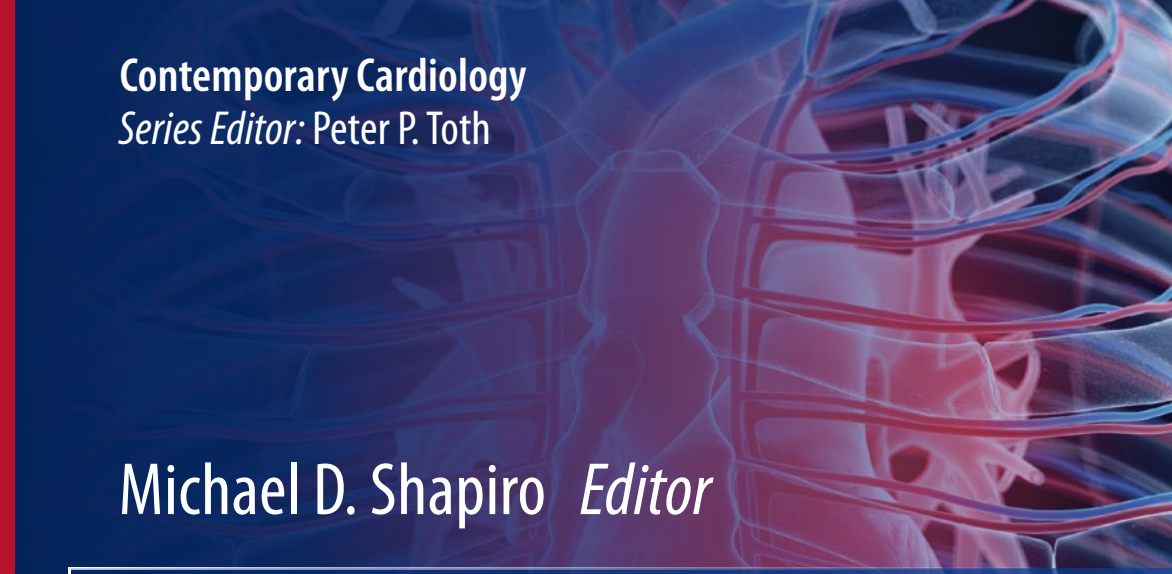

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Cardiovascular Risk Assessment in Primary Prevention

Humana Press

Contemporary Cardiology

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Preface

Although management of established atherosclerotic cardiovascular disease has improved dramatically, less has been achieved with regard to early detection and risk mitigation in primary prevention. The life trajectory of the average person (with stress, poor diet, excess body weight, inactivity, smoking, exposure to pollutants, and poor management of metabolic comorbidities) still leads straight to the development of this disease. Therefore, we have an unprecedented opportunity to focus on the prevention of atherosclerosis before cardiovascular events occur, an endeavor that starts with expert cardiovascular risk assessment.

This is the first comprehensive text dedicated to risk assessment in the primary prevention of atherosclerotic cardiovascular disease, the number one cause of death and disability in the world. It provides a summary of current evidence regarding approaches to risk assessment, traditional and emerging risk factors, and atherosclerosis imaging for refinement of risk estimation. This book will empower readers to perform state-of-the-art risk assessment to facilitate the prevention of cardiovascular disease. In addition, this volume provides a glimpse into the future of the field with in-depth discussion regarding the latest advances and exciting developments in the pipeline. Multiple tables, figures, and illustrations complement the text.

It is my sincere hope that *Cardiovascular Risk Assessment in Primary Prevention* will become a valuable resource for physicians, residents, fellows, and medical students in cardiology, endocrinology, primary care, and health promotion and disease prevention. May science lead the way to a healthier future.

Winston Salem, NC, USA
1/31/2022

Michael D. Shapiro

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Part I
Global Approaches to Risk Assessment

Chapter 1
Cardiovascular Risk Assessment in Primary Prevention

Aliza Hussain, Mahmoud Al Rifai, Umair Khalid, and Salim S. Virani

Introduction

Cardiovascular disease (CVD) is the leading cause of mortality in the United States, accounting for over 840,000 deaths annually (Benjamin et al. 2019). There have been significant advancements in therapies targeting cardiovascular risk factors with a resulting reduction in the incidence of CVD and cardiovascular death. Between 2006 and 2016, the overall cardiovascular mortality decreased by 18.6% in the United States (Benjamin et al. 2019). However, a significant proportion of high-risk populations are still not receiving therapies with proven benefits in

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cardiovascular risk reduction (Pokharel et al. 2016; Virani et al. 2015; Cutler et al. 2008; Thorndike et al. 2007), which may lead to disease progression and CVD events. On the other hand, pharmacological treatment options do not come without side effects, financial burden, and concern regarding medication compliance. In order to find the right balance, one approach to improve health-care delivery in regard to primary prevention of CVD is to accurately estimate a patient's absolute risk for CVD and identify those who will derive the greatest absolute benefit from therapy with minimal risk. By using risk assessment models, matching treatment intensity with CVD risk constitutes one of the fundamental tenets of preventive cardiovascular medicine.

Global cardiovascular risk assessment is crucial to inform clinical decision-making regarding initiation and intensification of cardiovascular risk-reducing therapies for primary prevention of CVD. Simply put, it is a calculation of the absolute risk of having a cardiovascular disease event, such as myocardial infarction, ischemic stroke, or incident heart failure, over a specified period of time. Traditionally, risk assessment has been based on empirical equations such as the pooled cohort equations (PCEs) (Goff Jr et al. 2014), which combine cardiovascular risk-modifying variables such as blood pressure, diabetes, and cholesterol levels. In some cases, such as the use of PCE, these risk assessment tools are also sex- and race-specific. Although risk assessment tools like PCE work well at a population level, they have limitations when applied to individual patients and can over- or underestimate risk in certain populations, including contemporary cohorts, racially diverse non-US populations, and chronic inflammatory conditions [e.g., lupus, rheumatoid arthritis, human immunodeficiency virus (HIV)] (Andersson et al. 2015; Chia et al. 2014; DeFilippis et al. 2015). As a result, there is growing focus on the identification of novel risk-enhancing conditions and use of biomarkers and cardiovascular imaging to further improve risk stratification and risk reclassification.

In this chapter, we aim to provide the rationale behind global CVD risk assessment, highlight major concepts related to risk assessment based on traditional risk factors, and summarize use of novel biomarkers and cardiovascular imaging, either currently under research or used in clinical practice that may help personalize cardiovascular risk assessment.

Importance of Global Cardiovascular Risk Assessment

One of the fundamental principles of preventive cardiovascular medicine is to identify patients that are most likely to benefit from risk-reducing therapies. Although relative risk reduction from blood pressure lowering (e.g., 10 mmHg lower systolic blood pressure) or lowering of LDL-C (e.g., 40 mg/dL) may be the same for two individuals, the absolute risk reduction will still be higher for the individual with a baseline risk that is higher. Moreover, in reverse, this may also help identify patients that are more likely to be harmed than helped from therapies such as aspirin, intensive lipid lowering, and/or antihypertensive medications. The reality is that

health-care resources are finite, so allocation of health-care resources to match treatment intensity with CVD risk is imperative. Moreover, preventive therapies are more cost-effective when used in those with higher absolute risk. Therefore, assessment of global cardiovascular risk is important to identify those who are most likely to benefit from them.

Several factors determine the individual cardiovascular risk for each patient. While earlier models of risk assessment utilized the presence or absence of risk factors for atherosclerotic CVD (including age, gender, family history of premature coronary heart disease, smoking status, hypertension), multiple epidemiological studies have indicated that all risk factors do not contribute equally (Wilson et al. 1998) and the risk is altered by the presence of other nontraditional risk determinants. As a result, several validated population-based risk calculators or tools were developed to accurately define risk by assigning weightage to individual factors. Some of these risk calculators have been adopted by multinational guidelines. The American Heart Association (AHA)/American College of Cardiology (ACC) cholesterol (Grundy et al. 2019) and hypertension (Whelton et al. 2018) guidelines, US Preventive Task Force guideline for aspirin, and European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines for the management of dyslipidemia (Mach et al. 2020) recommend the use of global CVD risk to guide primary prevention of CVD.

Global CVD Risk Assessment in Clinical Practice

The 2013 AHA/ACC cholesterol guideline (Goff Jr et al. 2014) recommended that clinicians focus on 10-year absolute atherosclerotic cardiovascular disease (ASCVD) risk. While two different individuals may derive the same relative risk reduction from a particular statin medication, the absolute risk reduction will naturally be higher in the individual with higher absolute ASCVD risk. It is for this reason that the intensity of statin therapy was intended to match the absolute risk of CVD with high-risk individuals recommended high-intensity statin and low- to moderate-risk individuals targeted with less intensive therapy. With removal of LDL-C cutoffs in the 2013 guideline, some have mistakenly believed that it is no longer necessary to measure a lipid profile. However, cholesterol measurements continue to remain necessary not only for monitoring response to statin therapy ($\geq$ 50% LDL-C lowering with high-intensity statin and 30–50% with moderate-intensity statin) but also for assessing medication adherence.

Absolute ASCVD risk is estimated using the pooled cohort equations (PCEs), the risk score introduced by the 2013 AHA/ACC guidelines. The PCEs are sex- and race-specific equations for four groups: white men, white women, black men, and black women. The PCE includes the same risk factors as its predecessor, the Framingham Risk Score (FRS), with two differences: (1) inclusion of stroke as an end point in addition to coronary heart disease (CHD) making ASCVD event as the primary outcome of interest and (2) separate equations for blacks and whites. The

PCE was derived using several NHLBI-funded population-based cohorts, which included large samples of blacks and whites, unlike FRS, which included only whites. The PCE is therefore better calibrated than the FRS, but in general can overestimate ASCVD risk because the populations included in these cohorts were enrolled a few decades ago when ASCVD event rates were higher compared to contemporary populations. Using the PCE risk cutoff of ≥7.5%, a larger sample of adults now became eligible for statin therapy and there is a concern for overtreatment. This cutoff was chosen as the threshold above which benefits of statin therapy outweigh risks, that is, when the net clinical benefit favors statin therapy.

Along with the use of PCE for risk estimation, the 2013 AHA/ACC cholesterol guidelines identified four major statin benefit groups that the 2018 cholesterol guideline (Grundy et al. 2019) continued to endorse: (1) clinical ASCVD, (2) LDL-C ≥ 190 mg/dL, (3) diabetes mellitus and LDL-C 70–189 mg/dL, and (4) no diabetes, LDL-C 70–189 mg/dL, and ASCVD risk ≥7.5% (Table 1.1). Central to both the 2013 and 2018 guidelines was the clinician–patient risk discussion (CPRD) that incorporates patient preferences and values and the risks and benefits of statin. Patients belonging to these statin benefit groups are not automatically assigned to a statin, but rather in the context of a CPRD, initiation of statin therapy is a shared decision-making process. Importantly, lifestyle recommendations of diet and exercise should be discussed and emphasized among all patients regardless of risk, and statin therapy should be decided together with therapeutic lifestyle changes.

A similar shift in clinical practice was also seen in hypertension management, whereby the 2017 ACC/AHA blood pressure (BP) guideline moved away from recommending antihypertensive therapies based solely on absolute BP values to one based on both BP and underlying CVD risk. Specifically, in adults with BP between 130–139/80–89 mmHg and without clinical ASCVD, DM, or CKD, the guideline

Table 1.1 Absolute risk thresholds for intervention for primary prevention of ASCVD

	Absolute risk of ASCVD event over 10 years			
Intervention	<5%	≥5 to <10%	≥10 to <20%	≥ 20%
Lifestyle modifications[a]	Yes	Yes	Yes	Yes
Antihypertensive therapy (if BP ≥ 140/90 mmHg)	Yes	Yes	Yes	Yes
Antihypertensive therapy (if BP ≥ 130/80 mmHg)	No	No	Yes	Yes
Statin therapy	No	≥5 to <7.5%: may consider ≥7.5% to <20: consider CAC scoring: may be used if patient undecided or has experienced statin-associated side effects in the past		Yes
Smoking cessation counseling and pharmacological aides	Any patient who smokes			

Recommendations based on information from ACC/AHA 2018 cholesterol guidelines (Grundy et al. 2019) and guidelines on the management of high blood pressure (Whelton et al. 2018)
ASCVD atherosclerotic cardiovascular disease; *BP* blood pressure
[a]Lifestyle modifications include a heart-healthy diet, weight management, and regular physical activity

recommends the use of PCE to evaluate 10-year ASCVD risk (Table 1.1). In this group, for individuals with PCE risk ≥10% antihypertensive therapy is indicated in addition to lifestyle modification for blood pressure lowering.

Risk Calculators to Estimate CVD Risk

The Framingham Risk Score (FRS) was the first scoring tool developed to assess the risk of coronary heart disease and was adapted by the third National Cholesterol Education Program, Adult Treatment Panel III (NCEP ATP-III). Since then, several risk assessment tools have emerged to estimate cardiovascular risk in adults. Table 1.2 highlights some of the widely available and validated risk calculators for

Table 1.2 Summary of some of the ASCVD risk calculators used in clinical practice

Risk calculator	Guidelines	Outcome	Strength	Weakness
Framingham Risk Score (FRS)	ATP III (2001), NLA (2014)	10-Year risk of definite MI or death	Hard cardiovascular end points increase reliability in risk estimation	Predominantly white population in the Framingham cohort Does not include stroke or HF
Pooled cohort equations (PCEs)	ACC/AHA cholesterol guidelines (2013 and 2017), 2018 ACC/AHA hypertension guidelines	10-Year and lifetime risk of ASCVD (included coronary death, nonfatal MI, or fatal or nonfatal stroke)	Lack specificity for ethnicities/ races other than AA and white	Better representation of AA Included stroke in outcomes
Reynolds Risk Score	None	10-, 20-, and 30-year risk of MI, stroke, or revascularization	Not adopted in any guideline	Includes family history of hs-CRP Predicts better than FRS in white and AA women
Systematic COronary Risk Evaluation (SCORE)	2019 ESC/EAS guidelines for the management of dyslipidemia	10-Year risk of fatal atherosclerotic cardiovascular events, including sudden cardiac death	Risk chart offers risk calculation and management advice in 17 languages and has country-specific calculators Hard, reproducible outcomes	Derived from European population and so not generalizable to global populations Cannot be used in individuals > 65 years old

Table 1.2 (continued)

Risk calculator	Guidelines	Outcome	Strength	Weakness
Multi-Ethnic Study of Atherosclerosis (MESA)	None	10-Year coronary heart disease risk (MI, resuscitated cardiac arrest, fatal CHD, and revascularization)	Hispanic and Chinese populations included Can integrate CAC score into risk calculation with improved CHD risk prediction than risk factors alone	Only evaluates CHD outcomes and other peripheral atherosclerotic events

ASCVD atherosclerotic cardiovascular disease, *ATP* Adult Treatment Panel, *NLA* National Lipid Association, *AA* African-American, *ACC* American College of Cardiology, *AHA* American Heart Association, *CHD* coronary heart disease, *MI* myocardial infarction, *ESC/EAS* European Society of Cardiology/European Atherosclerosis Society, *hs-CRP* high-sensitivity C-reactive protein

assessing the 10-year risk of ASCVD, including FRS, PCE, Multi-Ethnic Study of Atherosclerosis (MESA), Reynolds Risk score, and SCORE (in European guidelines) risk calculators for 10-year risk assessment.

