of US adults [10], identifying an unmet need for providers to address. Some evidence suggests brief yet motivational counseling along with specific exercise prescriptions in the primary care setting, use of Internet-delivered interventions, and improved access to gyms or active outdoor space have been shown to increase the amount of physical activity achieved [10]. Supervised exercise in the form of cardiac rehabilitation reduces mortality in patients with history of myocardial infarction, percutaneous coronary intervention, coronary artery bypass surgery, heart failure, stable angina, valvular heart disease, and heart transplantation [11]. Unfortunately, less than half of eligible patients are referred to cardiac rehabilitation, and a similarly low number complete the traditional 36 1-hour sessions, due to barriers such as cost and accessibility [11]. Increased ownership from referring providers and individualized, innovative cardiac rehabilitation options are needed.

Nutrition is our fuel for physical activity. Overall, a focus on plant-based and Mediterranean diets has been shown to confer significant mortality benefits [4]. Diets should incorporate fruits, vegetables, nuts, and lean animal or plant proteins, understanding that some patients will have sensitivities or allergies to foods that will require individualized dietary approaches. Dietary changes can be difficult to

sustain; however, accountability measures such as food diaries and longitudinally scheduled counseling with practitioners can have significant lasting impact [12].

Dietary adjustments for hypertension include decreasing sodium intake, increasing plant protein and potassium intake, and decreasing sugar-sweetened beverages [13]. Reduction in daily sodium intake of 50 mmol per day (or approximately 1150 mg) has been linked to reductions of 4 and 2.5 mmHg in systolic and diastolic blood pressure (SBP and DBP), respectively [14]. Potassium deficiency can lead to sodium retention, and simply adding 50 mEq of potassium either through diet (i.e., potassium-containing fruits and vegetables) or supplements can improve cardiovascular health and blood pressure [14]. The Dietary Approaches to Stop Hypertension (DASH) diet can help attain many of these goals with its focus on the consumption of low sodium (<2000 mg/day), fruits, vegetables, and low-fat dairy and was found to reduce SBP and DBP by 5.5 and 3 mmHg, respectively [15].

Additionally, high-quality, adequate sleep (>6 hours for most) and limiting alcohol intake is important for blood pressure regulation and overall cardiovascular health [4].

4 Nutraceuticals

Many patients seeking integrative cardiology care have experienced side effects to prescription medications or are opposed to taking prescription medications and desire a more natural approach. Commonly used nutraceuticals within integrative cardiology are included in Table 1, including evidence-based proposed mechanism of action, key components, indication, dosing, contraindications, and interactions. Here we review common nutraceuticals used in primary and secondary prevention.

4.1 Primary Prevention: Dyslipidemia, Hypertension, and Insulin Resistance/Diabetes

4.1.1 Dyslipidemia

Many patients are statin-intolerant or not interested in starting a statin. For those taking statins or statin-like compounds, supplementation with coenzyme Q10 (CoQ10) can help replenish stores that are depleted by statins [16], helping to prevent or ameliorate statin-induced myopathy or myalgia [17]. Banach et al. outlined evidence-based nutraceutical options for lowering LDL in statin-intolerant patients which included red yeast rice, berberine, bergamot, artichoke, garlic, fiber, and phytosterols (or plant sterols), with potency being highest for red yeast rice and berberine [18]. In a clinical trial of nearly 5000 Chinese patients with a prior myocardial infarction, red yeast rice extract showed a 45% reduction in coronary events and 33% reduction in total mortality compared to placebo [19]. LDL cholesterol decreased by 20% by

Table 1 Supplement and botanical resource

Name of supplement or botanical	Key components/ form	Proposed mechanism of action	Efficacious cardiac clinical use(s)	Level of evidence	Dose and form	Cautions/contraindications[a]
Acetyl-L-carnitine [21]	Ester of the amino acid, L-carnitine	Transfer long-chain fatty acids to allow the body to turn fat into energy	Diabetic neuropathy, possibly effective for diabetes	C-LD	1 gram twice daily	Gastrointestinal upset, headache Interactions: Moderate (LOE D): Acenocoumarol, warfarin Herbs/supplements: D-Carnitine
Alpha lipoic acid (ALA) [21]	Antioxidant produced naturally in the body or obtained through diet	Anti-inflammatory (reduce TNF-alpha and IL-6) and antioxidant effects	Diabetes, hyperlipidemia	C-LD	300–1800 mg daily	Gastrointestinal upset Interactions: Moderate: Alkylating agents (LOE D), anticoagulant/antiplatelet drugs (LOE D), antitumor antibiotics (LOE D), thyroid hormone (LOE D) Minor: Antidiabetes drugs (LOE B) Herbs/supplements: Those with anticoagulant/antiplatelet or hypoglycemic potential, thyroid extract
Artichoke	Perennial plant, leaves mostly used	Inhibit HMG-CoA reductase, reduce LDL oxidation [21]	Hyperlipidemia [20, 21]	B [18]	500–1920 mg daily [21]	Gastrointestinal upset [21] Interactions: Moderate (LOE D): CYP2B6 or CYP2C19 substrates
Beetroot	Flowering perennial plant	Fiber: Increases cholesterol secretion and lowers cholesterol [21] Nitrates: vasodilatory effect	HTN, hyperlipidemia [21]	C-LD [21]	500 mL juice/ day [21] ~200–350 mg/ day capsule	Pink urine, red stools [21] Interactions: None known

(continued)

Table 1 (continued)

Name of supplement or botanical	Key components/ form	Proposed mechanism of action	Efficacious cardiac clinical use(s)	Level of evidence	Dose and form	Cautions/contraindications[a]
Berberine	Alkaloid found in roots and various stem barks [21]	Inhibit cholesterol absorption, increase bile acid synthesis, increase insulin receptor expression, increase glucagon-like peptide-1 secretion [21] PCSK9 inhibitor, upregulation of LDL receptors [18]	Diabetes, hyperlipidemia, hypertension [21]	Hyperlipidemia (A) [18], diabetes and hypertension (C-LD) [21]	500 mg 2–3×/ day [21]	Gastrointestinal upset, rash, headache, transaminitis. Avoid during pregnancy, given it may cross the placenta and kernicterus has been described in infants [21] Interactions: Moderate: Amlodipine (LOE A), anticoagulant/antiplatelet (LOE D), antihypertensive drugs (LOE D), central nervous system depressants (LOE D), CYP2C9 (LOE B), CYP2D6 (LOE B) and CYP3A4 (LOE A) substrates, dextromethorphan (LOE B), losartan (LOE B), midazolam (LOE B), pentobarbital (LOE D), tacrolimus (LOE D) Major: Cyclosporine (LOA A)
Bergamot	Citrus fruit native to Italy [21]	Inhibits HMG-CoA reductase and ACAT and others, decreases intestinal absorption of cholesterol [18]	Hyperlipidemia [21]	B [18]	1300 mg/day [18]	Rare heartburn, dizziness Interactions: Moderate: Antidiabetes drugs and photosensitizing drugs (LOE D)

Cocoa	Found in cocoa tree seeds, includes phytonutrients [21]	Antioxidant effect, increased synthesis of nitric oxide, reduce endothelial dysfunction [21]	Hypertension, decreasing cardiovascular disease risk [21]	Cardiovascular disease (B), hypertension (B-NR) [21]	16.6–1080 mg flavonoids/day [21] 450 mg 2×/day of flavanols	Gastrointestinal upset [21] Interactions: Moderate: ACE inhibitors (LOE D), adenosine (LOE B), alcohol (LOE D), anticoagulant/antiplatelet drugs (LOE D), antidiabetic drugs (LOE D), antihypertensive drugs (LOE D), beta-adrenergic agonists (LOE D), clozapine (LOE B), dipyridamole (LOE B), disulfiram (LOE B), ephedrine (LOE D), ergotamine (LOE D), estrogens (LOE B), fluvoxamine (LOE D), lithium (LOE D), monoamine oxidase inhibitors (LOE D), pentobarbital (LOE B), phenylpropanolamine (LOE B), quinolone antibiotics (LOE B), riluzole (LOE D), stimulant drugs (LOE C), theophylline (LOE B), verapamil (LOE D) Minor: Cimetidine (LOE B), contraceptive drugs (LOE B), fluconazole (LOE B), mexiletine (LOE B), terbinafine (LOE B) Herbs/supplements: Those with anticoagulant/antiplatelet, caffeine or hypotensive potential, bitter orange, calcium, iron, magnesium

(continued)

Table 1 (continued)