As seen in Table 1.2, each risk calculator has certain advantages and disadvantages. All of these risk calculators are based on large population cohorts. While these risk calculators work well at the population level, they may over- or underpredict cardiovascular risk at an individual level, especially for certain underrepresented ethnicities/races, low socioeconomic status, and high-risk conditions such as HIV and autoimmune diseases. Lastly, although heart failure is an important clinical outcome, especially when treating blood pressure, most risk calculators do not assess the future risk of heart failure development (Colantonio et al. 2017; Crowson et al. 2017; Triant et al. 2018). Therefore, it is important to (1) individualize risk assessment using guideline-based risk enhancers, cardiac biomarkers, and imaging, as detailed below and (2) integrate shared decision-making and the CPRD to individualize therapy.

Role of Risk Enhancers for Refining and Personalizing Risk Assessment

The 2018 AHA/ACC cholesterol guideline also proposed four major statin benefit groups, but there were a few important differences when compared to the 2013 guideline. Rather than a PCE binary cutoff of 7.5% to distinguish high from low risk, the 2018 guideline stratified individuals into the following four categories when evaluating for primary prevention: low risk (<5%), borderline risk (5–<7.5%),

intermediate risk (7.5 − <20%), and high risk (≥20%). High-risk individuals are recommended high-intensity statin therapy (class I recommendation) along with lifestyle modification. Among intermediate- and borderline-risk individuals, the presence of risk-enhancing factors should be assessed to guide statin therapy (class I and IIb recommendation, respectively), while statin therapy is not recommended in low-risk individuals (class I). For all risk groups, a heart-healthy lifestyle is recommended with or without statin therapy.

The risk enhancers as shown in Table 1.3 included clinical factors such as family history of premature ASCVD, chronic kidney disease, chronic inflammatory conditions, premature menopause or preeclampsia, South Asian ethnicity, low ankle–brachial index (ABI <0.9), and lipid and inflammatory biomarkers [LDL-C ≥ 160 mg/

Table 1.3 Risk enhancers, biomarkers, and cardiovascular imaging useful in refining and personalizing risk assessment

Clinical risk enhancers
Family history of premature ASCVD (males <55 years, female <65 years)
Chronic kidney disease
Primary hypercholesterolemia (LDL-C 160–189 mg/dL or non-HDL 190–219 mg/dL)
Metabolic syndrome
Abnormal ABI (if measured)
Inflammatory conditions such as RA, HIV, and psoriasis
Pregnancy-related complications (e.g., preeclampsia, premature delivery), early menopause
High-risk ethnicities (e.g., South Asian)
Social deprivation
Physical inactivity
Psychosocial stress
Major psychiatric illness
Atrial Fibrillation
Left ventricular hypertrophy
Obstructive sleep apnea
Non-alcohol fatty liver disease
Biomarkers of cardiovascular risk
Apolipoprotein B ≥ 130 mg/dL (if measured)
Lipoprotein(a) ≥ 50 mg/dL or ≥ 125 (if measured)
Triglyceride level ≥ 175 mg/dL
hs-CRP ≥ 2 mg/L
Imaging (selective use)
Coronary artery calcium score
Carotid intima thickness/plaque
In research and development
NT-proBNP
High-sensitivity cardiac troponin I and T
Polygenic risk scores
Peripheral ultrasound

Risk enhancer as identified by the ACC/AHA cholesterol guidelines (Grundy et al. 2019) and ESC/EAS guidelines on the management of dyslipidemia (Mach et al. 2020)

ASCVD atherosclerotic cardiovascular disease, *LDL-C* low-density lipoprotein cholesterol, *ABI* ankle–brachial index, *RA* rheumatoid arthritis, *HIV* human immunodeficiency virus, *hs-CRP* high-sensitivity C-reactive protein, *NT-proBNP* N-terminal pro b-type natriuretic peptide

dL, persistently elevated triglycerides of ≥175 mg/dL, Lp(a) ≥ 50 mg/dL (> = 125 nmol/L), and apo(B) ≥130 mg/dL, hs-CRP ≥ 2 mg/L].

The European Society of Cardiology/European Atherosclerosis Society (EAS/ESC) guideline for the management of dyslipidemia identified "risk modifiers" (Table 1.3), including the following: socioeconomic status, family history, body mass index, or diagnostic evidence of subclinical cardiovascular disease, for example, coronary artery calcium, carotid plaque, or ankle–brachial index (ABI) (discussed below).

Cardiovascular Risk Biomarkers

Lipid Parameters

Although LDL-C is the primary lipid parameter for risk stratification and goal-directed therapy, other atherogenic lipid particles are also known to contribute to atherosclerosis and increased ASCVD risk. These include triglyceride-rich remnant lipoproteins (TGRL) and lipoprotein(a) [Lp(a)]. The contribution of all atherogenic lipids is accounted for by non-HDL-C. With the growing burden of cardiometabolic disease and obesity in the United States, greater importance is placed on lipid risk markers that account for residual non-LDL-C risk. Elevation in non-HDL-C can improve the selection of those at increased ASCVD risk (Sniderman et al. 2011). Similarly, apolipoprotein B (apoB) is a direct measure of all atherogenic lipoprotein particles as LDL, VLDL, and Lp(a) carry apoB on their surface. ApoB levels correlated with non-HDL-C and both demonstrate a strong association with ASCVD (stronger than LDL-C) (Sniderman et al. 2011; Ramjee et al. 2011) (Grundy et al. 2009). An apoB level of greater than 130 mg/dL is considered a marker of elevated ASCVD risk as per the 2018 AHA/ACC cholesterol guideline.

Lp(a) is an LDL-like particle with an added glycoprotein, apolipoprotein(a), which has both atherogenic and prothrombotic potential. Increased levels of Lp(a) have been associated with a 1.5-fold higher risk of MI and a two-fold higher risk of stroke (Paré et al. 2019). An elevation in Lp(a) of greater than 50 mg/dL or 125 nmol/L is considered a risk-enhancing factor as per the 2018 AHA/ACC cholesterol guideline (Tsimikas 2017; Willeit et al. 2014).

Moderate and persistent primary elevations in triglyceride (TG) levels are also considered a risk-enhancing factor. Multiple genetic (genome-wide association and Mendelian randomization) studies have shown that elevated levels of TG are independent predictors of major coronary and cerebrovascular events (Assmann et al. 1996; Freiberg et al. 2008).

Inflammatory Marker: – hs-CRP

Atherosclerosis is an inflammatory process. Among several biomarkers, hs-CRP is a well-known marker of inflammation and has been shown to be associated with incident cardiovascular disease events (Ridker et al. 2000; Koenig et al. 1999; Yousuf et al. 2013). Moreover, greater absolute benefit derived from preventive therapies such as aspirin or statin has been demonstrated in individuals with baseline elevations in hs-CRP levels (Ridker et al. 1997; Ridker et al. 2009). The JUPTER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) study demonstrated that, in nearly 18,000 patients with LDL-C < 130 mg/dL and hs-CRP >2 mg/L, patients randomized to rosuvastatin experienced a 44% relative risk reduction in incident major cardiovascular events compared to placebo (Ridker et al. 2008). Therefore, hs-CRP may identify residual inflammatory risk beyond residual cholesterol risk.

Future Directions

NT-proBNP is a marker of myocardial stretch/stress and has been associated with increased risk for cardiovascular disease and heart failure (Wang et al. 2004). Moreover, individuals with elevated levels of NT-proBNP, despite normal blood pressure, are at increased risk of developing hypertension. Similarly, troponin T and I are markers of cardiac injury. Beyond their ability to diagnose acute myocardial infarction, the newer generation high-sensitivity troponin assays have been shown to predict increased risk of coronary heart disease, heart failure, and mortality (Saunders et al. 2011; de Filippi et al. 2010; de Lemos et al. 2010; Jia et al. 2019). Therefore, there is increasing interest in the clinical role of these biomarkers to identify individuals with elevated CVD risk who may benefit from preventive therapies. An exploratory analysis of SPRINT has shown that higher baseline values of high-sensitivity cardiac troponin or NT-proBNP were associated with greater risk of death and heart failure, with highest risk among those with abnormal levels of both biomarkers who in turn derived greatest benefit from aggressive blood pressure lowering (Jarett 2020). In line with this, a pooled analysis from ARIC, MESA, and DHS showed that individuals with elevated NT-proBNP or high-sensitivity cardiac troponin and elevated blood pressure or stage 1 hypertension had a 10-year risk of ASCVD or heart failure of >10%. Moreover, compared to nonelevated levels of both biomarkers, individuals with elevations in either biomarker had higher risk of ASCVD or HF and lower number needed to treat to prevent one CVD event with intensive BP lowering (to target systolic BP <120 mm Hg) (Pandey et al. 2019). Future clinical trials are needed to assess whether biomarker-based strategies for CV risk stratification to guide preventive treatment decisions could lead to improvement in cardiovascular outcomes.

Risk Stratification for Secondary ASCVD Prevention

The, 2018 AHA/ACC cholesterol guideline also included risk stratification for secondary prevention of ASCVD for the very first time, introducing the concept of the "very high-risk ASCVD" patient. This category includes individuals with either multiple major ASCVD events or one major ASCVD event plus multiple major risk factors. These patients have the highest risk of recurrent ASCVD events and are therefore likely the ones to derive the most benefit from nonstatin therapies on top of maximally tolerated statin therapy. These nonstatin therapies include ezetimibe and proprotein convertase subtilisin/kexin type 9 inhibitors.

Tools to Screen for Subclinical Atherosclerosis

Risk Reclassification Using Coronary Artery Calcium Scoring

In the 2018 AHA/ACC cholesterol guideline, the use of coronary artery calcium (CAC) for additional risk stratification was assigned a IIa level of recommendation (LOR), up from IIb from the 2013 guideline. The updated recommendation was based on a number of studies showing the superiority of CAC compared to other risk markers for ASCVD risk discrimination and reclassification. Importantly, in the context of global ASCVD risk overestimation using the PCE, a CAC score of 0 is useful for downgrading to a low-risk stratum where individuals would not be expected to derive benefit from statin treatment. A study of over 4500 individuals with 10-year follow-up examined the association between CAC score and cardiovascular event rate. In participants with a CAC score = 0 who would otherwise be eligible for statin therapy based on 10-year ASCVD risk of ≥7.5%, the actual ASCVD event rate was significantly lower than the accepted threshold of ≥7.5% 10-year ASCVD risk for initiation of statin therapy (Budoff et al. 2018). Similar results have been reported by other studies for primary prevention. Therefore, if there is statin disutility such as the patient being reluctant to take a statin or the clinician being uncertain about the benefits of initiating this therapy, CAC 0 would strongly argue in favor of withholding statin therapy. This "power of zero CAC" is a vital tool in risk reclassification ("de-risking") and has now been integrated in the 2018 guideline on blood cholesterol for these select groups of patients. After assessing a patient's ASCVD risk using PCE and incorporating ASCVD risk enhancers, if there is still uncertainty on the part of either the clinician or the patient regarding the use of statin therapy or if there is a concern regarding the side effects of statin therapy, the use of the CAC score can be pursued as the next step as a class IIa recommendation to further guide decision-making in intermediate-risk adults (≥7.5% to <20% 10-year ASCVD risk) or select borderline-risk adults (5% to <7.5% 10-year ASCVD risk). In these patients, if the CAC score = 0, statin therapy can be delayed or deferred. In contrast, CAC >0 would support initiating statin therapy as

individuals with even very low risk score (110) have a significantly higher risk compared to those with CAC 0. Those with CAC ≥100 may experience ASCVD event rates similar to secondary prevention populations, thereby strongly favoring statin therapy (Martin et al. 2014).

It is important to point out that the CAC score is not recommended as a population screening test but rather as a "tie breaker" in select borderline- and intermediate-risk adults when there is clinical equipoise or patient reluctance regarding statin therapy. CAC may also be used for personalized allocation of aspirin and antihypertensive treatment as well, but current guidelines have not yet incorporated the use of CAC for this purpose.

Carotid Plaque

High-resolution B-mode ultrasound of the left and right common and internal carotid arteries or femoral arteries can be used to assess plaque burden. Assessment of carotid and femoral plaque burden has been shown to be an independent predictor of CVD events (McDermott et al. 2017; Sillesen et al. 2018; Baber et al. 2015). Although the ACC/AHA cholesterol guidelines do not specifically endorse the use of ultrasound to assess peripheral/carotid plaque burden, the EAS/ESC guidelines recommend that the presence of carotid or femoral plaque may reclassify moderate-risk individuals to higher-risk category.

Ankle–Brachial Index (ABI)

The evaluation of systolic ABI is a simple and well-validated method to detect subclinical asymptomatic stages of peripheral atherosclerotic disease (PAD) (Carter 1968; Fowkes 1988). Several population studies have demonstrated the positive association of low ABI with incident atherosclerotic cardiovascular events (Criqui et al. 1992; Newman et al. 1993; Leng et al. 1996). Therefore, measurement of ABI can be a prognostic marker to identify individuals with elevated cardiovascular risk and is considered a "risk enhancer" in the 2018 ACC/AHA cholesterol guideline.

Assessment of Lifetime ASCVD Risk

Age is a significant driver of risk in current risk calculators. Therefore, younger adults are estimated to have a lower short-term risk of cardiovascular disease and would be unlikely to exceed the 10-year risk thresholds set by multisociety guidelines to initiate preventive drug therapy. However, primary ASCVD prevention should begin early in life. Therefore, for adults aged 20–30 years, it may be useful

for clinicians to consider using 30-year or lifetime risk as a tool to emphasize and promote healthy lifestyle choices, diet, weight loss, and exercise. The 2013 and 2018 cholesterol guidelines propose the ASCVD risk calculator to estimate 30-year or lifetime risk which can be helpful in assessing the long-term effects of exposure to a single elevated clinical risk factor or the aggregate of multiple risk factors. Lifetime risk assessment may be useful to define and communicate ASCVD risk in younger adults with low 10-year risk but with high lifetime risk due to significant uncontrolled risk factors and help promote healthy lifestyle changes.

Risk Assessment in the Context of Shared Decision-Making

Shared decision-making and collaboration between a clinician and patient are important aspects in risk assessment and primary prevention of ASCVD. Provider–patient discussions regarding personalized ASCVD risk estimation have important implications on the patient's perception of their own risk as well as their willingness to adopt healthy lifestyle habits or adhere to medical therapies. Moreover, a systematic review found that repeated assessment and communication of global risk and repeated counseling showed a significant reduction in predicted CHD risk (0.2–2%) over 10 years. Although the absolute difference was small in this study, this may still have important implications when considered at a population level (Sheridan et al. 2010).