Name of supplement or botanical	Key components/ form	Proposed mechanism of action	Efficacious cardiac clinical use(s)	Level of evidence	Dose and form	Cautions/contraindications[a]
Chromium [21]	Mineral in food	Increase insulin sensitivity via activation of glucose transporter 4, reduce insulin resistance by reducing TNF-alpha	Diabetes, hyperlipidemia	C-LD	200–1000 mcg daily	Headache, sleep disturbance, mood changes Interactions: Moderate: Antidiabetes drugs (LOE A), insulin (LOE B), levothyroxine (LOE B) Minor: Aspirin (LOE D), nonsteroidal anti-inflammatory drugs (LOE D) Herbs/supplements: Those with hypoglycemic potential, chromium-containing herbs, vitamin C, iron, zinc
Coenzyme Q10 (CoQ10)	Naturally occurring fat-soluble compound in the body	Antioxidant, membrane stabilizer, cofactor for metabolic pathways	Coenzyme Q10 deficiency, mitochondrial myopathies [21], statin-induced myalgia and myopathy [17] Possibly effective: CHF, myocardial infarction [21]	A [17, 39]	CoQ10 deficiency: 150–2400 mg/ day (often split into three doses/ day) Other indications: 100–300 mg/ day (often split into two doses/ day) [21] Occurs in low levels in food: meat and seafood [21]	Rare: Gastrointestinal upset, headache [21] Interactions: Moderate: Alkylating agents (LOE D), antihypertensive drugs (LOE B), warfarin (LOE D) Minor: Doxorubicin (LOE B) [21]

D-Ribose	Simple carbohydrate	Increases intracellular PRPP and initiates purine nucleotide synthesis and salvage [39]	Congestive heart failure [21, 39], coronary artery disease [21]	B-R [39, 86]	10–15 g/day (often split into 3×/day, suggest not more than 10 g per dose) [39]	Gastrointestinal discomfort [39], lightheadedness [39], headache [21], decreased blood glucose [21] Interactions: Major: Antidiabetes drugs (LOE B) [21], insulin (LOE B) [21]
Garlic	Herb	Inhibit HMG-CoA reductase, reduce activity of enzymes involved in cholesterol synthesis [21]	Atherosclerosis, hyperlipidemia, hypertension	B [18]	Atherosclerosis: 150–300 mg/day [21] Hyperlipidemia: 1000–7000 mg/day [18, 21] Many different formulations; most common is oral tablet, powder, or whole garlic cloves	Bad breath and body odor, gastrointestinal upset, dizziness, increased bleeding risk [21] Interactions: Moderate: Antidiabetes drugs (LOE B), antihypertensive drugs (LOE D), atazanavir (LOE D), CYP2E1 and CYP3A4 substrates (LOE B), isoniazid (LOE D), protease inhibitors (LOE B), saquinavir (LOE B), tacrolimus (LOE B), warfarin (LOE D) Herbs/supplements: Those with anticoagulant/antiplatelet, hypotensive and hypoglycemic potential, EPA/fish oil
Hawthorn	Flowering shrub from rose family, most extracts derived from leaves and flowers	Increase intracellular cAMP increasing coronary blood flow and vasodilation and increasing inotropic effects [21]	Angina, CHF [21]	CHF (B-NR) [21] Angina (C-LD)	CHF: 160–900 mg (divided into two to three doses/day) [21] CAD: 400 mg 3×/day	Gastrointestinal upset, headache [21] Interactions: Major (LOE D): Nitrates, phosphodiesterase-5 inhibitors Moderate (LOE D): Beta-blockers, calcium channel blockers, digoxin Herbs/supplements: Those with anticoagulant/antiplatelet or hypotensive potential

(continued)

Table 1 (continued)

Name of supplement or botanical	Key components/ form	Proposed mechanism of action	Efficacious cardiac clinical use(s)	Level of evidence	Dose and form	Cautions/contraindications[a]
L-Arginine	Amino acid necessary for protein synthesis, naturally found in meat, fish, and dairy products [21]	Precursor to nitric oxide leading to vasodilation, decrease platelet aggregation, reduce activity of angiotensin-converting enzyme [21]	Angina, hypertension, peripheral artery disease, erectile dysfunction [21] Possible: enhance exercise [21]	Hypertension (B) [87] IV use in PAD (C) [88]	Varied dose 4–24 g/day [21], usual starting dose 500 mg 2×/day oral route Intravenous and topical preparations have been used in other doses though less well-studied	Oral: Abdominal pain, gastrointestinal upset Intravenous: Infusion reactions, allergic reactions Interactions (all LOE D): Moderate: ACE inhibitors, angiotensin receptor blockers, anticoagulant/ antiplatelet drugs, antidiabetes drugs, antihypertensives, isoproterenol, nitrates, potassium-sparing diuretics, sildenafil [21] Herbs/supplements: Those with anticoagulant/antiplatelet/ hypoglycemic/hypotensive potential, xylitol
Magnesium	Chemical element important for bone structure and cellular reactions [21]	Essential for all ATPase activity, helps facilitate movement of calcium across cell membrane [21]	Vasospastic angina, hypercholesterolemia, coronary heart disease, arrhythmia	Arrhythmia (A) [21] Angina, hyperlipidemia, coronary heart disease (C-LD)	Daily recommended dietary allowance for adults ~420 mg men, ~320 mg women [21] 500–1200 mg/ day via tablet or dietary intake IV form for vasospastic angina	

Omega-3 polyunsaturated fatty acid (nonprescription)	Fish oil; docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)	Reduce synthesis of hepatic VLDL and triglycerides, increase oxidation of fatty acids, reduce fatty acid and phospholipid synthesis [18]	Hyperlipidemia, secondary prevention of atherosclerotic cardiovascular disease [21, 89]	A [21, 89]	EPA with or without DHA 1–4 g/day [21] Can obtain from eating fish high in DHA and EPA	Fish taste, belching, headache, dizziness [21] No increase in risk for bleeding or arrhythmia in average dose used in clinical trials of 1 gram/day [89]
Phytosterol	Plant sterols such as beta-sitosterol, campesterol, stigmasterol [21]	Competitive inhibition of dietary and biliary cholesterol absorption [21] Secretion of apoB, modulation of cholesterol cascade [18]	Hyperlipidemia, including familial hypercholesterolemia [21]	B [18]	2–3 g/day (with meals), form includes tablet, oil, dairy products, margarine spreads, and others [21]	Rare diarrhea Interactions: Minor: Pravastatin (LOE B) may lower sterol level Herbs/supplements: Alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein, lycopene, vitamin E, zeaxanthin, carotenoid-containing foods, vitamin E-containing foods [21]
Red yeast rice	Monacolin K which is identical to some HMG-CoA reductase inhibiting compounds (e.g., lovastatin) [21] and other mevinic acids, sterols, and pigments	Competitively inhibit HMG-CoA reductase, antioxidant, anti-inflammatory, and others [21]	Hyperlipidemia (decease LDL and triglycerides) [21]	A [18]	2400 mg 1–2 times daily, usual starting dose 600 mg 2×/day	Gastrointestinal upset, headache, dizziness, transaminitis, myopathy. Avoid during pregnancy, since lovastatin has led to fetal skeletal issues in animals [21] Interactions (all drugs moderate interaction, LOE D): Statins, niacin, alcohol, cyclosporine, CYP3A4 inhibitors, gemfibrozil, hepatotoxic drugs, grapefruit may increase serum levels, St. John's wort may decrease serum levels [21]

continued

Table 1 (continued)

Name of supplement or botanical	Key components/ form	Proposed mechanism of action	Efficacious cardiac clinical use(s)	Level of evidence	Dose and form	Cautions/contraindications[a]
Turmeric	Spice derived from the turmeric plant root, native to India and Southeast Asia [21]	Reduce inflammatory cytokines, increase conversion of cholesterol to bile acids, decrease formation of cholesterol by decreasing HMG-CoA reductase, upregulate LDL receptors	Hyperlipidemia	C-LD [21]	500–1000 mg 2×/day (increase bioavailability in formulations with piperine, lipid particles, and nanoparticles)	Gastrointestinal upset [21] Interactions: Minor: CYP1A2 and CYP1A1 substrates (LOE D), docetaxel (LOE D), estrogens (LOE D), glyburide (LOE B), norfloxacin (LOE D), p-glycoprotein substrates (LOE D), paclitaxel (LOE D) Moderate: Alkylating agents (LOE D), anticoagulant/antiplatelet drugs (LOE B), antidiabetes drugs (LOE B), antitumor antibiotics (LOE D), CYP3A4 substrates (LOE D), sulfasalazine (LOE B), tacrolimus (LOE D), talinolol (LOE B), topoisomerase I inhibitors (LOE D), warfarin (LOE D) Herbs/supplements: Those with anticoagulant/antiplatelet and hypoglycemic potential, iron