Multiple studies have shown that clinicians with knowledge of a patient's global risk are more likely to initiate preventive care and prescribe risk-reducing therapy to those at high risk of a CHD-related event (Hall et al. 2003; Montgomery et al. 2000; Usher-Smith et al. 2015). From a patient's perspective, provision of risk information and counseling on their cardiovascular risk factors has been shown to improve the accuracy of risk perception (Usher-Smith et al. 2015) and increased willingness to accept cardiovascular preventive care (Karmali et al. 2017; Nieuwkerk et al. 2012). The use of coronary artery calcium or carotid/femoral plaque assessment may be useful in this regard. Studies have shown that allowing patients to see arterial calcification on CT scan may motivate them to adhere to a healthy diet, exercise, aspirin, and/or statin treatment(Kalia et al. 2006; Johnson et al. 2015).

Conclusion

Global cardiovascular risk assessment is a calculation of the patient's absolute risk of having a cardiovascular disease event, for example, coronary heart disease, ischemic stroke, and heart failure, over a specified period of time. Both AHA/ACC and European guidelines recommend clinicians to use risk calculators, for example,

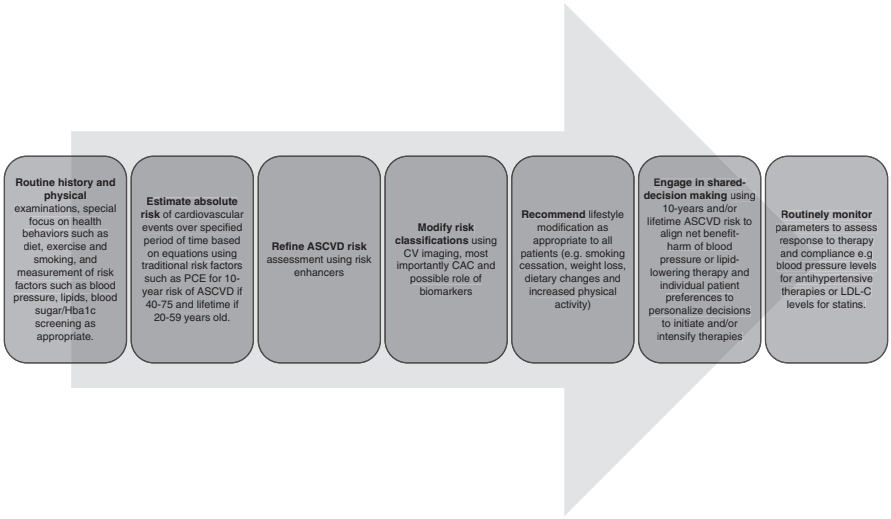

Fig. 1.1 Step-by-step guide for cardiovascular risk assessment, refinement, and personalization in primary prevention

PCE or SCORE, to evaluate short-term risk and lifetime risk to help inform decision-making around early, aggressive lifestyle changes and possible consideration of certain pharmacological therapies. While the risk calculators work well on population level, they may over- or underestimate risk in certain groups or races/ethnicities or socioemotional strata. Therefore, it is important to adopt an individualized risk assessment based on specific patient risk enhancers or modifiers that include comorbidities, family history, and biomarkers of CVD risk (lipid, inflammatory cardiac stress/injury). Finally, assessment of subclinical atherosclerosis using imaging may help to further reclassify risk. Ultimately, shared decision-making and collaboration between a clinician and patient is the most important aspect of risk assessment and decisions regarding lifestyle choices and treatment initiation for cardiovascular disease prevention (Fig. 1.1).

References

Andersson C, Enserro D, Larson MG, Xanthakis V, Vasan RS. Implications of the US cholesterol guidelines on eligibility for statin therapy in the community: comparison of observed and predicted risks in the Framingham Heart Study Offspring Cohort. J Am Heart Assoc. 2015;4(4):e001888. https://doi.org/10.1161/JAHA.115.001888.

Assmann G, Schulte H, von Eckardstein A. Hypertriglyceridemia and elevated lipoprotein(a) are risk factors for major coronary events in middle-aged men. Am J Cardiol. 1996;77:1179–84. https://doi.org/10.1016/s0002-9149(96)00159-2.

Baber U, Mehran R, Sartori S, Schoos MM, Sillesen H, Muntendam P, et al. Prevalence, impact, and predictive value of detecting subclinical coronary and carotid atherosclerosis in asymptomatic adults: the BioImage study. J Am Coll Cardiol. 2015;65:1065–74.

Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke Statistics-2019 update: a report from the American Heart Association. Circulation. 2019;139(10):e56–e528. https://doi.org/10.1161/CIR.0000000000000659.

Budoff MJ, Young R, Burke G, Carr J, Detrano RC, Folsom AR, et al. Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD) events: the multiethnic study of atherosclerosis (MESA). Eur Heart J. 2018;39:2401–8. https://doi.org/10.1093/eurheartj/ehy217.

Carter SA. Indirect systolic pressures and pulse waves in arterial occlusive diseases of the lower extremities. Circulation. 1968;37:624–37. https://doi.org/10.1161/01.cir.37.4.624.

Chia YC, Lim HM, Ching SM. Validation of the pooled cohort risk score in an Asian population - a retrospective cohort study. BMC Cardiovasc Disord. 2014;14:163. https://doi.org/10.1186/1471-2261-14-163.

Colantonio LD, Richman JS, Carson AP, Lloyd-Jones DM, Howard G, Deng L, et al. Performance of the atherosclerotic cardiovascular disease pooled cohort risk equations by social deprivation status. J Am Heart Assoc. 2017;6(3):e005676. https://doi.org/10.1161/JAHA.117.005676.

Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med. 1992;326:381–6. https://doi.org/10.1056/NEJM199202063260605.

Crowson CS, Gabriel SE, Semb AG, van Riel PLCM, Karpouzas G, Dessein PH, et al. Rheumatoid arthritis-specific cardiovascular risk scores are not superior to general risk scores: a validation analysis of patients from seven countries. Rheumatology. 2017;56(7):1102–10. https://doi.org/10.1093/rheumatology/kex038.

Cutler JA, Sorlie PD, Wolz M, Thom T, Fields LE, Roccella EJ. Trends in hypertension prevalence, awareness, treatment, and control rates in United States adults between 1988–1994 and 1999–2004. Hypertension. 2008;52(5):818–27.

de Filippi CR, de Lemos JA, Christenson RH, Gottdiener JS, Kop WJ, Zhan M, et al. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. JAMA. 2010;304:2494–502. https://doi.org/10.1001/jama.2010.1708.

de Lemos JA, Drazner MH, Omland T, Ayers CR, Khera A, Rohatgi A, et al. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. JAMA. 2010;304:2503–12. https://doi.org/10.1001/jama.2010.1768.

De Filippis AP, Young R, Carrubba CJ, McEvoy JW, Budoff MJ, Blumenthal RS, et al. An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. Ann Intern Med. 2015;162(4):266–75. https://doi.org/10.7326/M14-1281.

Fowkes FG. The measurement of atherosclerotic peripheral arterial disease in epidemiological surveys. Int J Epidemiol. 1988;17:248–54. https://doi.org/10.1093/ije/17.2.248.

Freiberg JJ, Tybjaerg-Hansen A, Jensen JS, Nordestgaard BG. Nonfasting triglycerides and risk of ischemic stroke in the general population. JAMA. 2008;300:2142–52. https://doi.org/10.1001/jama.2008.621.

Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S49–73. https://doi.org/10.1161/01.cir.0000437741.48606.98.

Grundy SM, Vega GL, Tomassini JE, Tershakovec AM. Correlation of non-high-density lipoprotein cholesterol and low-density lipoprotein cholesterol with apolipoprotein B during simvastatin + fenofibrate therapy in patients with combined hyperlipidemia (a subanalysis of the SAFARI trial). Am J Cardiol. 2009;104(4):548–53. https://doi.org/10.1016/j.amjcard.2009.04.018.

Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019;73(24):3168–209. https://doi.org/10.1016/j.jacc.2018.11.002.

Hall LM, Jung RT, Leese GP. Controlled trial of effect of documented cardiovascular risk scores on prescribing. BMJ. 2003;326:251–2. https://doi.org/10.1136/bmj.326.7383.251.

Jia X, Sun W, Hoogeveen RC, Nambi V, Matsushita K, Folsom AR, et al. High-sensitivity troponin I and incident coronary events, stroke, heart failure hospitalization, and mortality in the ARIC Study. Circulation. 2019;139(23):2642–53. https://doi.org/10.1161/CIRCULATIONAHA.118.038772.

Johnson JE, Gulanick M, Penckofer S, Kouba J. Does knowledge of coronary artery calcium affect cardiovascular risk perception, likelihood of taking action, and health-promoting behavior change? J Cardiovasc Nurs J Cardiovasc Nurs. 2015;30:15–25. https://doi.org/10.1097/JCN.0000000000000103.

Kalia NK, Miller LG, Nasir K, Blumenthal RS, Agrawal N, Budoff MJ. Visualizing coronary calcium is associated with improvements in adherence to statin therapy. Atherosclerosis. 2006;185:394–9. https://doi.org/10.1016/j.atherosclerosis.2005.06.018.

Karmali KN, Persell SD, Perel P, Lloyd-Jones DM, Berendsen MA, Huffman MD. Risk scoring for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2017;3:CD006887. https://doi.org/10.1002/14651858.CD006887.pub4.

Koenig W, Sund M, Fröhlich M, Fischer HG, Löwel H, Döring A, et al. C-Reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. Circulation. 1999;99:237–42. https://doi.org/10.1161/01.cir.99.2.237.

Leng GC, Fowkes FG, Lee AJ, Dunbar J, Housley E, Ruckley CV. Use of ankle brachial pressure index to predict cardiovascular events and death: a cohort study. BMJ. 1996;313:1440–4. https://doi.org/10.1136/bmj.313.7070.1440.

Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111–88. https://doi.org/10.1093/eurheartj/ehz455.

Martin SS, Blaha MJ, Blankstein R, Agatston A, Rivera JJ, Virani SS, et al. Dyslipidemia, coronary artery calcium, and incident atherosclerotic cardiovascular disease: implications for statin therapy from the multi-ethnic study of atherosclerosis. Circulation. 2014;129:77–86. https://doi.org/10.1161/CIRCULATIONAHA.113.003625.

McDermott MM, Kramer CM, Tian L, Carr J, Guralnik JM, Polonsky T, et al. Plaque composition in the proximal superficial femoral artery and peripheral artery disease events. JACC Cardiovasc Imaging. 2017;10:1003–12.

Montgomery AA, Fahey T, Peters TJ, MacIntosh C, Sharp DJ. Evaluation of computer based clinical decision support system and risk chart for management of hypertension in primary care: randomised controlled trial. BMJ. 2000;320:686–90. https://doi.org/10.1136/bmj.320.7236.686.

Newman AB, Sutton-Tyrrell K, Vogt MT, Kuller LH. Morbidity and mortality in hypertensive adults with a low ankle/arm blood pressure index. JAMA. 1993;270:487–9.

Nieuwkerk PT, Nierman MC, Vissers MN, Locadia M, Greggers-Peusch P, Knape LP, et al. Intervention to improve adherence to lipid-lowering medication and lipid-levels in patients with an increased cardiovascular risk. Am J Cardiol. 2012;110:666–72. https://doi.org/10.1016/j.amjcard.2012.04.045.

Pandey A, Patel KV, Vongpatanasin W, Ayers C, Berry JD, Mentz RJ, et al. Incorporation of biomarkers into risk assessment for allocation of antihypertensive medication according to the 2017 ACC/AHA high blood pressure guideline: a pooled cohort analysis. Circulation. 2019;140:2076–88. https://doi.org/10.1161/CIRCULATIONAHA.119.043337.

Paré G, Çaku A, McQueen M, Anand SS, Enas E, Clarke R, et al. Lipoprotein(a) levels and the risk of myocardial infarction among 7 ethnic groups. Circulation. 2019;139(12):1472–82. https://doi.org/10.1161/CIRCULATIONAHA.118.034311.

Pokharel Y, Gosch K, Nambi V, Chan PS, Kosiborod M, Oetgen WJ, et al. Practice-level variation in statin use among patients with diabetes: insights from the PINNACLE Registry. J Am Coll Cardiol. 2016;68(12):1368–9. https://doi.org/10.1016/j.jacc.2016.06.048.

Presented by Dr. Jarett D. Berry at the American Heart Association Virtual Scientific Sessions, November 15, 2020.

Ramjee V, Sperling LS, Jacobson TA. Non-high-density lipoprotein cholesterol versus apolipoprotein B in cardiovascular risk stratification: do the math. J Am Coll Cardiol. 2011;58(5):457–63. https://doi.org/10.1016/j.jacc.2011.05.009.

Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med. 1997;336:973–9. https://doi.org/10.1056/NEJM199704033361401.

Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med. 2000;342:836–43. https://doi.org/10.1056/NEJM200003233421202.

Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359:2195–207. https://doi.org/10.1056/NEJMoa0807646.

Ridker PM, MacFadyen JG, Fonseca FA, Genest J, Gotto AM, Kastelein JJ, et al. Number needed to treat with rosuvastatin to prevent first cardiovascular events and death among men and women with low low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein: justification for the use of statins in prevention: an intervention trial evaluating rosuvastatin (JUPITER). Circ Cardiovasc Qual Outcomes. 2009;2:616–23. https://doi.org/10.1161/CIRCOUTCOMES.109.848473.

Saunders JT, Nambi V, de Lemos JA, Chambless LE, Virani SS, Boerwinkle E, et al. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. Circulation. 2011;123:1367–76. https://doi.org/10.1161/CIRCULATIONAHA.110.005264.

Sheridan SL, Viera AJ, Krantz MJ, Ice CL, Steinman LE, Peters KE, et al. The effect of giving global coronary risk information to adults: a systematic review. Arch Intern Med. 2010;170:230–9. https://doi.org/10.1001/archinternmed.2009.516.

Sillesen H, Sartori S, Sandholt B, Baber U, Mehran R, Fuster V. Carotid plaque thickness and carotid plaque burden predict future cardiovascular events in asymptomatic adult Americans. Eur Heart J Cardiovasc Imaging. 2018;19:1042–50.

Sniderman AD, Williams K, Contois JH, Monroe HM, McQueen MJ, de Graaf J, et al. A meta-analysis of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B as markers of cardiovascular risk. Circ Cardiovasc Qual Outcomes. 2011;4(3):337–45. https://doi.org/10.1161/CIRCOUTCOMES.110.959247.

Thorndike AN, Regan S, Rigotti NA. The treatment of smoking by US physicians during ambulatory visits: 1994–2003. Am J Public Health. 2007;97(10):1878–83.

Triant VA, Perez J, Regan S, Massaro JM, Meigs JB, Grinspoon SK, et al. Cardiovascular risk prediction functions underestimate risk in HIV infection. Circulation. 2018;137(21):2203–14. https://doi.org/10.1161/CIRCULATIONAHA.117.028975.

Tsimikas S. A test in context: lipoprotein(a): diagnosis, prognosis, controversies, and emerging therapies. J Am Coll Cardiol. 2017;69(6):692–711. https://doi.org/10.1016/j.jacc.2016.11.042.

Usher-Smith JA, Silarova B, Schuit E, Moons KG, Griffin SJ. Impact of provision of cardiovascular disease risk estimates to healthcare professionals and patients: a systematic review. BMJ Open. 2015;5:e008717. https://doi.org/10.1136/bmjopen-2015-008717.