Level of evidence based on the "ACC/AHA Clinical Practice Guideline Recommendation Classification System" [90]
Not all supplements are created equal. It is the responsibility of the prescribing provider to find trusted, high-quality brands and compounding pharmacies or otherwise to ensure their patients are receiving appropriate and effective therapies
[a]Many of the supplement interactions listed are based on theoretical and lab-based results, many with a low level of evidence rating. Provider supplement suggestions should be based on known risks and benefits

6–8 weeks after randomization, and levels were maintained throughout the study, compared to a 3.5% decrease in the placebo group. LDL small-density particles can be decreased with phytosterols, fish oil, and berberine [20]. While evidence does exist for several of these therapies for reducing levels of cholesterol, many of the nutraceuticals have limited evidence for reducing the risk of cardiovascular events [21]. The REDUCE-IT trial studied 8179 patients with known CVD or CVD risk factors with triglyceride levels 135–499 mg/dL, on appropriate statin with a median LDL cholesterol level of 75 mg/dL, and demonstrated that use of prescription strength icosapent ethyl (pure eicosapentaenoic acid (EPA) ethyl ester) 4 g daily decreases the risk of cardiovascular death by 20% compared to placebo [22]. In this trial, there were a decrease of 18.3% and increase of 3.1% in triglyceride and LDL cholesterol levels, respectively, at 1 year. However, combination therapy with EPA and docosahexaenoic acid (DHA) has not demonstrated similar benefit [23]. If triglycerides are the primary target for therapy, there is evidence for the use of omega-3s, artichoke, garlic, turmeric, beetroot powder, berberine, or red yeast rice [18]. In addition, various nutraceuticals can be used in combination to increase effectiveness or used as adjuncts to pharmaceutical lipid-lowering therapy in order to minimize dose-related side effects. Combination nutraceutical therapy that has been tested includes red yeast rice along with either berberine, artichoke, or plant sterols, showing reductions of LDL by a range from 14% [24] to 38% [25]. In addition, bergamot [26], plant sterols [27], fiber [28], and garlic [29] have been used in combination with statins to achieve enhanced LDL reduction. More specifically, in an open-label, parallel group study on 77 patients, addition of bergamot 1000 mg/day to rosuvastatin 10 mg/day resulted in a significant lowering of LDL compared to rosuvastatin 10 mg alone, an effect which was similar to that of the group receiving rosuvastatin 20 mg/day [26]. In a small study of 11 patients with hyperlipidemia treated with 3 months of simvastatin 20 mg/day, the addition of plant stanol ester margarine (2.25 g of stanols/day) reduced LDL by 13% [27]. In a study of the adjunctive effects of fiber intake (25 g daily) with cholesterol-lowering medications, 117 patients with hyperlipidemia were divided into treatment groups including rosuvastatin 40 mg/day and fiber, rosuvastatin 40 mg/day alone, simvastatin 40 mg/day and ezetimibe 10 mg/day plus fiber, or simvastatin 40 mg/day and ezetimibe 10 mg/day. While LDL and triglyceride reduction were similar across groups, those treated with fiber had statistically significant decreases in weight, blood glucose, and campesterol (a sterol intestine absorption marker) [28]. Finally, in a randomized trial of 258 patients with hyperlipidemia, patients were assigned to simvastatin 10 mg daily plus placebo or black seed 500 mg daily and garlic oil 250 mg daily [29]. There was a 2.1–2.9 times greater reduction in lipid profile in the simvastatin plus garlic versus the placebo arm.

4.1.2 Hypertension

There are many nutraceuticals that have demonstrated promise in lowering blood pressure and have been used in treating mild hypertension (HTN) or as adjunctive therapy with other antihypertensives. A clinically meaningful reduction of 5 mmHg of systolic blood pressure is associated with a 7% reduction in all-cause mortality.

Some of the nutraceuticals which have an antihypertensive effect include magnesium, beetroot juice, soy isoflavones, garlic, cocoa flavonoids, and L-arginine. Among those showing the most clinically meaningful effects on BP are magnesium [30], which is associated with a mean SBP reduction of 5.6 mmHg in those with mild HTN; beetroot juice which shows dose-dependent changes in SBP (mean reduction of −4.4 mmHg) [31]; soy isoflavones which reduce SBP (average reduction of −5.9 mmHg) [32]; and aged garlic extract (average reduction of −9 mmHg in SBP) [33]. In a study of 50 Chinese patients with hypertension, patients were systematically allocated to conventional medical therapy (dihydrochlorothiazide followed by atenolol if needed) or traditional Chinese herbal treatment (herbal mixtures, including but not limited to oyster shell, magnetite, earthworm, chrysanthemum, mulberry mistletoe, different roots). After 3 weeks, both groups demonstrated clinically significant improvement in blood pressure with a greater improvement in the conventional arm (30.9/19.7 mmHg lowering of SBP/DBP) versus 21.8/15.4 mmHg SBP/DBP decrease in group combining conventional and traditional Chinese herbal treatment methods [34].

4.1.3 Insulin Resistance/Diabetes

Various supplements have shown modest effects in lowering blood glucose. Some of these include chromium, alpha lipoic acid (ALA), acetyl-L-carnitine, berberine, omega-3 polyunsaturated fatty acids, and several polyphenols. Cocoa flavanols have been shown to improve insulin resistance [35]. A meta-analysis of 1133 subjects showed that green tea consumption can modestly lower both fasting blood glucose and hemoglobin A1c (HbA1c) by 0.09 mmol/L and 0.30%, respectively [36]. Berberine, which has been shown to increase insulin receptor expression, has been shown to have similar effects as low-dose metformin, with HbA1c reduction from 9.5% to 7.5%, fasting blood glucose from 10.6 ± 0.9 mmol/L to 6.9 ± 0.5 mmol/L, postprandial blood glucose (PBG; from 19.8 ± 1.7 to 11.1 ± 0.9 mmol/L, $P < 0.01$), and plasma triglycerides (from 1.13 ± 0.13 mmol/L to 0.89 ± 0.03 mmol/L, $P < 0.05$) [37].

4.2 Secondary Prevention: Coronary Artery Disease, Angina, Arrhythmia, Congestive Heart Failure, and Peripheral Vascular Disease

Studies examining the use of supplements or botanical medicine in secondary prevention have largely shown modest or no benefit. However, there are some supplements that have shown significant effects in reducing symptoms, such as angina, shortness of breath, and claudication in smaller studies that need to be replicated in larger studies. Use of aged garlic extract is associated with decreased progression

of coronary artery calcium score in a longitudinal randomized controlled study [38]. In this double-blind, randomized pilot study, 23 patients were randomized to garlic extract or placebo, and at 1 year the garlic group had a 7.5 ± 9.4% increase in coronary calcium score compared to an increase of 22.2 ± 18.5% in the placebo group. In addition to its use in statin-intolerant patients, CoQ10 has been studied to increase ATP generation and is potentially effective for congestive heart failure [39]. Hawthorn has been used in the treatment of angina [18] and suggested to improve left ventricular ejection fraction and decrease symptoms in heart failure patients [40]. In a double-blind, placebo-controlled trial of 120 patients with heart failure, NYHA classes II–III, patients were randomized to hawthorn 450 mg twice daily or placebo for 6 months [41]. The subgroup of patients with EF <40% appeared to have a relatively modest increase in ejection fraction of 3–4% compared to placebo; however when analyzing the entire cohort, ejection fraction was essentially unchanged and did not differ significantly by study group. A double-blind, clinical trial of patients with angina showed that hawthorn 100 mg three times daily for 4 weeks demonstrated a significant improvement in angina compared to placebo (hawthorn group, 23.9% with marked improvement, 60.9% with some improvement, and 8.7% with no improvement; placebo group, 4.4% with marked improvement and 32.6% with some improvement), including a reduced intake of nitroglycerin tablets in the hawthorn arm [42]. L-Arginine, a precursor to nitric oxide, can be used to treat angina through the mechanism of vasodilation and its effects on endothelial dysfunction [21]. There is some evidence that intravenous magnesium can help treat and prevent vasospastic (Prinzmetal's) angina [21]. Magnesium supplementation can help prevent arrhythmias [21]. A meta-analysis revealed that magnesium supplementation post-cardiac surgery reduces development of atrial fibrillation (RR 0.69; 95% CI, 0.56–0.86; $p = 0.003$) and reduces ventricular arrhythmias (RR = 0.45; 95% CI, 0.24–0.89; $p = 0.004$) [43]. Another meta-analysis revealed that magnesium supplementation reduces the rate of supraventricular (10.36% vs 23.91%) and ventricular arrhythmias (11.88% vs 24.24%) post-coronary revascularization compared to placebo [44]. L-Carnitine supplementation has shown some benefit for intermittent claudication [45, 46], and a randomized controlled trial found improvement in walking distances in those with moderate-severe peripheral vascular disease (PVD) [47]. More specifically, 485 patients with claudication were randomized to placebo or propionyl-L-carnitine 1 g twice daily, and at 1 year, those on treatment with a maximal walking distance ≤250 m at baseline had a 98 ± 16% increase in walking distance (placebo group with 54 ± 10% improvement) and improvement in initial claudication distance of 99 ± 21% (placebo group with 51 ± 8% improvement) [47]. In those with the ability to walk >250 m at baseline, there was no difference in outcomes between treatment and placebo. Recently, 44 patients with peripheral vascular disease were randomized to flavanol-rich cocoa 15 g daily or placebo, and those on treatment were found to have an improvement of 6-minute walk distance by 42.6 m at 2.5 hours post-cocoa intake and 18 m at 24 hours post-cocoa intake, compared to placebo [48].