Virani SS, Woodard LD, Ramsey DJ, Urech TH, Akeroyd JM, Shah T, et al. Gender disparities in evidence-based statin therapy in patients with cardiovascular disease. Am J Cardiol. 2015;115(1):21–6. https://doi.org/10.1016/j.amjcard.2014.09.041.

Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Omland T, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. N Engl J Med. 2004;350:655–63. https://doi.org/10.1056/NEJMoa031994.

Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: execu-

tive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2018;138(17):e426–83. https://doi.org/10.1161/CIR.0000000000000597.

Willeit P, Kiechl S, Kronenberg F, Witztum JL, Santer P, Mayr M, et al. Discrimination and net reclassification of cardiovascular risk with lipoprotein(a): prospective 15-year outcomes in the Bruneck Study. J Am Coll Cardiol. 2014;64:851–60. https://doi.org/10.1016/j.jacc.2014.03.061.

Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97(18):1837–47. https://doi.org/10.1161/01.cir.97.18.1837.

Yousuf O, Mohanty BD, Martin SS, Joshi PH, Blaha MJ, Nasir K, et al. High-sensitivity C-reactive protein and cardiovascular disease: a resolute belief or an elusive link? J Am Coll Cardiol. 2013;62:397–408. https://doi.org/10.1016/j.jacc.2013.05.016.

Chapter 2
Global Approaches to Risk Assessment: The US Guidelines

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Introduction

Assessment of absolute cardiovascular disease (CVD) risk and aligning the intensity of treatment with estimated risk have long served as the cornerstones of CVD prevention (Wilson et al. 1998; Goff Jr et al. 2014; Arnett et al. 2019). Estimating absolute CVD risk has advantages, including a population-based understanding of patient prognosis, a foundation for effective risk communication, and balance of potential benefits and harms of preventive therapies (net clinical benefit) (Lloyd-Jones et al. 2019). Thus, estimated CVD risk serves as the yardstick that informs clinician–patient discussions aimed at reducing risk in asymptomatic individuals. Assessment of risk is critical for determining the intensity of cardiovascular prevention efforts, including lifestyle management as well as initiation and maintenance of pharmacological therapy. The US guideline-recommended approach to cardiovascular risk assessment involves the estimation of absolute risk using risk prediction algorithms, ideally, embedded in electronic medical record systems to allow for rapid estimation of risk. This recent improvement in ease of use has led to increasing adoption of these risk estimation tools in diverse clinical settings.

In the United States, the pooled cohort equations (PCEs) are the most commonly used risk prediction algorithm to estimate the 10-year risk of developing an atherosclerotic cardiovascular disease (ASCVD) event in asymptomatic individuals (Goff Jr et al. 2014). Absolute risk estimated using the PCE serves as the starting point for guiding clinician–patient discussions regarding ASCVD prevention strategies (Lloyd-Jones et al. 2019). These equations are an integral part of the US American

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College of Cardiology(ACC)/American Heart Association (AHA)/multi-society cholesterol and hypertension management guidelines, and have been validated in several populations (Grundy et al. 2019; Whelton et al. 2018). It is important to note that this cardiovascular risk assessment approach utilizes population levels of select traditional cardiovascular risk factors to predict the natural course of ASCVD in individual patients (Lloyd-Jones et al. 2019). Therefore, the ASCVD risk predicted by PCE needs to be personalized and refined by considering unique cardiovascular risk and resilience factors in each individual. In this chapter, we discuss cardiovascular risk assessment approaches promulgated by the US guidelines, their limitations, and opportunities for enhancement in the future.

US Guideline Recommendations

The 2013 ACC/AHA guideline for cardiovascular risk assessment introduced the race- and sex-specific PCE for predicting 10-year risk of developing a first ASCVD event [defined as nonfatal myocardial infarction (MI) or coronary heart disease (CHD)-related death, or fatal or nonfatal stroke] among non-Hispanic white and non-Hispanic black individuals free from clinical CVD (Goff Jr et al. 2014). These guidelines further recommended that the sex-specific PCE for non-Hispanic whites be considered for risk estimation in other race/ethnic groups (Goff Jr et al. 2014). The PCEs were an update to the Framingham Risk Score, (Wilson et al. 1998) the most commonly used risk prediction algorithm in the United States at the time. The formulation of separate risk prediction equations for black individuals and the inclusion of stroke as a clinical end point of interest were recognized as favorable changes to the cardiovascular risk assessment paradigm in 2013.

The PCE risk prediction algorithm utilizes information regarding age, sex, race, diabetes status, current smoking, systolic blood pressure, antihypertensive use, total cholesterol level, and high-density lipoprotein cholesterol (HDL-C) level to predict 10-year ASCVD risk (Goff Jr et al. 2014). These equations have been derived from five longitudinal community-based epidemiological cohorts in the United States: 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 studies (Goff Jr et al. 2014). Since inception, the PCEs have been externally validated in several patient populations and are known to be well-calibrated near treatment decision thresholds (7.5–10% 10-year ASCVD risk) among study samples comprising broad US populations (Lloyd-Jones et al. 2019).

The 10-year ASCVD risk predicted by PCE is useful for guiding cholesterol and blood pressure (BP) management strategies. PCE-predicted 10-year ASCVD risk plays a central role in guiding cholesterol management strategies in the primary prevention setting. The 2018 cholesterol management guidelines recommend that 10-year ASCVD risk should be the starting point of the clinician–patient risk discussion among individuals aged 40–75 years with low-density lipoprotein

cholesterol (LDL-C) 70–190 mg/dL and without diabetes (Grundy et al. 2019). Based on the estimated absolute 10-year ASCVD risk, asymptomatic individuals are divided into four risk categories: low (<5%), borderline (5–7.5%), intermediate (≥7.5–20%), and high (≥20%) risk (Grundy et al. 2019). The guidelines recommend emphasizing a healthy lifestyle in everyone to help reduce cardiovascular risk regardless of estimated ASCVD risk. Moderate-intensity statin therapy may be considered in individuals with borderline risk (Class of Recommendation IIb) and is recommended in those with intermediate risk (Class of Recommendation I) (Grundy et al. 2019). Among individuals with borderline or intermediate risk, the guidelines recommend personalizing risk assessment by considering risk-enhancing factors (discussed below). Furthermore, coronary artery calcium (CAC) testing can be considered for refining ASCVD risk estimation in individuals when risk decision is uncertain (Class of Recommendation IIa) (Grundy et al. 2019). Lastly, initiation of high-intensity statin therapy with a goal of reducing LDL-C level ≥ 50% is recommended among high-risk individuals (Class of Recommendation I) (Grundy et al. 2019). These recommendations are summarized in Fig. 2.1.

The 2017 hypertension management guidelines established new BP categories for Americans: normal [systolic blood pressure (SBP) <120 mmHg and diastolic blood pressure (DBP) <80 mmHg], elevated (SBP 120–129 and DBP <80 mmHg), stage 1 hypertension (SBP 130–139 or DBP 80–89 mmHg), and stage 2 hypertension (SBP ≥140 or DBP ≥90 mmHg) (Whelton et al. 2018). The guidelines recognized PCE-predicted 10-year ASCVD risk threshold of 10% as an important threshold for guiding BP management in the primary prevention setting among individuals with stage 1 hypertension. Specifically, the hypertension guidelines recommend that individuals with 10-year ASCVD risk ≥10% should be treated with both

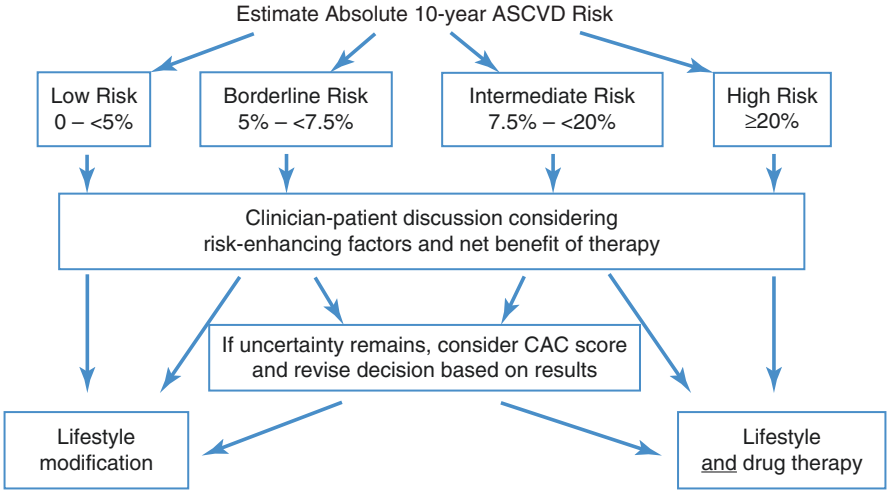

Fig. 2.1 Summary of risk assessment and clinician–patient risk discussion regarding atherosclerotic cardiovascular disease primary prevention. (Reproduced with publisher's permission from Lloyd-Jones et al. 2019)

pharmacological and nonpharmacological therapies (Class of Recommendation I), while those with risk <10% be treated with nonpharmacological therapies and have repeat BP evaluation in 3–6 months (Class of Recommendation I) (Whelton et al. 2018). Individuals with stage 2 hypertension should be managed with combination nonpharmacological and antihypertensive drug therapy (with two agents of different classes) regardless of 10-year ASCVD risk and have a repeat BP evaluation in 1 month (Whelton et al. 2018).

Risk-Enhancing Factors

As mentioned previously, the 2018 cholesterol management guidelines recommend considering certain risk-enhancing factors to guide primary prevention strategies among individuals with borderline (5–7.5%) or intermediate (≥7.5–20%) 10-year ASCVD risk (Grundy et al. 2019). These risk-enhancing factors are listed in Table 2.1, (Lloyd-Jones et al. 2019) and the list is a composite of risk factors that

Table 2.1 Cardiovascular risk enhancing factors for clinician-patient risk discussion

1.	Family history of premature ASCVD (males age < 55 years, females age < 65 years)
2.	Primary hypercholesterolemia (LDL-C 160–189 mg/dL, non-HDL-C 190–219 mg/dL)
3.	Metabolic syndrome [increased waist circumference, elevated triglycerides (>150 mg/dL), elevated blood pressure, elevated glucose, and low HDL-C (<40 mg/dL in men; <50 mg/dL in women) are factors; tally of three makes the diagnosis)
4.	Chronic kidney disease (eGFR 15–59 mL/min/1.73 m^2 with or without albuminuria, not treated with dialysis or kidney transplantation)
5.	Chronic inflammatory conditions such as psoriasis, RA, or HIV/AIDS
6.	History of premature menopause (before age 40 years) and history of pregnancy-associated conditions that increase later ASCVD risk such as preeclampsia
7.	High-risk race/ethnicities (e.g., South Asian ancestry)
8.	Lipid/biomarkers: associated with increased ASCVD risk
	Persistently elevated, primary hypertriglyceridemia (≥175 mg/dL)
	Elevated high-sensitivity C-reactive protein (≥2.0 mg/L)
	Elevated Lp(a): 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)
	Elevated apoB ≥130 mg/dL: a relative indication for its measurement would be triglyceride ≥200 mg/dL A level ≥ 130 mg/dL corresponds to an LDL-C > 160 mg/dL and constitutes a risk-enhancing factor
	ABI <0.9

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AIDS acquired immunodeficiency syndrome, *ABI* ankle–brachial index, *apoB* apolipoprotein B, *ASCVD* atherosclerotic cardiovascular disease, *eGFR* estimated glomerular filtration rate, *HDL-C* high-density lipoprotein cholesterol, *HIV* human immunodeficiency virus, *LDL-C* low-density lipoprotein cholesterol, *Lp(a)* lipoprotein (a); *RA* rheumatoid arthritis

have been shown to be independently associated with increased cardiovascular risk in epidemiological studies.

Primary hypercholesterolemia (elevated LDL-C or non-HDL-C), (Silverman et al. 2016; Brunner et al. 2019) primary hypertriglyceridemia, (Michael et al. 2011) elevated lipoprotein(a), (Virani et al. 2012) and apolipoprotein B levels (Sniderman et al. 2019) are well-established markers of increased cardiovascular risk. Family history of premature ASCVD is a predictor of cardiovascular risk that reflects the shared genetic and environmental predilection to cardiovascular disease (Anurag et al. 2020). Chronic systemic inflammation is a key driver of atherosclerosis, (Willerson and Ridker 2004) and as such, the presence of chronic inflammatory conditions and elevated high-sensitivity C-reactive protein are considered risk-enhancing factors. Along similar lines, metabolic syndrome, (Grundy 2004) chronic kidney disease, (Sarnak et al. 2019) premature menopause, (Honigberg et al. 2019a) and preeclampsia (Honigberg et al. 2019b) are other determinants of atherosclerosis pathobiology and considered risk-enhancing factors. Low ankle–brachial index is reflective of atherosclerotic peripheral arterial insufficiency and is associated with increased cardiovascular risk (Ankle Brachial Index Collaboration et al. 2008). Lastly, South Asian ancestry is also considered a risk-enhancing factor because these individuals harbor biological and behavioral risk factors that predispose them to early-onset severe ASCVD (Mehta et al. 2020).

The presence of one or more risk-enhancing factors can serve as a useful marker for reclassifying ASCVD risk. Specifically, the guidelines recommend statin initiation or therapy intensification among intermediate-risk individuals with risk-enhancing factors (Class of Recommendation IIa) (Grundy et al. 2019). Among individuals at borderline risk, the guidelines recommend that the presence of risk-enhancing factors may justify the initiation of moderate-intensity statin therapy (Class of Recommendation IIb) (Grundy et al. 2019).

Coronary Artery Calcium Score

CAC is measured using noncontrast, electrocardiographically gated cardiac computed tomography and is quantified using the Agatston score (Greenland et al. 2018). CAC is considered a marker of subclinical coronary atherosclerosis that reflects the cumulative exposure to both measured and unmeasured cardiovascular risk factors over the lifetime (Toth 2008). Several epidemiological studies have demonstrated that the CAC score is independently associated with ASCVD risk in diverse patient populations and improves risk discrimination and reclassification among asymptomatic individuals (Polonsky et al. 2010; Erbel et al. 2010; Elias-Smale et al. 2010; Paixao et al. 2015; Baber et al. 2015; Hoffmann et al. 2016). Additionally, in studies comparing the CAC score with other nontraditional risk markers, CAC uniformly outperforms other markers, including several risk-enhancing factors discussed above, for improving cardiovascular risk assessment and guiding treatment strategies (Mehta et al. 2017).

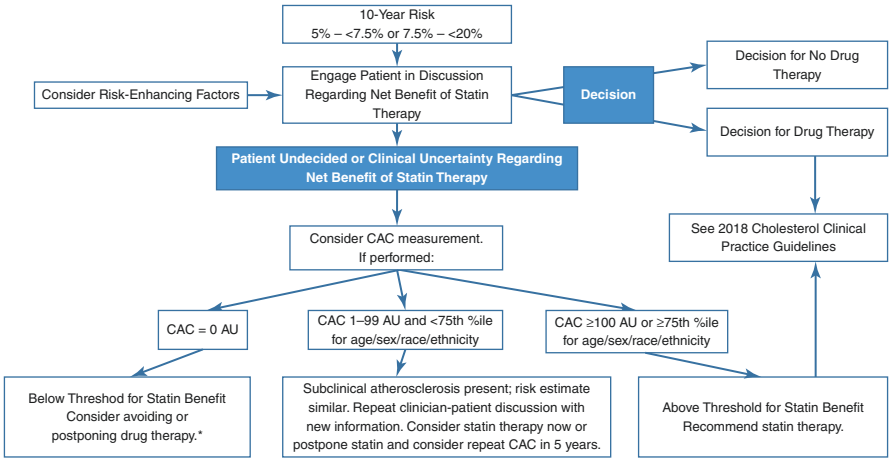

Fig. 2.2 Incorporating coronary artery calcium score in risk assessment among borderline and intermediate-risk patients. (Reproduced with publisher's permission from Lloyd-Jones et al. 2019)

The 2018 cholesterol management guidelines recommend considering the measurement of CAC if the decision regarding statin therapy is uncertain among individuals with intermediate (≥7.5–20%) and select individuals with borderline (5–7.5%) estimated 10-year ASCVD risk (Class of Recommendation IIa) (Grundy et al. 2019). In these scenarios, the CAC score can be used to guide decisions regarding deferring, delaying, or initiating statin therapy (Fig. 2.2). If the CAC score is zero, it is reasonable to withhold statin therapy and reassess in 5–10 years as long as high-risk conditions like diabetes, smoking, and family history of premature ASCVD are absent (Lloyd-Jones et al. 2019). Recent evidence from the Multi-Ethnic Study of Atherosclerosis (MESA) suggests that the ideal timeline for rescanning individuals with CAC score of zero is 3–7 years (Dzaye et al. 2020). Study authors suggest that the interscan interval depends on individual demographic characteristics and cardiovascular risk profile (Dzaye et al. 2020). A CAC score of 1–99 Agatston units favors statin therapy, especially in those older than 55 years age (Lloyd-Jones et al. 2019). Lastly, if the CAC score is greater than 100 Agatston units or higher than 75th percentile for age/sex/race, initiating statin therapy to reduce cardiovascular risk is recommended (Lloyd-Jones et al. 2019).

Lifetime Risk Assessment

Age is the predominant factor that influences PCE-predicted 10-year ASCVD risk (Karmali et al. 2014). Therefore, young individuals with a high burden of traditional risk factors are often deemed to be at low 10-year ASCVD risk (Karmali et al. 2014). In such scenarios, lifetime cardiovascular risk assessment is an important

tool for understanding the impact of aggregate risk factor burden on long-term ASCVD risk trajectory (Lloyd-Jones et al. 2019). Current US guidelines recommend considering lifetime or 30-year ASCVD risk assessment using the PCE among adults 20–39 years of age and for those 40–59 years of age who are at <7.5% 10-year ASCVD risk (Class of Recommendation IIb) (Arnett et al. 2019). This information can be a useful communication strategy for guiding clinician–patient risk discussion and facilitating healthy lifestyle interventions.

Limitations of Current Approaches to Risk Assessment

Cardiovascular risk assessment has evolved significantly since the field of preventive cardiology was born in 1961 when Dr. William B. Kannel, then director of the Framingham Heart Study, coined the term "risk factors" for coronary heart disease (Kannel et al. 1961). This evolution has been fueled by advances in cardiovascular epidemiology through the establishment of large population-based epidemiological cohorts, improvement in data analysis techniques, and identification of novel risk factors. Our current guideline-based approaches to risk assessment and ASCVD prevention discussed above reflect significant progress made in the field over the last several decades. However, there are several limitations to our current approach that may benefit from refinement.

It is important to remember that all risk estimation tools, including the PCE, apply population-based risk estimates to individual patients. In other words, the level of PCE-estimated risk for a given individual is calculated using risk prediction models that were created using data obtained from participants of five longitudinal community-based epidemiological cohorts in the United States. These cohorts recruited participants at least three decades ago, and expectedly, the population burden of cardiovascular risk factors, as well as the use of preventive therapies, has changed in this time frame. These secular trends lead to a mismatch between PCE-predicted and observed cardiovascular risk that has been reported in several studies since the PCE risk prediction algorithm was published in 2013 (Cook and Ridker 2014; Kavousi et al. 2014; Muntner et al. 2014; DeFilippis et al. 2015). Second, there is a lack of race/ethnic diversity in the epidemiological cohort studies used for the creation of the PCE with the vast majority of participants being non-Hispanic white or non-Hispanic black men and women. As such, this lack of race/ethnic representation in our primary risk estimation tool is a limitation for accurate risk assessment, and thus, prevention of ASCVD in underrepresented minority populations. Third, the risk estimated by PCE is calculated using a prediction model that incorporates data regarding age, sex, race, diabetes status, current smoking, systolic blood pressure, antihypertensive use, total cholesterol level, and HDL-C level. This information is available for many asymptomatic individuals interacting with healthcare systems in the United States. However, it is worth noting that this approach has evolved little in the past two decades (Wilson et al. 1998). In addition, several novel

risk markers have been extensively studied and are awaiting further validation and consideration, which may make risk assessment more precise. Lastly, our current approach does not include measures of social determinants of health that have a significant impact on cardiovascular risk.

Considerations for Enhancing Cardiovascular Risk Assessment

Considerations for enhancing our current approach to cardiovascular risk assessment should focus on addressing the limitations discussed above. These new approaches can be grouped together into three main categories as discussed below.

Larger and More Diverse Contemporary Epidemiological Cohorts

As mentioned previously, the epidemiological cohorts used for creating the PCE were established decades ago and lack race/ethnic diversity. Establishing larger and more diverse contemporary epidemiological cohorts that can be used for updating current risk estimation tools is the first step toward improving cardiovascular risk assessment. This has been the focus of the National Institutes of Health (NIH) and other research organizations that have invested in diverse epidemiological cohort studies such as the MESA, (Bild et al. 2002) the Jackson Heart Study, (Sempos et al. 1999) the Dallas Heart Study, (Victor et al. 2004) the Hispanic Community Health Study/Study of Latinos, (Perreira et al. 2020) the Mediators of Atherosclerosis in South Asians Living in America Study, (Kanaya et al. 2013) and the Strong Heart Study. (Lee et al. 1990) These cohorts continue to provide crucial scientific information that are useful for improving risk assessment and ASCVD prevention among race/ethnic minorities. More recently, a mega-scale NIH-funded epidemiological cohort called the "All of Us" initiative was launched in the United States in 2018 (All of Us Research Program Investigators et al. 2019). The study aims to recruit a diverse group of over one million Americans from a network of more than 340 geographically diverse recruitment sites. The "All of Us" study is collecting participant data from health questionnaires, electronic health records, physical measurements, and biospecimens (All of Us Research Program Investigators et al. 2019). Once completed, this initiative will be invaluable for improving cardiovascular risk assessment and fostering innovation that ushers in an era of precision medicine with refined risk prediction and individualized targeted therapies.

Precision Medicine

Precision medicine can be defined as the use of diagnostic tools and treatments targeted to the needs of an individual patient based on the genetic, biomarker, or psychosocial characteristics (Ramaswami et al. 2018). Advances in genomic technologies hold a promising role in enhancing our ability to assess cardiovascular risk. An example of this approach is the use of polygenic risk scores that estimate an individual's genetic susceptibility to ASCVD and are calculated according to genotypic profile and genome-wide association study data (Choi et al. 2020). Polygenic risk scores are novel tools that may help identify patients at the highest cardiovascular risk at a young age even in the absence of traditional cardiovascular risk factors (Khera et al. 2018). These individuals may benefit from earlier and more aggressive preventive interventions to help offset ASCVD risk (Khera et al. 2016). However, two recent studies have demonstrated that polygenic risk scores failed to improve ASCVD risk prediction beyond PCE among middle-aged white individuals living in the United States and the United Kingdom. Future research work is needed to clarify the potential role of polygenic risk scores for enhancing cardiovascular risk assessment (Mosley et al. 2020; Elliott et al. 2020). Clonal hematopoiesis of indeterminate potential (CHIP) is an acquired genetic risk factor for ASCVD that acts through inflammatory pathways (Jaiswal et al. 2017). CHIP refers to clonal expansion of hematopoietic stem cells due to acquired somatic mutations that occur during the aging process (Jaiswal et al. 2017). Deficiency of TET2 (tet methylcytosine dioxygenase 2), one of the key genes associated with CHIP, was shown to promote atherogenesis through an IL-1β-dependent and NLRP3 inflammasome-dependent mechanism (Libby et al. 2019). CHIP is surprisingly common, occurring in up to 20% of septuagenarians, and though it rarely transforms to acute leukemia (occurring 0.5–1% per year in carriers), CHIP confers a 40% increased risk of CVD, and thus, has emerged as a novel risk factor (Libby et al. 2019). Investigations are underway to determine optimal approaches to integrate CHIP in cardiovascular risk assessment. In addition to genetic markers of cardiovascular risk, biomarkers that are distal to the genome and proximal to the disease phenotype are being leveraged to improve risk assessment. These approaches encompass the transcriptomics, (Pedrotty et al. 2012) proteomics, (Lindsey et al. 2015) and metabolomics (Lewis et al. 2008). In addition to serving as risk factors, biomarkers identified using these high-throughput technologies may also serve as emerging targets for reducing ASCVD risk. Importantly, these novel risk markers need to be systematically evaluated in epidemiological studies. The ability to improve risk discrimination, risk reclassification, and diagnostic accuracy beyond traditional cardiovascular risk factors should be studied using accepted statistical techniques like the C-statistic, net reclassification index, integrated discrimination index, discrimination slope, and predicted-to-observed event rates (Hlatky et al. 2009).

Social Determinants of Health

Social determinants of health (SDOH) have a significant and measurable impact on ASCVD risk. In high-income countries, four measures of SDOH have been consistently associated with ASCVD risk: income level, educational attainment, employment status, and neighborhood socioeconomic factors (Schultz et al. 2018). The association of SDOH with ASCVD risk is in part mediated by increased burden of traditional risk factors like hypertension, diabetes, smoking, and obesity. Integration of SDOH into traditional ASCVD risk prediction models may improve risk assessment and allow improved management of high-risk individuals (Schultz et al. 2018). However, cultural and regional differences in SDOH make generalized implementation challenging.

Conclusion

Assessment of cardiovascular risk is the backbone of cardiovascular disease prevention. Current US guidelines for cardiovascular risk assessment recommend using the race- and sex-specific pooled cohort equations for estimating the 10-year risk of an ASCVD event in asymptomatic individuals. The PCE-predicted 10-year ASCVD risk serves as the starting point for guiding shared decision-making regarding primary ASCVD prevention. Current guidelines have developed provisions for personalizing and refining ASCVD risk estimates by recommending considerations for risk-enhancing factors and quantification of CAC. Future research efforts should focus on improving our current approach to risk assessment by studying larger and more diverse epidemiological cohorts, leveraging the power of precision medicine, and incorporating measures of social determinants of health in risk prediction algorithms.

References

All of Us Research Program Investigators, Denny JC, Rutter JL. The “All of Us” Research Program. N Engl J Med. 2019;381:668–76.

Ankle Brachial Index Collaboration, Fowkes FGR, Murray GD. Ankle brachial index combined with framingham risk score to predict cardiovascular events and mortality: a meta-analysis. JAMA. 2008;300:197–208.

Anurag M, Virani SS, Ayers CR, Wensheng S, Hoogeveen RC, Anand R, Berry JD, Joshi PH, Ballantyne CM, Amit K. Lipoprotein(a) and family history predict cardiovascular disease risk. J Am Coll Cardiol. 2020;76:781–93.

Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;140:e596–646.

Baber U, Mehran R, Sartori S, et al. Prevalence, impact, and predictive value of detecting subclinical coronary and carotid atherosclerosis in asymptomatic adults: the BioImage study. J Am Coll Cardiol. 2015;65:1065–74.

Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol. 2002;156:871–81.

Brunner FJ, Waldeyer C, Ojeda F, et al. Application of non-HDL cholesterol for population-based cardiovascular risk stratification: results from the Multinational Cardiovascular Risk Consortium. Lancet. 2019;394:2173–83.

Choi SW, Mak TS-H, O'Reilly PF. Tutorial: a guide to performing polygenic risk score analyses. Nat Protoc. 2020;15:2759–72.

Cook NR, Ridker PM. Further insight into the cardiovascular risk calculator: the roles of statins, revascularizations, and underascertainment in the Women's Health Study. JAMA Intern Med. 2014;174:1964–71.

DeFilippis AP, Young R, Carrubba CJ, McEvoy JW, Budoff MJ, Blumenthal RS, Kronmal RA, McClelland RL, Nasir K, Blaha MJ. An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. Ann Intern Med. 2015;162:266–75.

Dzaye O, Dardari ZA, Cainzos-Achirica M, et al. Warranty period of a calcium score of zero: comprehensive analysis from the Multiethnic Study of Atherosclerosis. JACC Cardiovasc Imaging. 2020; https://doi.org/10.1016/j.jcmg.2020.06.048.

Elias-Smale SE, Proenca RV, Koller MT, Kavousi M, van Rooij FJ, Hunink MG, Steyerberg EW, Hofman A, Oudkerk M, Witteman JC. Coronary calcium score improves classification of coronary heart disease risk in the elderly: the Rotterdam study. J Am Coll Cardiol. 2010;56:1407–14.

Elliott J, Bodinier B, Bond TA, Chadeau-Hyam M, Evangelou E, Moons KGM, Dehghan A, Muller DC, Elliott P, Tzoulaki I. Predictive accuracy of a polygenic risk score-enhanced prediction model vs a clinical risk score for coronary artery disease. JAMA. 2020;323:636–45.

Erbel R, Mohlenkamp S, Moebus S, et al. Coronary risk stratification, discrimination, and reclassification improvement based on quantification of subclinical coronary atherosclerosis: the Heinz Nixdorf Recall study. J Am Coll Cardiol. 2010;56:1397–406.

Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63:2935–59.

Greenland P, Blaha MJ, Budoff MJ, Erbel R, Watson KE. Coronary calcium score and cardiovascular risk. J Am Coll Cardiol. 2018;72:434–47.

Grundy SM. Obesity, metabolic syndrome, and cardiovascular disease. J Clin Endocrinol Metab. 2004;89:2595–600.

Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019;73:3168–209.

Hlatky MA, Philip G, Arnett DK, et al. Criteria for evaluation of novel markers of cardiovascular risk. Circulation. 2009;119:2408–16.

Hoffmann U, Massaro JM, D'Agostino RB, Kathiresan S, Fox CS, O'Donnell CJ. Cardiovascular event prediction and risk reclassification by coronary, aortic, and valvular calcification in the Framingham Heart Study. J Am Heart Assoc. 2016;5:e003144. https://doi.org/10.1161/JAHA.115.003144.