5 Mind-Body Interventions

One of the areas that integrative medicine has the strongest contribution to the practice of cardiovascular diseases is the understanding and appreciation of the role of mind-body health to heart health. There is general awareness of the role of mental well-being and emotional health in CVD; however, assessment and therapeutic strategies are seldom implemented in clinical practice. Negative emotional states such as stress, depression, and anxiety are known to increase the risk of developing CVD [49]; moreover, depression has been identified as a risk factor for poor prognosis in patients with acute coronary syndrome and during the follow-up after the event [50]. The ENRICHD trial randomized approximately 1500 adults with recent myocardial infarction and a diagnosis of depression and/or low perceived social support to usual care or cognitive behavioral therapy plus pharmacotherapy if indicated [51]. At 6 months, there was no difference between groups in outcomes of recurrence of myocardial infarction or death, although there were improvements in depression score and social isolation. Additionally, in a study of 783 patients, social isolation was found to be independently associated with risk of having coronary artery calcification [52]. Stress and anxiety diagnosed in early life as well as trauma exposure in early life have now been linked to increasing the risk of cardiovascular events decades later [53]. More specifically, a survey of nearly 50,000 Swedish men ages 18–20 revealed that in those with anxiety, there was an increased risk for coronary heart disease (hazard ratio 2.17; 95% CI, 1.28–3.67) and acute myocardial infarction (hazard ratio 2.51; 95% CI, 1.38–4.55). Interventions to address and nurture the mind-body interaction with particular focus on reduction in perceived stress, anxiety, and depression, in theory, would therefore decrease cardiovascular risk. Here we discuss the evidence behind commonly utilized mind-body modalities.

5.1 Transcendental Meditation

Transcendental Meditation and other meditative practices have been shown to play a role in CVD prevention by decreasing stress and lowering blood pressure [54]. This type of meditation has been described as a psychophysiological, effortless, mantra-based process where the meditator will enter a state of "transcendental consciousness," a state of being that will work to bring the body to a state of homeostasis, practiced approximately 20 minutes twice daily [55, 56]. A small study of 21 patients with known coronary artery disease was assigned to either 8 months of Transcendental Meditation or a control group, and the intervention group was found to have a significant improvement in exercise tolerance (14.7%), maximal workload (11.7%), and an 18% delay in onset of ST-segment depression [57]. Stress reduction with Transcendental Meditation has been described to decrease blood pressure, cholesterol, and cardiovascular events, and while these trends are promising, larger, randomized controlled trials will be needed to show

clear benefit [55]. Primary prevention of CVD is not clearly benefitted by Transcendental Meditation given the small, varying quality and limited cardiovascular endpoints in the existing literature; a Cochrane Review is underway for a more systematic approach to the evidence [58]. There are other types of meditative practices that can take many forms, including movement- or rest-based positions, while focusing the mind on reflection or deep contemplation. Overall, given that there are promising signals for meditation decreasing known cardiovascular risk factors (randomized, placebo-controlled clinical trial showing that 16 weeks of Transcendental Meditation significantly improved systolic blood pressure (mean improvement 3.4 mmHg) and insulin resistance (mean improvement 0.75 of a formula incorporating fasting plasma glucose and insulin levels) [59], tobacco use (randomized clinical trial demonstrating mindfulness training decreased cigarette use and trended toward abstinence compared to non-mindfulness smoking cessation program) [60], blood pressure (Transcendental Meditation has demonstrated a 5 and 2.8 mmHg decrease in SBP and DBP, respectively) [54, 61], stress response, and others), coupled with its low risk and cost, the American Heart Association has suggested that meditation (described as Samatha, Vipassana, mindful, Zen, Raja, and loving-kindness meditations, Transcendental Meditation, and relaxation response) can be considered as an adjunct treatment for cardiovascular risk reduction [56]. Yoga and tai chi, among others, are considered types of meditation [61], as we describe below.

5.2 Yoga, Mindfulness-Based Stress Reduction (MBSR), and Tai Chi

Increasing the dose of aerobic physical activity has well-known health benefits, including reduction in cardiovascular morbidity and mortality. The practice of yoga has been around for thousands of years and has many different types, all including focus on postures, breathing, meditation, and devotion [62]. Yoga has demonstrated modest improvements in DBP (mean decrease of 2.9 mmHg) and cholesterol (triglycerides mean decrease by 0.27 mmol/L and HDL cholesterol mean decrease by 0.08 mmol/L) [62].

MBSR, often an 8-week course led by a knowledgeable practitioner focusing on meditation and yoga, is an evidence-based intervention for reducing stress and anxiety [63]. MBSR practice has been associated with decreasing stress and inflammatory markers as well as improving tobacco abstinence, though not having a significant effect on blood pressure lowering [56]. More specifically, a randomized controlled trial of 40 healthy adults revealed decreased loneliness, a downregulation of NF-kB gene expression (mean prevalence ratio = 0.67 and 0.53 for the two NF-kB patterns tested), and a trend toward reduced C-reactive protein in the group randomized to 8 weeks of MBSR versus control [64]. Additionally, a clinical trial of 71 breast cancer survivors randomized to a 6-week mindfulness program or control demonstrated a decrease in stress (effect size 0.67), reduced activity of NF-kB, and increased activity of the anti-inflammatory glucocorticoid receptor (GR) [65].

Tai chi is a mental and physical practice that has roots in Chinese martial arts, including movement, meditation, and deep breathing [66]. There is some evidence to suggest that tai chi improves cholesterol (two trials revealed LDL decreased 0.76 to 0.59 mmol/L and triglycerides decreased 0.46 to 0.37 mmol/L), blood pressure (six trials revealed SBP decreased 22 to 11.5 mmHg and DBP decreased 12.2 to 4.43 mmHg), and quality of life; however, rigorous randomized controlled trials with appropriate control arms and with long-term follow-up are required before conclusions can be made about the benefit of tai chi for reducing cardiovascular risk and primary prevention of CVD [66].

5.3 Biofeedback Therapy

Biofeedback is a process by which biologic metrics, such as heart rate and muscle relaxation, are monitored and shared with a patient, whereby they actively make adjustments, such as altering breathing patterns, to impact the biologic metrics [67]. Biofeedback intervention has been shown to improve depression inventory measures [67]. In a pilot study, 14 patients with depression and 2 healthy volunteers were assigned to 6 sessions of biofeedback over 2 weeks, and 12 were assigned to the control group, and the Beck Depression Inventory (BDI) was significantly improved in those with depression (BDI 6; 2–20; median 25%–75% quartile) compared to baseline (BDI 22; 15–29) [68]. Furthermore, a few studies have demonstrated that this therapy improves blood pressure and increases heart rate variability [40], both of which have been associated with a decrease in cardiovascular events.

5.4 Acupuncture

Acupuncture, acupressure, and moxibustion (heat applied by burning moxa, a cone or stick made of group mugwort leaves, near the skin surface) are based on targeting various small physical nodes or acupuncture points (acupoints) that lay along 12 principal channels or meridians of energy and have been part of traditional Chinese medical therapy for over 3000 years [69]. According to Chinese medicine, yin, yang, and qi qualities and energies must be balanced, and acupuncture is one such modality to restore this balance [70]. Many of the meridians lie over major neural pathways that contain both sensory and motor nerves. Evidence from animal and human studies show that acupuncture needles, penetrating the skin, activate sensory neural pathways providing input to the central nervous system areas that regulate sympathetic and likely parasympathetic outflow which then influence cardiovascular function [71, 72].

Evidence for the effectiveness of acupuncture in cardiovascular conditions is mixed as there is great heterogeneity and general lack of agreement about the specificity of treatment of various acupoints for different conditions. For instance, some

acupoints like those overlying the median nerve in the wrist (the pericardial meridian) exert a stronger influence on the cardiovascular system than other acupoints [73]. In addition to the specificity involving acupoint selection, mode of acupuncture also is a factor in determining response. The mode of sensory nerve stimulation (manual or electrical), the duration of stimulation, and the extent of release of neurotransmitters released in the central nervous system can all vary, making it difficult to compare studies on the use of acupuncture. Low-frequency (2–6 Hz) or manual acupuncture for 30–45 minutes seems to be the most effective in reducing sympathetic outflow 10–15 minutes after stimulation and lasting for minutes to days after acupuncture treatment, depending on mode and duration of treatment [71]. The clinical effectiveness of acupuncture treatment has been assessed in a number of cardiovascular risk factors including hypertension, obesity, and dyslipidemia as well as in CAD, stroke, and PVD. We discuss a few of these areas below.

Acupuncture and electroacupuncture have been shown to improve SBP and DBP, approximately 8 mmHg and 4 mmHg improvement, respectively, in sham-controlled trials, both in patients on and off antihypertensive medications (Fig. 1) [74, 75]. While the World Health Organization supports the use of acupuncture for HTN [76], many studies have inconsistent findings due to methodological variation in use

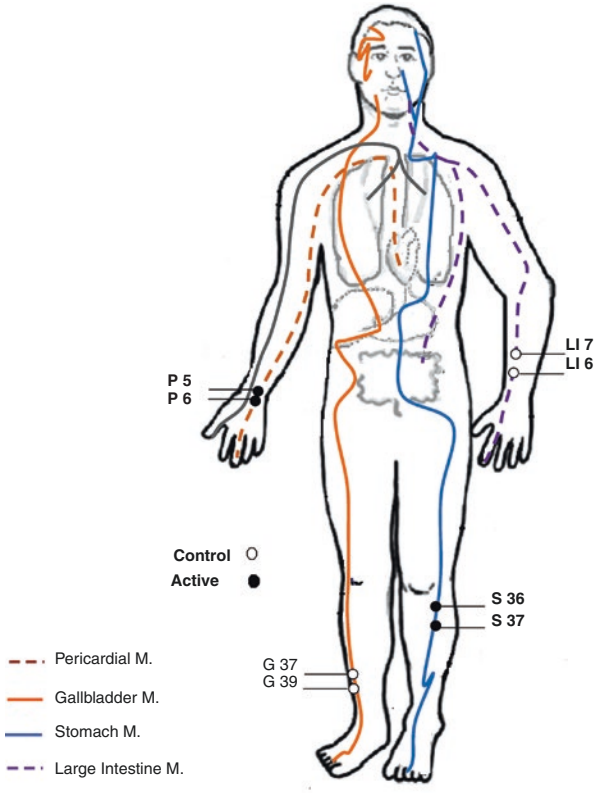

Fig. 1 Acupuncture meridians and acupoints used in electroacupuncture for HTN study (Li et al.)

of sham-control, length of follow-up, and specificity of acupoints being used [77]. In order to understand the role for acupuncture in treatment of hypertension, future studies must include treatment by acupuncturists with a standardized set of acupoints, addition of sham-control acupuncture, and longer-term follow-up to evaluate lasting effect on this chronic condition [77].

Acupuncture has shown promising effects in the treatment of angina and microvascular disease [76]. These effects are thought to occur because of the improvement in autonomic dysregulation [78] as well as increasing endogenous opioid production [79]. A systemic review and meta-analysis of over 1500 subjects found a statistically significant decrease in self-reported number of angina episodes when using acupuncture compared to sham or control (RR, 1.25; 95% CI, 1.11–1.39; $p = 0.0001$); however, there was no change in angina intensity or use of anti-anginal medications [80]. A large randomized controlled study by Zhao et al. showed that adjunctive acupuncture treatment at specific disease-related acupoints led to lower rates of angina than in those treated with non-disease-related or sham acupoints [81]. Over a 4-week period, the angina frequency decreased by 7.96 attacks in the disease-related acupuncture arm, by 3.89 attacks in the non-disease-related acupuncture arm, by 2.78 attacks in the sham acupuncture arm, and by 2.33 attacks in the wait-list control group, with the disease-related acupuncture arm showing 5.63 fewer attacks than in the wait-list group ($p < 0.001$). Pointing to possible mechanism, Mehta et al. showed that targeted acupuncture in stable ischemic heart disease resulted in improvement in heart rate variability, a measure of autonomic function [82]. The role of acupuncture has long had a place within integrative therapies, and while current evidence is promising for CVD, further high-quality evidence is needed in the field.

6 Role of Chelation Therapy, Environmental Exposures

Chelation therapy has been proposed as a treatment for vascular disease with the hypothesized mechanism being reduced oxidative stress and involves infusions of disodium ethylene diamine tetraacetic acid (EDTA), a substance that acts as a chelator with a magnetically charged pocket that can bind a metal and allow its excretion in the urine. Metals such as cadmium are thought to promote atherosclerosis via indirectly depleting antioxidants and increasing reactive oxygen species; disodium EDTA can bind and remove cadmium and is proposed as a mechanism for delaying development of coronary atherosclerosis [83]. Disodium EDTA chelation therapy is usually administered each week for 20–40 sessions. Chelation therapy has been associated with decreased cardiovascular events and symptoms of angina [84]. The Trial to Assess Chelation Therapy (TACT) was a double-blind randomized trial enrolling 1708 patients over 50 years old with a history of prior myocardial infarction who were assigned to receive chelation therapy versus placebo and a vitamin, mineral combination or placebo [85]. Chelation therapy consisted of 40 infusions of a chelation solution containing a mixture of EDTA, ascorbate, B vitamins,

electrolytes, procaine, and heparin. The intervention arm with EDTA was found to decrease their primary composite endpoint (death, reinfarction, stroke, coronary revascularization, or hospitalization for angina) by 18% compared to placebo. This effect was even more pronounced in those with diabetes where there was a 41% relative risk reduction of combined cardiovascular events when compared to placebo. EDTA infusions appeared to be well-tolerated, but there were rare adverse events including heart failure, hypocalcemia, and death, and infusion duration over weeks is substantial. Further evaluation is required before chelation therapy can be incorporated into clinical practice [84]; thus the TACT2 trial is underway to evaluate if chelation therapy will prevent recurrent cardiovascular events in diabetic patients with a history of prior myocardial infarction when compared to placebo.

7 Resources and Continuing Medical Education

As the fields of integrative medicine and cardiology continue to grow, there are many resources that develop and evolve. There are approximately 20 integrative medicine fellowships available across the country. The American Board of Integrative Medicine certifies qualified providers who have attended an integrative fellowship and have a command of the medical knowledge. The Academic Consortium for Integrative Health and Medicine (ACIHM), Academy of Integrative Health and Medicine (AIHM), and National Center for Complementary and Integrative Health (NCCIH) work to promote education, networking, and science as established medical societies in the field. Furthermore, interested providers can opt to do a residency or fellowship rotation or site visit to an established integrative center to learn more.

There are many resources for integrative medicine, including Cochrane Reviews for various topics (https://cam.cochrane.org/cochrane-reviews-related-complementary-medicine) and "Herbs at a Glance" from the NCCIH website (https://www.nccih.nih.gov/health/providers) that provides side effects, data, and further readings. The evidence-based supplement database, www.naturalmedicines.com, requires a subscription but provides a comprehensive guide for practitioners on indications, dosing, safety, interactions, and other key information.