Honigberg MC, Zekavat SM, Aragam K, Finneran P, Klarin D, Bhatt DL, Januzzi JL, Scott NS, Natarajan P. Association of premature natural and surgical menopause with incident cardiovascular disease. JAMA. 2019a;322:2411–21. https://doi.org/10.1001/jama.2019.19191.

Honigberg MC, Maryam ZS, Krishna A, Derek K, Bhatt DL, Scott NS, Peloso GM, Pradeep N. Long-term cardiovascular risk in women with hypertension during pregnancy. J Am Coll Cardiol. 2019b;74:2743–54.

Jaiswal S, Natarajan P, Silver AJ, et al. Clonal hematopoiesis and risk of atherosclerotic cardiovascular disease. N Engl J Med. 2017;377:111–21.

Kanaya AM, Kandula N, Herrington D, Budoff MJ, Hulley S, Vittinghoff E, Liu K. Mediators of atherosclerosis in South Asians living in America (MASALA) study: objectives, methods, and cohort description. Clin Cardiol. 2013;36:713–20.

Kannel WB, Dawber TR, Kagan A, Revotskie N, Stokes J. Factors of risk in the development of coronary heart disease--six year follow-up experience. The Framingham Study. Ann Intern Med. 1961;55:33–50.

Karmali KN, Goff DC, Ning H, Lloyd-Jones DM. A systematic examination of the 2013 ACC/AHA pooled cohort risk assessment tool for atherosclerotic cardiovascular disease. J Am Coll Cardiol. 2014;64:959–68.

Kavousi M, Leening MJ, Nanchen D, Greenland P, Graham IM, Steyerberg EW, Ikram MA, Stricker BH, Hofman A, Franco OH. Comparison of application of the ACC/AHA guidelines, adult treatment Panel III guidelines, and European Society of Cardiology guidelines for cardiovascular disease prevention in a European cohort. JAMA. 2014;311:1416–23.

Khera AV, Emdin CA, Drake I, et al. Genetic risk, adherence to a healthy lifestyle, and coronary disease. N Engl J Med. 2016;375:2349–58.

Khera AV, Chaffin M, Aragam KG, et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. Nat Genet. 2018;50:1219–24.

Lee ET, Welty TK, Fabsitz R, Cowan LD, Le NA, Oopik AJ, Cucchiara AJ, Savage PJ, Howard BV. The Strong Heart Study. A study of cardiovascular disease in American Indians: design and methods. Am J Epidemiol. 1990;132:1141–55.

Lewis GD, Asnani A, Gerszten RE. Application of metabolomics to cardiovascular biomarker and pathway discovery. J Am Coll Cardiol. 2008;52:117–23.

Libby P, Sidlow R, Lin AE, et al. Clonal hematopoiesis: crossroads of aging, cardiovascular disease, and cancer: JACC review topic of the week. J Am Coll Cardiol. 2019;74:567–77.

Lindsey ML, Manuel M, Gomes AV, et al. Transformative impact of proteomics on cardiovascular health and disease. Circulation. 2015;132:852–72.

Lloyd-Jones DM, Braun LT, Ndumele CE, Smith SC, Sperling LS, Virani SS, Blumenthal RS. Use of risk assessment tools to guide decision-making in the primary prevention of atherosclerotic cardiovascular disease: a special report from the American Heart Association and American College of Cardiology. J Am Coll Cardiol. 2019;73:3153–67.

Mehta A, Blaha MJ, Miller J III, Joshi PH. Coronary artery calcium scoring: a valuable aid in shared decision making among non-traditional risk markers. Curr Cardiovasc Imaging Rep. 2017;10:33. https://doi.org/10.1007/s12410-017-9431-3.

Mehta A, Singh S, Saeed A, Mahtta D, Bittner VA, Sperling LS, Virani SS. Pathophysiological mechanisms underlying excess risk for diabetes and cardiovascular disease in South Asians: the perfect storm. Curr Diabetes Rev. 2020; https://doi.org/10.2174/1573399816666200703182458.

Michael M, Stone NJ, Christie B, et al. Triglycerides and cardiovascular disease. Circulation. 2011;123:2292–333.

Mosley JD, Gupta DK, Tan J, et al. Predictive accuracy of a polygenic risk score compared with a clinical risk score for incident coronary heart disease. JAMA. 2020;323:627–35.

Muntner P, Colantonio LD, Cushman M, Goff DC, Howard G, Howard VJ, Kissela B, Levitan EB, Lloyd-Jones DM, Safford MM. Validation of the atherosclerotic cardiovascular disease Pooled Cohort risk equations. JAMA. 2014;311:1406–15.

Paixao AR, Ayers CR, El Sabbagh A, et al. Coronary artery calcium improves risk classification in younger populations. JACC Cardiovasc Imaging. 2015;8:1285–93.

Pedrotty DM, Morley MP, Cappola TP. Transcriptomic biomarkers of cardiovascular disease. Prog Cardiovasc Dis. 2012;55:64–9.

Perreira KM, de LA Abreu M, Zhao B, et al. Retaining hispanics: lessons from the Hispanic Community Health Study/Study of Latinos. Am J Epidemiol. 2020;189:518–31.

Polonsky TS, McClelland RL, Jorgensen NW, Bild DE, Burke GL, Guerci AD, Greenland P. Coronary artery calcium score and risk classification for coronary heart disease prediction. JAMA. 2010;303:1610–6.

Ramaswami R, Bayer R, Galea S. Precision medicine from a public health perspective. Annu Rev Public Health. 2018;39:153–68.

Sarnak MJ, Amann K, Bangalore S, et al. Chronic kidney disease and coronary artery disease: JACC state-of-the-art review. J Am Coll Cardiol. 2019;74:1823–38.

Schultz WM, Kelli HM, Lisko JC, et al. Socioeconomic status and cardiovascular outcomes: challenges and interventions. Circulation. 2018;137:2166–78.

Sempos CT, Bild DE, Manolio TA. Overview of the Jackson heart study: a study of cardiovascular diseases in African American Men and Women. Am J Med Sci. 1999;317:142–6.

Silverman MG, Ference BA, Im K, Wiviott SD, Giugliano RP, Grundy SM, Braunwald E, Sabatine MS. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. JAMA. 2016;316:1289–97.

Sniderman AD, Thanassoulis G, Glavinovic T, Navar AM, Pencina M, Catapano A, Ference BA. Apolipoprotein B particles and cardiovascular disease: a narrative review. JAMA Cardiol. 2019;4:1287–95.

Toth PP. Subclinical atherosclerosis: what it is, what it means and what we can do about it. Int J Clin Pract. 2008;62:1246–54.

Victor RG, Haley RW, Willett DL, et al. The Dallas Heart Study: a population-based probability sample for the multidisciplinary study of ethnic differences in cardiovascular health. Am J Cardiol. 2004;93:1473–80.

Virani SS, Brautbar A, Davis BC, et al. Associations between lipoprotein(a) levels and cardiovascular outcomes in black and white subjects: the Atherosclerosis Risk in Communities (ARIC) Study. Circulation. 2012;125:241–9.

Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71:1269–324.

Willerson JT, Ridker PM. Inflammation as a cardiovascular risk factor. Circulation. 2004;109:II2–10.

Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97:1837–47.

Chapter 3
European Guidelines for Risk Assessment in the Primary Prevention of Cardiovascular Disease

Christian Cawley and John W. McEvoy

Introduction

The European Society of Cardiology (ESC) first published joint recommendations on the prevention of cardiovascular disease (CVD) in 1994 (Pyörälä et al. 1994). With continuous review of the most contemporaneous evidence in CVD prevention, the ESC has since published six further revisions to these prevention guidelines (Visseren et al. 2021). The most recent set of guidelines, published in 2021, provide updated recommendations for both CVD risk estimation and risk factor management. In particular, the publication of the Systematic COronary Risk Evaluation 2 (SCORE2) CVD risk assessment tool in early 2021 now allows estimation of both nonfatal and fatal CVD events for European patient populations. Therefore, SCORE2 has a central role in the 2021 ESC CVD prevention guidelines (Hageman et al. 2021). However, these updated guidelines also endorse a number of new approaches to the use of risk in guiding CVD prevention therapies, including a two-step approach to personalizing risk factor targets, estimation of lifetime risk and expected lifetime treatment benefit in settings where 10-year risk

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estimates may not be optimal, and other more bespoke risk calculators for diabetics and older persons. In this chapter, we review the 2021 ESC guideline, focusing on the recommended CVD risk assessment tools in the first section and then on the use of CVD risk to inform the intensity of primary CVD prevention therapies in the second section.

Current European Recommendations for Risk Assessment in CVD Prevention

The 2021 ESC recommendations acknowledge the role of both systematic screening as well as opportunistic screening of patients felt to be at an increased CVD risk due to the presence of any genetic, lifestyle, or recognized comorbid risk factors. Although the guidelines acknowledge that validated CVD risk assessment scores may suffer from the imperfect application of mean population data to the individual patient – a practice that may over- or underestimate the magnitude of CVD risk on an individual basis – their routine use is still recommended in the 2021 guidelines.

The New SCORE2 Risk Estimator

One of the major changes found in the 2021 ESC guidelines lies in the recommended tool for evaluating CVD risk, specifically through the utilization of the recently upgraded and published SCORE2 risk prediction algorithm (Hageman et al. 2021). While the first and second ESC joint task force publications based their risk evaluation on the American Framingham Risk Score (FRS), the Systematic COronary Risk Evaluation (SCORE) model was developed in 2003 for use in European patient populations and had remained the backbone of ESC CVD prevention guidelines since then (Wilson et al. 1998; Conroy et al. 2003).

Despite its widespread use in both guidelines and clinical practice, the original SCORE model had a number of acknowledged flaws (Conroy et al. 2003). First, the SCORE risk outcome focused exclusively on fatal CVD events, a clear difference from the American standard FRS and its more recent iteration [the pooled cohort equations (PCE)], both of which estimate total CVD [i.e., fatal CVD, nonfatal myocardial infarction (MI), and nonfatal stroke] (Wilson et al. 1998; Conroy et al. 2003; Goff et al. 2013). The authors of the original SCORE estimator rationalized the decision to estimate fatal CVD only by pointing to the paucity of quality nonfatal MI and stroke data collected in the European studies used to derive this score (Conroy et al. 2003). The authors concluded that "hard" data relating to fatal CVD events was more uniformly available across European states due to readily

accessible national death registries. However, the inability to estimate nonfatal CVD outcomes can attenuate the clinical relevance of CVD risk estimation using SCORE, particularly for younger patient populations in whom the risk of fatal CVD is low. As a consequence, the overall CVD risk among young adults may be underestimated when nonfatal events are excluded. Second, the original SCORE algorithm did not account for non-CVD mortality as a competing risk event, which has an increasing relevance for multimorbid patient cohorts and older persons. Not accounting for non-CVD deaths can result in an overestimation of the true CVD risk observed in these subgroups. Finally, many of the cohort studies on which the first SCORE algorithm was based are now considered quite dated (e.g., baseline data collection in the 1980s) and may no longer be reflective of the modern European patient population.

The SCORE2 algorithm seeks to improve on the design of its predecessor in the following ways: providing risk evaluation for both nonfatal myocardial infarction or stroke as well as fatal CVD events; accounting for the impact of competing non-CVD mortality risk; and incorporating contemporary European population data. The data gathered for SCORE2 were taken from the large longitudinal United Kingdom Biobank (UKB) cohort study as well as 46 cohorts selected from the Emerging Risk Factors Collaboration (ERFC). To exclude less relevant data, ERFC cohorts were selected based on strict inclusion criteria, including documented information on baseline risk factor status; cohorts whose participants approximately corresponded to that of the general population; baseline year of cohort not before the year 1990; and available data on cause-specific mortality and nonfatal CVD events for at least 1-year post follow-up. Individuals with established CVD or diabetes and those individuals from outside the SCORE2 age range of 40–69 years were censored from analysis. Unlike the data gathered for the original SCORE algorithm, the use of the UKB and ERFC cohort studies allows for risk estimation of both fatal and nonfatal CVD events using SCORE2. Additionally, the aforementioned maximum baseline survey cutoff of 1990 meant that the data presented was more contemporaneous, and therefore more relevant, to the modern European population. The algorithm was then externally validated using a selection of study cohorts whose methodological criteria matched that of the cohorts used to derive SCORE2 (Hageman et al. 2021; Ollier et al. 2005; Collaboration ERF 2007).

Another new aspect of SCORE2 is the inclusion of four risk regions for Europe (Fig. 3.1), each with distinct risk equations, which contrasts with the two regions offered by SCORE. It is worth emphasizing here that SCORE2 is designed for *non-diabetic adults only*. The 2021 ESC guidelines recommend that separate risk equations be used among diabetics (see below).

Much like the previously utilized Framingham score (and the current PCE score used in the United States), the inclusion of nonfatal events has translated to higher cutoffs for categorizing CVD risk with the use of SCORE2 compared to the first SCORE algorithm (Hageman et al. 2021; Conroy et al. 2003). Indeed, because both the SCORE and SCORE2 equations predict different outcomes, it can be difficult to

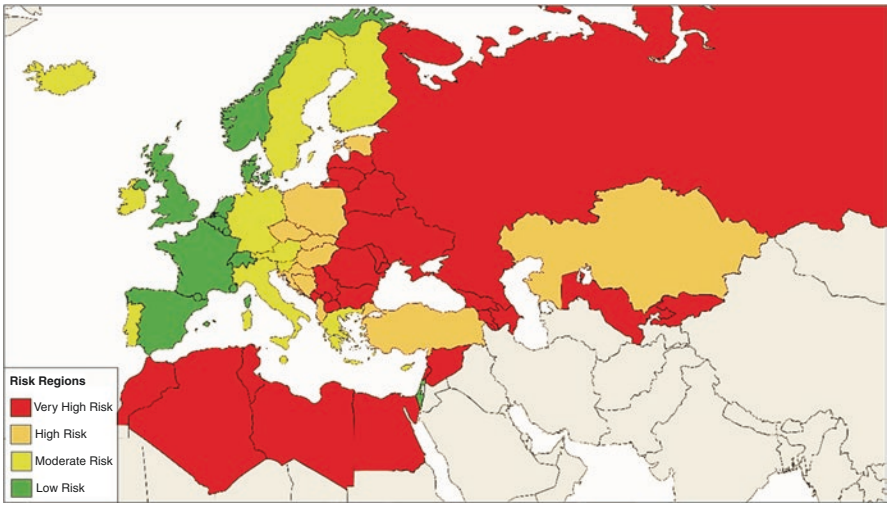


Fig. 3.1 European risk regions based on standardized CVD mortality rates reported by the WHO

Table 3.1 Comparison of percentage 10-year CVD risk thresholds across the pooled cohort equations (PCE) (Mora et al. 2018), SCORE (Piepoli et al. 2016), and SCORE2 (Visseren et al. 2021) algorithms

10-Year Risk Category	PCE (ACC/AHA 2013)	SCORE (ESC 2003)	SCORE2 (ESC 2021)		
	No age criteria	No age criteria	<50 years	50–69 years	≥ 70 years
Very Low	N/A	≤1%	<2.5% "Low to moderate"	<5% "Low to moderate"	<7.5% "Low to moderate"
Low	<5%	2%			
Moderate	5–7.4%	3–4%			
Elevated	7.5 –14.9%	5–9%			
High	≥15%	10–14%	2.5–7.4%	5–9.9%	7.5–14.9%
Very High	N/A	≥15%	≥ 7.5%	≥ 10%	≥ 15%

Although there are several risk category subdivisions within the PCE algorithm, the threshold of significant risk elevation is >7.5%; this percentage relates to total CVD risk. The original SCORE algorithm provides predictive risk estimates based on fatal CVD events only, thereby excluding risk prediction for nonfatal MI or CVA. The SCORE2 risk calculation provides information on total CVD risk

PCE pooled cohort equations, *SCORE* Systematic COronary Risk Evaluation, *SCORE2* Systematic COronary Risk Evaluation 2, *N/A* not applicable

directly compare one with another. In addition, SCORE2 risk categories are now subdivided into three groups as opposed to the six defined by the original SCORE algorithm. These three categories encompass a spectrum from low-to-moderate risk to high risk to very high risk, which importantly now depend on one's age, and range from 10-year total CVD risk estimates of <2.5% to ≥ 15% (Table 3.1). In contrast to SCORE2, the lower end of the categorical risk spectrum was defined as

individuals with a SCORE risk of <1% at 10 years and no additional risk modifiers – categorized as "low risk." Individuals deemed to be of "low-to-moderate risk" were those shown to have a calculated risk of 1–<5% or by the presence of any dyslipidemia, hypertriglyceridemia, sedentary lifestyle, abdominal obesity, lower socioeconomic class, and family history of premature coronary artery disease. The "elevated-to-high–risk" profile individuals were characterized by SCORE risks of 5–<10% or by the presence of familial dyslipidemias or severe hypertension. Finally, those at the highest risk ("very high risk") were defined by a SCORE risk of >10% or by the presence of known CVD, moderate to severe CKD, and type 2 DM (T2DM) or type 1 DM (T1DM) with target organ damage. Table 3.1 provides rough comparisons of the categorical 10-year risk thresholds for PCE vs. SCORE vs. SCORE2.