8 Integrative Cardiology Clinical Program Components

Integrative cardiology takes the predictive, preventive, and personalized approach of many preventive cardiology programs that offer subclinical disease screening as well as advanced biomarker assessment to tailor integrative therapies for optimal risk factor modification (Fig. 2). In addition to an emphasis on lifestyle modification, including dietary therapy and exercise prescription, the awareness and offering of stress mitigation strategies like meditation and yoga, nutraceutical approaches for

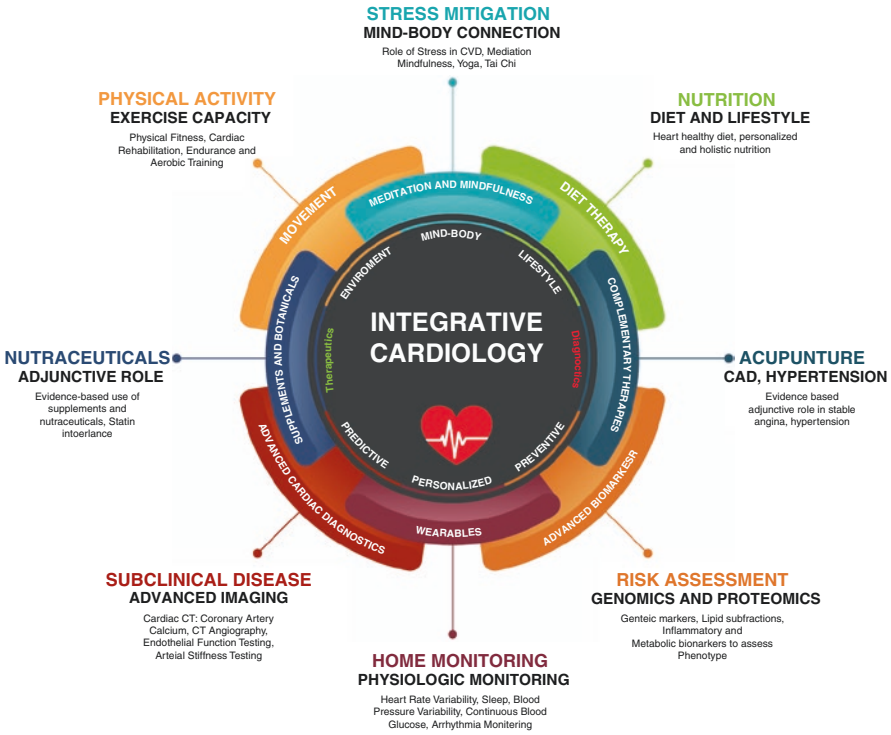

Fig. 2 Integrative cardiology programs would ideally combine a preventive, predictive, and personalized diagnostic approach with a therapeutic approach that is based on lifestyle modification but also takes into account the important role of stress mitigation while offering holistic modalities such as acupuncture and nutraceuticals

adjunctive effects as well as for medication intolerance, and understanding the complementary role of therapies such as acupuncture add additional therapeutic tools to an integrative cardiology clinical program (Fig. 2).

Components of a successful integrative cardiology practice depend on a patient-centered care approach with a primary prevention focus and collaboration with specialists and holistic care providers. Medical leadership can be comprised of integrative cardiologists, primary care physicians, and advanced practice providers. Their well-rounded integrative team could include the following: naturopathic practitioners, nutritionists, acupuncturists, yoga and tai chi instructors, mindfulness experts for MBSR courses, biofeedback specialists, healing touch specialists, exercise physiologists, physical therapists, pain specialists, women's health specialists, and others. The atmosphere should focus on healing and relaxation. Resources, testing, and treatments, such as coronary calcium testing and laboratory access, should be ideally located on site to promote collaboration of specialists and provide ease of access to the patient. Telemedicine is another option to improve access to some services for patients who may have barriers to cost, transportation, or others.

Practitioners should lead by example and ensure they are living a well-balanced lifestyle that will be apparent to colleagues and patients alike. Healing and meditation gardens, walking labyrinths, and healthy snack options could improve the healing atmosphere for all. If able, an exercise facility, including cardiac rehabilitation, yoga and tai chi classes, as well as cooking, nutrition, and mindfulness-based stress reduction classes can provide well-balanced options. If supplements are sold on site, it is important that the integrative center leadership team limit conflict of interest and ensure that the products are of the highest and safest quality. And, if not on site, then it is important for the practitioner to be familiar with trusted nearby compounding pharmacies or other accessible resources for patients. Although many of the components of care are paid for out-of-pocket, some capitated health systems or single-payer systems (VA) are providing many of these services outside of the fee-for-service model to reduce costs and improve outcomes.

9 Conclusion

Integrative cardiology plays an integral role in both primary and secondary prevention of CVD. Its focus on the connection of mind, body, and spirit and incorporation of evidence-based healing modalities is key to personalizing medical care and improving patient outcomes. Many health systems have started incorporating integrative and whole health programs, include the Veterans Health Administration (VA) system as well as Kaiser Permanente health system as part of the strategy to cut costs, and improve quality and outcomes. As the evidence base builds, many of the integrative therapeutic options we have discussed have the potential for wide adoption in clinical programs that aim to prevent disease. It is important for all practitioners to familiarize themselves with the evidence and understand which patients may benefit from a referral to an integrative cardiology center.

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Preventive Cardiology as Specialized Medical Art

Michael D. Shapiro and Sergio Fazio

Summary

- Despite decades of progress, cardiovascular disease remains the number one cause of death and disability worldwide.
- The medical community must now invest in cardiovascular disease prevention as past gains are threatened by increased rates of obesity and diabetes.
- The focus of cardiovascular disease management must transition from intervention to prevention.
- Given major developments in basic and translational science, diagnostic testing, and medical therapy, the specialty of preventive cardiology is emerging.
- The practice of preventive cardiology requires a multidisciplinary approach with an inclusive and wide-ranging expert and dedicated team.
- To take preventive cardiology to the next level, there is a need for standardization in training and creation of a path to and system for board certification.

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1 Introduction

The notion of actively attempting to prevent cardiovascular disease is intuitive but of difficult implementation. We all know what the pillars of cardiovascular health are: do not smoke, keep a healthy weight, exercise regularly, control your stress level, follow a prudent diet, and see your doctor to check on your blood sugar, cholesterol, and pressure. Despite these deceivingly simple action items, cardiovascular disease remains the number one cause of death and disability worldwide [1]. Moreover, despite four decades of improvement in cardiovascular mortality in the United States, it appears that we have hit a nadir, and current estimates project an actual increase in the rate of cardiovascular death due to the rising tides of obesity and diabetes. Sadly, this need not happen. Several concerted efforts are required to significantly improve this forecast, one of which is the creation of a dedicated subspecialty aimed at preventing cardiovascular disease [2]. Indeed, the medical art referred to as "preventive cardiology" has emerged organically, spontaneously, and necessarily as an integrated hybrid of components arising from internal medicine, endocrinology, cardiology, women's health, cardiac rehabilitation, imaging, genetics, public policy, and epidemiology, as well as from outstanding insights from the basic and translational sciences. While the idea of preventive cardiology has existed for years (some would say decades), it remains thinly dispersed, not standardized, and not recognized at the highest professional levels. Overcoming these limitations will be critical for the profession to take a meaningful hold. Moreover, training of the next generation of providers of dedicated cardiovascular disease prevention will require that professional and educational structure and standardization take place. This chapter summarizes the history of preventive cardiology, reviews the necessary structure and organization of a preventive cardiology center, explores the core competencies necessary to practice the art, offers recommendations for training, and provides a rationale for the necessity of a curriculum that provides a uniform path to board examination and to a credible and validated practice certification.

2 The Roots of Prevention

After the Second World War, it was evident that atherosclerotic cardiovascular disease (ASCVD), coronary heart disease, and stroke were the greatest threats to health in adults residing in the United States (USA). At that time, little was known regarding the origins and drivers of atherosclerosis. In 1948, the National Heart, Lung, and Blood Institute (then known as the National Heart Institute) funded the Framingham Heart Study (FHS) precisely to answer these questions [3]. The fundamental premise of this landmark population-based cohort study was to determine the factors that associate with development of ASCVD. Indeed, work that emanated from FHS led investigators to coin the term "risk factors" for coronary artery disease in its first publication in 1961 [4, 5] . The foundational understanding that high levels of blood

cholesterol and hypertension, diabetes, and smoking are linked to ASCVD marked an inflection point in interest in assessing and potentially preventing/delaying the onset of ASCVD. Up until that point, knowledge of the genesis and treatment of ASCVD was poor and stagnant. The FHS served as the major catalyst to accelerate investigation into the etiology of ASCVD. This research was ultimately transformative, and as a result, new therapies were discovered, developed, and commercialized. Since 1948, participants of the FHS continue to return every 2 years for a detailed medical history, physical examination, and laboratory testing. Based on the success of the cohort, in 1971, investigators enrolled a second generation – 5124 adult children of the original cohort's adult children and their spouses to participate in similar examinations. Remarkably, the FHS is now on its third generation of participants. There is perhaps no other study that has provided as much insight into the epidemiology and risk factors leading to CVD.

Beyond identifying the four commonly known traditional risk factors, the FHS also determined that obesity, physical inactivity, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol (HDL-C), age, gender, and psychosocial issues relate to risk of ASCVD. Perhaps of equal importance is the fact that the FHS clearly demonstrated that no single risk factor is responsible for ASCVD but rather multiple factors generally lead to its development [6]. This point will be emphasized again throughout this chapter and serves as one of the key motivators from merely focusing on lipids to a more comprehensive approach that takes into account a myriad of risk factors related to ASCVD. Importantly, the main findings from the FHS have been recapitulated in numerous cohorts from around the world, suggesting that the fundamental causes of atherosclerosis are largely similar across race, ethnicity, and gender [7–9]. These seminal observations served as the initial impetus for studying risk factor modification as a means of reducing the burden of ASCVD. Thus, the notion of prevention of cardiovascular disease was born. Along those lines, one of the key contributions from the FHS was the derivation and validation of the Framingham Risk Score [10]. Since that time, risk assessment has become one of the key elements in the primary prevention of ASCVD.

Since the time that the initial findings from FHS were reported, clinical trials extended the epidemiological findings to demonstrate that modifying the traditional risk factors improved cardiovascular outcomes. One of the most important advances in clinical science of the twentieth century was the discovery and development of the statin drugs. The 4S study (Scandinavian Simvastatin Survival Study) published in 1994 ushered in a new era in prevention of ASCVD. Immediately after 4S, there was a continuous stream of randomized cardiovascular outcomes trials that corroborated the efficacy of the statin drugs in essentially all clinically relevant patient groups [11]. When it was no longer ethical to perform placebo-controlled statin trials, study design evolved to statin-controlled (high-intensity vs. low- or moderate-intensity) trials. The reduction in cardiovascular events (and in some cases cardiovascular mortality) observed across these statin mega-trials was striking and remarkably consistent. Importantly, one of the major discoveries from these trials was that there was apparently no attenuation of cardiovascular benefit with further reduction of low-density lipoprotein cholesterol (LDL-C) level. This realization

transformed thinking about evaluation and management of hypercholesterolemia from simply treating elevated LDL-C with a lipid-lowering agent to contemporary standards of statin recommendation for all individuals above a certain risk threshold.

The statin mega-trials clearly established that lowering LDL-C is safe, easily achievable, and effective at reducing ASCVD risk. As a natural extension, national and international guidelines emphasized the primacy of LDL-C lowering for ASCVD risk management. Specialty lipid clinics arose in the wake of these developments to facilitate implementation of guideline-recommended lipid-lowering therapies, to evaluate and manage individuals with high-risk genetic lipid disorders, and to assist those with treatment-related side effects. For a while, it seemed that preventive cardiology was equivalent to lipid management. Nevertheless, it is now clear that ASCVD risk management is most often necessary for patients whose underlying risk emanates from a range of exposures and comorbidities, even though the fact remains true that lipid-lowering interventions reduce CVD risk irrespective of whether dyslipidemia is present. Accordingly, evaluation and management of alterations in levels of different lipid fractions serves as only a single component in a comprehensive intervention addressing numerous key risk factors (hypertension, diabetes, obesity, and suboptimal lifestyle habits), frequently including a combination of therapeutic lifestyle changes and medical therapies. The aforementioned insight is the conceptual basis for developing dedicated preventive cardiology programs, where all of these issues can be fully addressed together in a single clinic or program for optimal risk management. It became increasingly apparent that to prevent ASCVD most effectively, multiple risk factor interventions are required. With this understanding, the value of the lipid clinic model, often housed in an endocrinology environment, is limited, thus requiring the mandate for a discipline known as preventive cardiology.

If the FHS originally gave birth to the notion, feasibility, and pragmatic approaches to preventing cardiovascular disease, major developments in basic science (of lipoproteins, hemostasis, thrombosis, diabetes, atherosclerosis), population studies, cardiovascular outcomes trials, advances in diagnostic testing (novel biomarkers, polygenic risk cores, noninvasive atherosclerosis imaging), and an unending pipeline of promising novel therapies have dramatically reinvigorated the field. Preventive cardiology as a dedicated subspecialty of cardiovascular medicine is no longer a pipedream but rather a necessity to stem the rising tide of obesity and diabetes and the projected increase in cardiovascular mortality [1]. Table 1 summarizes recent and emerging therapies for cardiovascular risk reduction.

3 Structure, Personnel, and Organization of a Preventive Cardiology Center in the Academic Setting

By its very nature, preventive cardiology requires a multidisciplinary approach. The practice of preventive cardiology requires specialty knowledge of cardiovascular physiology, coronary anatomy, electrocardiography, atherosclerosis and vascular

Table 1 Recent and emerging therapies for cardiovascular risk reduction

Risk factor	Approach/scientific development	
Atherogenic lipids	PCSK9 inhibition	Monoclonal antibodies (alirocumab, evolocumab) siRNA (inclisiran)
	Triglycerides	Icosapent ethyl ApoCIII-Lrx
	Lipoprotein(a)	IONIS-$APO(a)_{Rx}$
Inflammation	IL-1β inhibition	Canakinumab
Diabetes	SGLT-2 inhibition	Canagliflozin, dapagliflozin, empagliflozin
	GLP-1 receptor agonism	Albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide
Obesity	Pharmacotherapy	Orlistat, locaserin, naltrexone-bupropion, phentermine-topiramate, liraglutide
	Bariatric surgery	Gastric bypass, sleeve gastrectomy, adjustable gastric band, biliopancreatic diversion with duodenal switch
Hypertension	Vasopeptidase inhibitors Aldosterone synthase and soluble epoxide hydrolase inhibitors, natriuretic peptide A agonists, vasoactive intestinal peptide receptor 2 agonists	
	Vaccines	Vaccines against angiotensin II and its receptor type I
	Catheter-based interventions	Renal denervation Baroreflex activation therapy
Antiplatelet and antithrombotic therapy	Low dose of direct-acting anticoagulant	Rivaroxaban

[a]*PCSK9* proprotein convertase subtilisin/kexin type 9, *siRNA* silencing RNA, *IL-1β* interleulkin-1β, *SGLT-2* sodium-glucose transport protein-2, *GLP-1* glucagon-like peptide-1

imaging, stress testing, and cardiac rehabilitation. Since the objective is to reduce risk of ischemic heart disease, the ability to prevent is by definition limited, and many of the patients seen are susceptible to move on to the symptomatic phase, the most appropriate setting for such programs is rooted in divisions of cardiology or in cardiovascular institutes. The recommended placement and structure of a Center for Preventive Cardiology in a division of cardiology stems mostly from logistics and efficiency and ease of coordination of care (diagnostic testing, cross-referral, curb-side consultations, etc.). Nonetheless, cardiologists are not the exclusive members of the preventive cardiology team. In contrast to other subspecialties within cardiovascular medicine, preventive cardiology should not only be made available to other specialists but offers the best care when other providers, such as internists, endocrinologists, family physicians, clinical pharmacists, dietitians, exercise physiologists,

nurses, and advanced practice providers (nurse practitioners and physician assistants), are part of the program and longitudinal patient management strategy.

It is critical to integrate an entire cardiovascular team into preventive cardiology programs, as the ability to transfer information and ownership of care to the patient increases progressively with the number of people reinforcing the concept and helping the patient on all fronts, from diet and lifestyle to genetic testing, from access to medication to connection with additional clinical services (i.e., general cardiology, interventional consults, bariatric surgery). Patient care teams integrating clinical pharmacists and cardiologists yield improved healthcare measures in patients with myriad CV diseases and risk factors, including hypertension, dyslipidemia, CAD, heart failure, and diabetes [12]. Collaboration between clinical pharmacists and cardiologists represents a natural alliance. There are numerous benefits that are borne out in the literature. First, including clinical pharmacists as part of the care team improves safety. Clinical pharmacists also enhance monitoring of patients with a variety of cardiovascular diseases and extend the reach of physicians by incorporating follow-up phone calls as well as in-person and remote visits [13]. Their involvement in patient care importantly improves medication adherence [14]. Perhaps most important to patients, clinical pharmacists possess expertise at optimizing cost-effectiveness for prescription medications [15]. Ultimately, by integrating a PharmD in a preventive cardiology program, patient care is enhanced in four major ways: (1) Increases contact with the healthcare team, (2) Reduces medication expense, (3) Improves medication adherence, and (4) Optimizes education regarding disease state and medical therapy.

Beyond that, clinical pharmacists can operationalize specialty services (e.g., PCSK9 inhibitor clinic, hypertension clinic, anticoagulation clinic, etc.) [16, 17]. It is also important to recognize that integration of a clinical pharmacist as part of the care team is endorsed by several large national societies including the National Lipid Association, the American College of Cardiology, and the Heart Failure Society of America. Moreover, demonstration of improved outcomes with this model is well substantiated in the literature, both in terms of clinical endpoints (both surrogate markers and hard outcomes) and improved adherence (due to decreased out-of-pocket costs and reduction in adverse drug events) [12, 18, 19]. Table 2 lists the multiple ways that the clinical pharmacist leverages provider time with patients.