The first step of calculating CVD risk using SCORE2 involves the input of several traditional risk factors, namely, sex, age, smoking status, systolic blood pressure, total cholesterol, and high-density lipoprotein-cholesterol (HDL-C) (Fig. 3.2) (Hageman et al. 2021). This yields a 10-year "crude" total CVD risk score through the application of risk factor coefficients and survival functions from sex-specific models developed from the UKB and ERFC cohorts. Note that this crude estimate is not seen by the clinician and also that these models account for non-CVD death as a competing risk event. The "crude" risk score is then recalibrated using sex- and region-specific rescaling factors to provide a recalibrated 10-year risk for total CVD for each of the four risk regions. It is these recalibrated risk estimates that the clinician sees.

The derivation of the rescaling factors used in the above recalibration process was complicated and is summarized in the right-hand section of Fig. 3.2. First, population-average risk factor levels for men and women in each of the four risk regions (which were taken from the NCDRisc study) were entered into the UKB- and ERFC-derived model to produce a "predicted CVD risk." (Sabanayagam et al. 2016) Second, an "expected CVD risk" was derived from World Health Organization (WHO) reports of sex- and region-specific annual total CVD mortality. These WHO figures for CVD death were converted to estimates of total CVD (fatal and nonfatal) using region-specific multiplication factors derived from CPRD/Finnish CVD Register/Swedish CVD Reigster for regions assigned as low to moderate risk and from Estonian Biobank/HAPIEE for high- to very-high-risk regions (Herrett et al. 2015; Schmermund et al. 2002; Leitsalu et al. 2015; Peasey et al. 2006; Ricci et al. 2018). Third, by plotting a regression of "predicted" on "expected" CVD risk, region- and sex-specific "rescaling factors" were then derived that convert crude 10-year risk of total CVD to a recalibrated 10-year risk of total CVD.

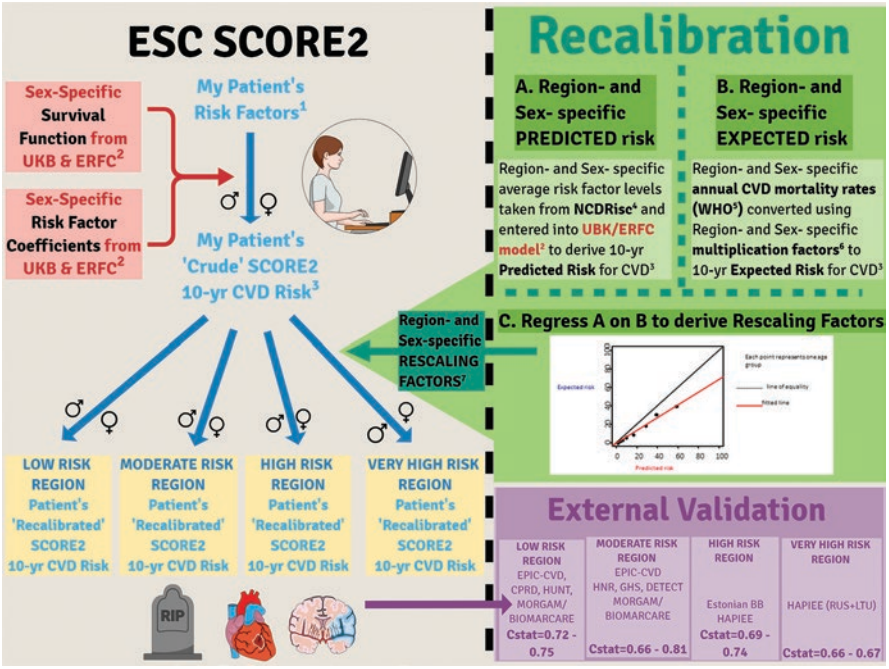
Results taken from the publication of SCORE2 demonstrate modest results for the prognostic discrimination of events in external validation cohorts, with C-indices ranging from 0.66 to 0.81, depending on the European risk region under consideration (Hageman et al. 2021). Interestingly, the results described suggest that the SCORE2 algorithm has similar discrimination when compared to its predecessor

SCORE, although it does now include nonfatal CVD events in the risk estimate, accounts for non-CVD competing death, and provides more granular information on the basis of four risk regions. As such, while it is acknowledged that SCORE2 does not offer a perfect solution to all of the issues found with the original SCORE algorithm, it nevertheless does provide a suitable and much needed update for CVD risk estimation in European populations.

Fig. 3.2 Summary of the ESC SCORE2 equation. The left panel in this image shows the practical estimation of ESC SCORE2. The physician enters their patients' risk factors into an online calculator or into a risk table to obtain a region- and sex-specific estimate of 10-year total CVD risk. The estimation of this 10-year total CVD risk involves two unseen steps. First, the patient's risk factors are applied to coefficients and the survival function from sex-specific models derived using UKB and ERFC datasets. This process yields a sex-specific "crude" 10-year total CVD risk estimate, which accounts for non-CVD death as a competing risk outcome. This "crude risk" estimate is not seen by the clinician. Second, the sex-specific "crude risk" is transformed into a sex- and region-specific "recalibrated risk" for total CVD over 10 years using sex- and region-specific rescaling factors derived from the recalibration process. It is only this sex- and region-specific recalibrated risk for total CVD events over 10 years that is seen by the clinician. The right panel in this image shows additional information (with further details provided in the Hageman et al. 2021 article and supplement) on the process of recalibration and external validation. It is not necessary to understand these latter two processes when using SCORE2 and so, for simplicity, the clinician may want to focus simply on the left panel of this image

1. Risk factors entered into the SCORE2 calculator are sex, age, smoking status, systolic blood pressure, total cholesterol, and HDL-cholesterol
2. The UKB and ERFC models are designed to estimate 10-year total CVD risk using non-CVD death as a competing risk outcome
3. Total CVD comprises of risk for fatal CVD, nonfatal MI, and nonfatal stroke events over 10 years.
4. For the recalibration, average risk factor levels according to region and sex are derived from NCDRisc and then used as input variables into the UKB/ERFC-derived models to obtain "predicted risks" for total CVD by sex and by region
5. Then World Health Organization (WHO) reports of sex- and region-specific annual CVD mortality are used in the process of deriving "expected risks" for total CVD by sex and by region.
6. To translate WHO sex- and region-specific annual CVD mortality into 10-year sex- and region-specific estimates of total (fatal and nonfatal) CVD among primary prevention nondiabetic adults using non-CVD death as a competing risk outcome, multiplication factors are used. These multiplication factors are derived from modeling of CPRD/HNR/Swedish National Registry and other studies for the low−/moderate-risk regions and modeling of Estonian Biobank/HAPIEE for the high−/very-high-risk regions
7. Then the predicted risks are regressed on expected risks for 10-year total CVD to derive rescaling factors used to recalibrate the sex-specific "crude" 10-year total CVD risk into sex- and region-specific "recalibrated" 1- year total CVD risk (i.e., the final output of the SCORE2 algorithm)

ESC SCORE2 European Society of Cardiology Systematic COronary Risk Evaluation 2, UKB United Kingdom Biobank, ERFC Emerging Risk Factors Collaboration, NCDRisC non-communicable diseases risk factor collaboration, CVD cardiovascular disease, WHO World Health Organization, EPIC-CVD European Prospective Investigation into Cancer and Nutrition – Cardiovascular Disease, CPRD Clinical Practice Research Datalink, HNR Heinz–Nizdorf Recall Study, Estonian BB Estonian Biobank, HAPIEE Health, Alcohol and Psychosocial factors in Eastern Europe Study, RUS + LTU Russia and Lithuania



Other Risk Scores Endorsed in the 2021 ESC Guideline

As noted above, the SCORE2 algorithm encompasses CVD risk estimation for non-diabetic individuals aged from 40 to 69 years without evidence of established CVD. A number of additional risk estimation algorithms are currently in development by the ESC, which will cater to specific patient populations not already covered by SCORE2.

SCORE-OP and Other Risk Algorithms Developed by ESC

One such risk prediction algorithm is for CVD risk estimation in older patients (i.e., those ≥70 years), which will tailors toward a typically more frail and multimorbid population. This tool is called Systematic Coronary Risk Evaluation 2 Older Persons (SCORE2-OP), and it was endorsed in 2021 ESC guidelines and made available to researchers in late 2021 (SCORE2-OP working group and ESC Cardiovascular risk collaboration). In addition, the first ESC-developed secondary prevention CVD risk prediction algorithm is also in development (named SMART2); this will allow for

risk estimation of recurrent CVD among adults with a known history of prior CVD. Furthermore, specific ESC risk estimation algorithms are also planned that will cater to both heart failure and arrhythmia/atrial fibrillation populations. While some of these algorithms have yet to be published, they will take into account the specific disease risk modifiers for each of these unique populations and aim to provide clinicians with more individualized guidance on risk factor management and preventive treatment intensification, as well as assisting in patient education.

In addition to SCORE2 and SCORE2-OP, the 2021 ESC guideline endorses the use of other risk estimators (Fig. 3.3). For example, diabetics are recommended to undergo risk assessment using the Action in Diabetes and Vascular Disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) risk score. Pending the publication of the SMART2-secondary prevention risk estimator, the guideline endorses the use of the Reduction of Atherothrombosis for Continued Health (REACH) and/or Secondary Manifestations of Arterial Disease (SMART) calculators in secondary prevention patients.

ADVANCE Risk Score Among Primary Prevention Diabetics (Endorsed but Not Developed by ESC)

The ADVANCE risk scoring system (which estimates both fatal and nonfatal CVD events in diabetic patients) was published in 2011 (Kengne et al. 2011). The ADVANCE study from which this prediction tool was constructed was aimed at assessing the impact of blood pressure and glycemic control on both microvascular and macrovascular outcomes in diabetic patients and was designed as a large multicenter factorial randomized controlled trial (RCT) spanning Asia, Australasia, Europe, and Canada, involving a total cohort of 11,460 patients (Patel et al. 2007). The estimation of CVD risk was derived from a smaller subgroup of 7168 patients without established CVD and took place over a follow-up period of 4.5 years, examining for total CVD events during that time (i.e., fatal and nonfatal MI, stroke, and cardiovascular death) (Kengne et al. 2011). The tool demonstrated a modest discrimination capacity with a c-statistic of 0.70. External validation using the DIABetes, HYpertension, microalbuminuria or proteinuria, CARdiovascular events, and Ramipril (DIABHYCAR) cohort demonstrated a similar c-statistic of 0.69.

Factors included within the ADVANCE risk calculator are sex, age at diabetes mellitus (DM) diagnosis, duration of time since DM diagnosis, presence of atrial fibrillation, evidence of retinopathy, history of hypertension, pulse pressure, HbA1c, and degree of albuminuria and non-HDLc level. Each factor is given appropriate weighting to derive the 4-year total CVD risk score. The authors noted that the inclusion of indicators of microvascular disease (albuminuria, retinopathy), along with measured HbA1c and duration of known DM, may give an improved approximation of total hyperglycemia exposure compared to previously established risk estimators.