The importance of dedicating resources (human and financial) to lifestyle counseling is of utmost importance and cannot be overstated. Indeed, for the vast majority, ASCVD is the manifestation and culmination of decades of suboptimal lifestyle habits. Numerous studies addressing various aspects of optimizing health behavior demonstrate improvement in cardiovascular outcomes in both primary and secondary prevention. Moreover, providing little time at the end of a patient encounter to provide generic advice across the spectrum of therapeutic lifestyle changes is not only ineffective but also sends a dangerous message to patients. If lifestyle modifications are not emphasized but rather a brief afterthought during a clinical encounter, patients are likely to get the message that diagnostic tests and medical therapy are most important but changes in behavior are secondary. Rather, preventive cardiology programs must invest in the services of a registered dietician nutritionist

Table 2 Ways in which the clinical pharmacist leverages provider time

Clinic visits	Remote patient services
Medication reconciliation	Clinic follow-up
Assess and manage medication side effects	Adherence/barriers
Patient/family history	Medication tolerability (e.g., statin-associated side effects)
Risk assessment	Medication dose titration (lipids, blood pressure, diabetes)
Optimize pharmacotherapy	Cost
Review objective data	

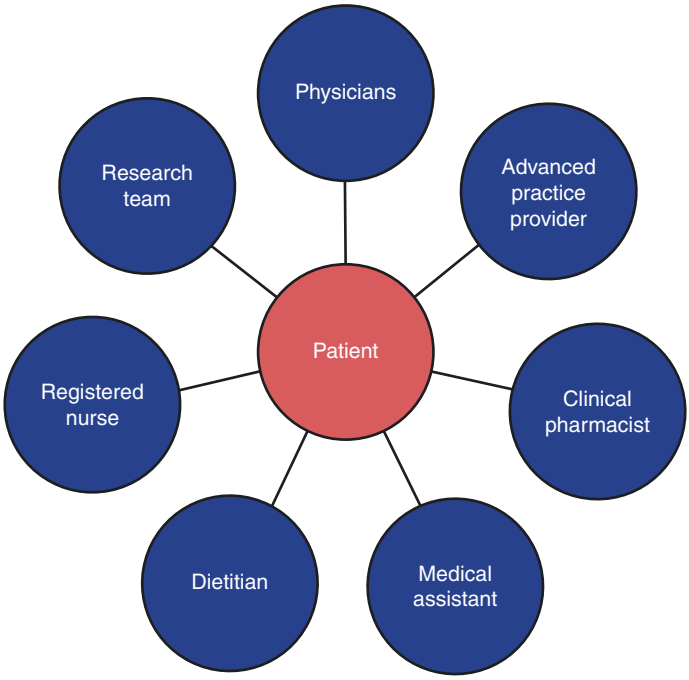

Fig. 1 The preventive cardiology team

(RDN) and lifestyle coaches (who may come from a variety of backgrounds), including exercise physiologists. In our practices, all new patients are evaluated by the RDN for nutritional and dietary counseling for ASCVD risk reduction. These encounters are not billed, as current reimbursement structure generally fails to cover the services required. Beyond evaluation by the dietitian, patients are selectively referred to the lifestyle coach based on need (e.g., exercise prescription, weight management, smoking cessation, and/or stress reduction). Clinical services rendered by the lifestyle coach are billable based on face-to-face time with the patient. Figure 1 delineates the recommended personnel for optimization of a preventive cardiology program.

4 Core Competencies

Though preventive cardiology established its roots decades ago, the understanding that there is a need for a dedicated subspecialty is relatively new. The emergence of preventive cardiology as a unique subspecialty of cardiovascular medicine is borne out of necessity. As discussed in the various chapters of the book, we have reached a tipping point with regard to scientific and therapeutic realization and development. There is simply too much for a general cardiologist, endocrinologist, internist, family practitioner, gynecologist, etc. to know regarding ASCVD risk evaluation and mitigation. And there is too much demand from the patient side to have a satisfying experience in a non-dedicated practice, such as general endocrine or cardiology clinic or even a lipid clinic or a cardio-metabolic center. Major breakthroughs in basic and translational science, clinical genetics, pharmacotherapy, atherosclerosis imaging, and biomarker testing have culminated in a subspecialty that has risen organically. Having said that, the concept is still new to most and in fact is a source of contention among various disciplines, including cardiologists, endocrinologists, and general practitioners. However, when applied at the expert level, it becomes clear that there is little redundancy with these individual specialties. In fact, many cardiologists, endocrinologists, and primary care providers ultimately refer patients to preventive cardiology programs as their understanding, interaction, and experience with these programs grow. Table 3 lists the core competencies in which a preventive cardiologist requires proficiency.

5 Referrals to Preventive Cardiology Programs

Given the fact that ASCVD is so pervasive, one might ask the question as to who should not be evaluated by a preventive cardiologist. Indeed, the exposure to and development of cardiovascular risk factors is ever present, and, as such, ASCVD is common and multifactorial. Fortunately, it is largely preventable and treatable. Nonetheless, not everyone needs to be evaluated by a preventive cardiologist. In general, young individuals (<40 years of age) from low-risk families and without comorbidities and risk exposures only need to keep following

Table 3 The necessary competencies for preventive cardiology

Lifestyle	Risk factor management and pharmacotherapy	Risk assessment
Exercise prescription	Lipid management	Biomarkers
Dietary counseling	Inflammatory risk	Genetics
Weight management	Diabetes	Noninvasive imaging
Treatment of obesity	Hypertension	
Tobacco cessation	Antiplatelet therapy	
Stress reduction	Antithrombotic therapy	

Table 4 Common referrals to preventive cardiology programs

Personal or family history of cardiovascular disease
Atherosclerotic cardiovascular disease with recurrent events
Severe/difficult to treat lipid disorders
Inherited lipid disorders (including children)
Genetic testing
Risk assessment with advanced lipid testing/novel biomarkers
Noninvasive atherosclerosis imaging
PCSK9 inhibitor evaluation and initiation
Lifestyle counseling
Smoking cessation
Weight management
Exercise prescription
Stress reduction techniques
Apparently healthy individuals interested in understanding and lowering cardiovascular risk
Review/consultation for preventive medical therapies
Participation in clinical trials of novel preventive therapies

the mandates of a healthy lifestyle. Table 4 delineates common referrals to preventive cardiology programs.

6 Training and Certification

Anyone calling herself or himself a preventive cardiologist today is often one of several backgrounds, including family practitioners, internists, cardiologists, or endocrinologists of different degrees of competency, and with additional a-la-carte advanced exposures to the nuances of clinical lipidology as offered by organizations such as the National Lipid Association. The only existing certification is with the American Board of Clinical Lipidology, which is not under the ABIM umbrella, does not require demonstration of specialized clinical training, and since its inception in 2005 has awarded less than 800 diplomas. There are also multiday courses such as the American Society for Preventive Cardiology's annual Experts Course; however, there is no formal test of competency given at present. More formalized and comprehensive training is needed. The COCATS4 (standards of training for cardiology fellows in American hospitals) only require minimal exposure to preventive services, such as 1-month rotations in cardiac rehabilitation or lipid clinics, etc., to satisfy criteria for taking the board examination [20]. The many preventive cardiology "fellowships" currently available are not uniformly equipped to provide the set of clinical competencies necessary to produce trained experts, but rather represent a mélange of locally funded programs mostly with focus on clinical or basic research [21]. What is needed is structure and uniformity of teaching, training, and preparation for a validated, comprehensive, and credible exam. The fellowship program should last at least 1 year and performed in an accredited center of proven excellence, and the exam should go well beyond knowledge of lipids. All this is currently in construction phase, spearheaded by organizations such as the American

Society for Preventive Cardiology (ASPC) and the American College of Cardiology (ACC) [22]. The ASPC has in fact recently launched *The American Journal of Preventive Cardiology*, which will be devoted to the definition, expansion, and standardization of the medical art through editorial, opinion papers, teaching articles, and original investigations with high translational and fully pragmatic value.

7 Conclusions

The main enemy of the new medical art of preventive cardiology is the false perception of its simplicity, intuitive value, and commonsense paradigms. Just like any other medical subspecialty before it, preventive cardiology must intelligently plan for a nondisruptive separation from the current main outlets of care, which most often include general cardiology and lipid clinic services, and for synergistic connection with all other services needed by the patient in need of preventive cardiology care (diabetes, hypertension, general cardiology, etc.). Until now, this has been done in fragmented ways and with nonuniform approaches. In the future, the individual provider that wants to have the full set of competencies in preventive cardiology should undergo proper training and certification, and the center that specializes in preventive cardiology must have the care team abilities to address the spectrum of needs of this ever-expanding category of patients.

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