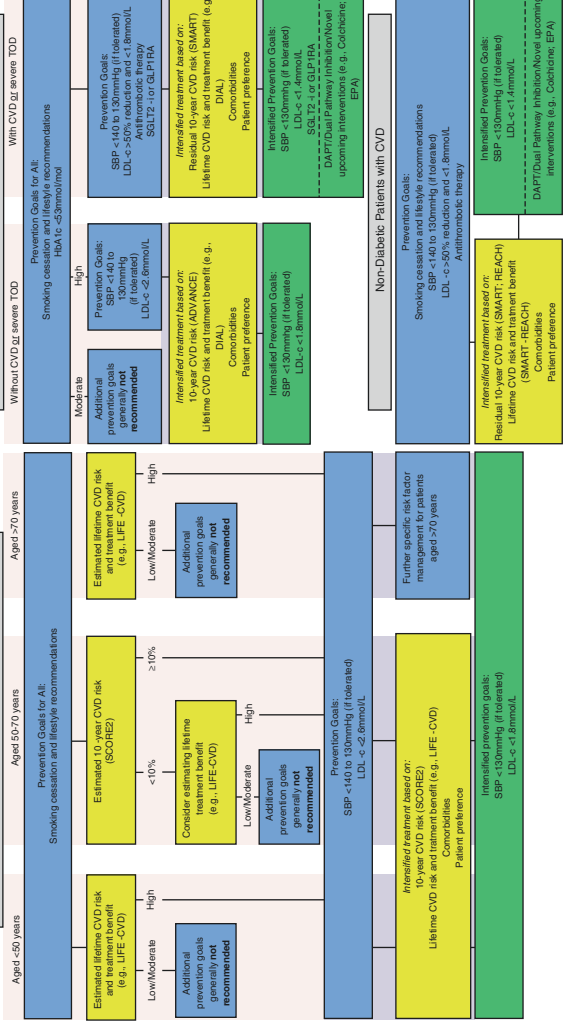


Fig. 3.3 Flowchart summarizing the 2021 ESC-recommended pathways for risk assessment and prevention goals across patients based on age among otherwise healthy primary prevention adults and based on the history of type 2 DM with or without CVD or target organ damage. Step 1 (blue boxes) typically involves the implementation of baseline uniform prevention goals before further stratifying patients based on individual risk and predicted benefit of treatment. This gives a recommended set of more specific prevention goals. Step 2 (green boxes) involves further CVD risk assessment and treatment benefit analysis with additional consideration given to patient comorbidities and most importantly patient preference. The results of this second more personalized analysis and discussion then inform the clinician's decision to pursue a more intensive set of prevention goals
CVD cardiovascular disease, LIFE-CVD LIFEtime-perspective CardioVascular Disease, SCORE2 Systematic COronary Evaluation 2, SBP systolic blood pressure, TOD target organ damage, SGLT2i sodium/glucose cotransporter 2 inhibitor, GLP1RA glucagon-like peptide 1 receptor agonist, ADVANCE Action in Diabetes and Vascular Disease: preterAx and diamicroN-MR Controlled Evaluation, DIAL diabetes lifetime-perspective prediction, DAPT dual antiplatelet therapy, SMART Secondary Manifestations of Arterial Disease, SMART-REACH Secondary Manifestations of Arterial Disease–Reduction of Atherothrombosis for Continued Health, EPA icosapent ethyl

Although the 2021 ESC guidelines recommend the ADVANCE risk estimator for CVD risk assessment in diabetic patients, there are several issues to consider with its use. First, the risk estimate is given as a 4-year total CVD risk score; this is a key difference from the numerical output from other contemporary CVD risk estimators that typically calculate a 10-year risk score. The authors of ADVANCE rationalized the limitation of the tool's estimation to a 4-year risk score as it was felt that the longer survival of certain participants would have a potentially disproportionate influence on parameter estimates. Interestingly, despite the quoted 4-year risk score, the 2021 ESC guidelines recommend the ADVANCE algorithm as a means for deciding on treatment intensification without indicating how to compare the 4-year risk estimates among diabetics with the 10-year risk estimates for nondiabetics produced by the various risk equations (though there are ways to recalibrate the ADVANCE score output to a 10-year risk estimate). Second, the participants included in ADVANCE were all aged 55 years or older, which may affect the accuracy of risk derivation for younger diabetic patients. Third, the study's participants also underwent randomized treatments during the course of ADVANCE, a factor that the algorithm's authors acknowledge may weigh on the tool's generalizability. Finally, while the authors of the ADVANCE score cited the large heterogeneous global cohort as a major strength of the tool, the algorithm does not provide region-specific or European-specific weighting – a factor that may lead to over- or under-estimation of risk depending on the population under consideration.

SMART-REACH Risk Score for Secondary Prevention Adults (Endorsed but Not Developed by ESC)

While the focus of this book and chapter is on risk assessment in primary prevention, it is worth mentioning that the new 2021 ESC prevention guidelines also suggest that risk assessment in certain secondary prevention adults may be worth considering when deciding on the intensity of preventive treatment. Previous ESC and American prevention guidelines have considered all secondary prevention adults to uniformly be at high-to-very high risk, and guidelines have generally recommended the same intensive prevention risk factor targets for all secondary prevention adults. However, in reality, there is some heterogeneity in risk among these adults. This heterogeneity may be important to consider in the context of emerging new medications that are effective for secondary prevention but are also expensive with varied cost-effectiveness. One way to allocate these more expensive secondary prevention options is to identify, using risk scores, who among the larger secondary prevention cohort is at highest risk. These individuals would be most likely to benefit from expensive newer therapies.

The Secondary Manifestations of Arterial Disease – REduction of Atherothrombosis for Continued Health (SMART-REACH) model, published in 2018, appears to be favored for secondary prevention risk assessment in the 2021 ESC guidelines, though the planned future publication of the SMART2-secondary prevention risk estimator developed by the ESC may see this recommendation for

SMART-REACH revised in subsequent guidelines (Kaasenbrood et al. 2018). SMART-REACH was developed using three patient cohorts with known cardiovascular disease and who were monitored for recurrent cardiovascular events, namely, SMART, REACH (Western Europe), and REACH (North America) (Simons et al. 1999; Bhatt et al. 2006). SMART is an ongoing single-center prospective cohort study involving patients with manifest cardiovascular disease recruited to the University Medical Center Utrecht, Netherlands (Simons et al. 1999). The REACH Registry was established as a large international multicenter prospective observational registry beginning in 2003 and encompassing a maximum of 4 years' follow-up. In the derivation of this risk estimator, the authors of the SMART-REACH model included data from 6959 patients enrolled in the SMART study between 1996 and 2014, 14,259 patients from REACH (Western Europe), and 19,170 patients from REACH (North America) (Bhatt et al. 2006; Dorresteijn et al. 2013). The combined 2018 SMART-REACH model can be used to calculate 10-year recurrent cardiovascular risk adjusted for noncardiovascular mortality (Kaasenbrood et al. 2018). A helpful addition to the SMART-REACH model is the ability to demonstrate estimated gains in life expectancy through therapy modification and/or intensification.

The overlapping risk factors identified between the SMART and REACH studies were sex, systolic blood pressure, active smoking, diagnosis of DM, diagnosis of atrial fibrillation, diagnosis of heart failure, creatinine level, total cholesterol level, and number of affected vascular territories. These predictors were then appropriately weighted to produce the risk estimates outlined above. The internally validated c-statistics for the SMART and REACH (North America) models were 0.68 and 0.67, respectively. We are not aware of any external validation for the combined SMART-REACH model.

The combined SMART-REACH model's ability to predict multiple risk scores, including 10-year recurrent CVD risk, life expectancy without recurrent cardiovascular events, and estimated gains in life expectancy through therapy modification, all provide a well-rounded and personalized approach to risk assessment. The latter aspect allows the clinician to demonstrate the benefit of such therapeutic changes to the patient, offering improved education and potentially also encouraging patient compliance with preventive therapy (though data are limited to support the latter statement). SMART-REACH's inclusion of noncardiovascular death as a competing risk improves the accuracy of the estimation tool, particularly when applied to older, multimorbid patients. However, the clinical utility of CVD risk estimation in secondary prevention patients remains, for now, unproven.

LIVE-CVD Score for Primary Prevention Adults Aged <50/>70 Years (Endorsed but Not Developed by ESC)

Finally, and perhaps most importantly, the 2021 ESC guideline promotes the consideration of lifetime risk estimation in young adults. It also departs from prior guidelines by suggesting, particularly for young (<50 years) and old adults

(>70 years), that the "estimated lifetime treatment benefit" be calculated when considering certain preventive therapies. Both lifetime risk and estimated lifetime treatment benefit can be calculated using the LIFEtime-perspective CardioVascular Disease (LIFE-CVD) score.

The LIFE-CVD tool was published in 2020 and is the 2021 ESC guidelines' preferred algorithm for CVD risk assessment for healthy adults who fall outside the age range applicable to SCORE2 (Jaspers et al. 2020). Specifically, LIFE-CVD has been validated for the use in healthy patients between the ages of 45 and 80 years. LIFE-CVD was developed using the Multi-Ethnic Study of Atherosclerosis (MESA), which was designed as a North American multicenter prospective cohort study enrolling patients aged 45–84 years with no evidence of CVD at baseline in 2000 (Bild et al. 2002). A total of 6715 study participants from MESA were selected in the development of LIFE-CVD with a median follow-up period of 13.0 years taking place between 2000 and 2014. This follow-up period encompassed 621 CVD events (defined as acute myocardial infarction, stroke, resuscitated cardiac arrest, or cardiovascular death) and 795 non-CVD deaths were included in derivation analyses.

Similar to the methodology of the SCORE2 and SMART-REACH tools, the LIFE-CVD model was constructed using two Fine and Gray competing-risk-adjusted left-truncated sub-distribution hazard functions that assessed the competing risks of hard CVD events and noncardiovascular mortality, respectively (Jaspers et al. 2020). This allows clinicians to use the tool for the prediction of 10-year CVD risk, overall life expectancy, and CVD-free life expectancy. Additionally, LIFE-CVD can be used to assess the impact of therapy and lifestyle modification, including a reduction in systolic blood pressure, commencing or intensifying statin therapy, smoking cessation, and the commencement of aspirin or an equivalent antithrombotic therapy. The effects of these therapies were predicted using relative risk reductions from published hazard ratios in preventive therapy trials combined with the absolute risk functions derived from the Fine and Gray competing-risk models. It is worth noting that the hazard ratios for given treatments are averages from the trial population and may not be accurate for any given individual. The LIFE-CVD risk estimator was externally validated using a number of international cohorts, namely, the Heinz Nixdorf Recall (n = 4177), Atherosclerosis Risk in Communities (n = 9250), Norfolk (n = 23,548), and European Prospective Investigation into Cancer and Nutrition – Netherlands (n = 25,833) studies. The calculated c-statistics from external validation ranged from 0.67 to 0.76.

The LIFE-CVD algorithm has some notable strengths, beyond its slightly wider age assessable age range. Along with LIFE-CVD's ability to provide the clinician with a variety of CVD risk formats as well as predicting potential prognostic benefits of a number of therapies (e.g., with specific doses for statins included in the algorithm), it also provides individualized illustrative graphics to the clinician to aid with patient education and discussion of management. In addition, the inclusion of noncardiovascular death as a competing risk (as discussed

for SMART-REACH) reduces the overestimation of risk for older multimorbid patients.

As both models were developed using a similar methodology, LIFE-CVD shares some of the pitfalls outlined in the above discussion of SMART-REACH. LIFE-CVD presumes a constant risk factor profile from baseline assessment extending across the patient's lifetime. Clearly, a patient's risk profile can evolve with time, either with increasing comorbidities over time or with improved preventive therapies and lifestyle modification. Revisiting a patient's risk factor profile and predicted risk periodically can assist with patient education, motivation, and vigilance. While the LIFE-CVD model can be used for patients diagnosed with DM, the binary entry within the algorithm loses the nuance of duration and severity of hyperglycemia exposure (as can be found in the ADVANCE tool discussed above). Similarly, the duration since diagnosis of other relevant comorbidities (e.g., hypertension, dyslipidemia) is not accounted for. Additionally, certain pertinent contributing comorbidities, including chronic kidney disease, are excluded entirely from the risk estimator. Unfortunately, while the LIFE-CVD model includes the prediction of benefit for pharmacotherapeutic interventions and intensification, the tool does not assess the impact of a number of positive lifestyle modifications, including aerobic physical exercise of at least moderate intensity, weight loss, and dietary modification. In addition, the LIFE-CVD model has not been well validated by external groups using diverse cohorts and the use of estimated lifetime treatment benefit to guide preventive therapy decisions is also relatively untested (as are the cutpoints chosen to identify persons suitable for a given therapy, such as the recommendation that 12 months of expected prolongation of life with a therapy be used as a cutpoint above which a therapy should be considered but below which a therapy might be considered unnecessary).

ESC 2021 Recommendation for the Use of CVD Risk Estimates in Risk Factor Management

Although intuitive, one of the other new (and arguably most innovative) aspects of the 2021 ESC guideline on cardiovascular disease prevention is the provision of a two-step approach to personalizing risk factor targets (Fig. 3.4). All patients are examined and investigated at their initial assessment and stratified based on their personalized CVD risk score. These results return baseline blood pressure and cholesterol levels, and patients are assessed for smoking status, DM, and relevant lifestyle factors. At this point, all patients should be encouraged to abstain from smoking and engage with dietary and lifestyle modification.

The initial risk factor targets outlined for patients <70 years without CVD (including healthy adults, patients with familial hypercholesterolemia, CKD, and DM without severe target organ damage) are relatively uniform, recommending systolic BP targets of <140 mmHg and LDL-C levels of <2.6 mmol/L. The systolic

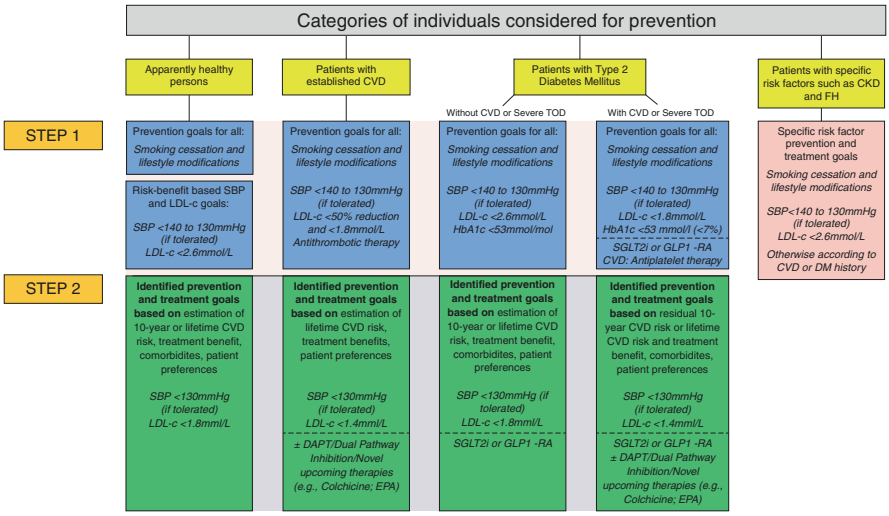


Fig. 3.4 Flowchart summarizing the ESC 2021 guideline two-step approach to risk stratification and treatment options. Step 1 encompasses a uniform set of prevention goals specific to the patient category. Step 2 details a more intensive set of prevention goals based on a combination of a patient's personalized CVD risk, predicted treatment benefits, and patient preferences regarding management. Notably, certain specific patient subgroups (e.g., CKD and familial hypercholesterolemia) are not formally included in the two-step prevention intensification plan but recommendations are applied based on the presence of either CVD or DM

CVD cardiovascular disease, CKD chronic kidney disease, FH familial hypercholesterolemia, DM diabetes mellitus, SBP systolic blood pressure, DAPT dual antiplatelet therapy, EPA icosapent ethyl, SGLT2i sodium/glucose cotransporter 2 inhibitor, GLP1-RA glucagon-like peptide 1 receptor agonist, TOD target organ damage

BP target of <140 mmHg for patients >70 years should be assessed in the setting of estimated lifetime benefit, comorbidities, and patient preference. For those patients with established CVD, or severe target organ damage in the setting of DM, LDL-C targets are further intensified to <1.8 mmol/L in the initial phase – patients with established CVD and familial hypercholesterolemia face an initial recommended target LDL-C of <1.4 mmol/L.

The second step involves a personalized intensification of risk factor targets based on individual risk factor levels and comorbidities along with a patient discussion regarding their own preferences for management and outcomes. Importantly, this step allows the patient's voice to be heard and also provides physicians some leeway and therapeutic options that can be individualized to patient preferences (Martin et al. 2015). This conversation should be further facilitated by the clinician's use of an appropriate CVD risk calculator as outlined above, which may demonstrate, for example, gains in life expectancy free of CVD as a means of keeping the patient informed as to the impact of further intensification of risk factor targets. Second step intensification targets for those without established CVD encompass systolic BP targets of <130 mmHg if tolerated and the further reduction

of LDL-C to <1.8 mmol/L. A further intensification of target LDL-C to <1.4 mmol/L is recommended for patients with established CVD or severe target organ damage in the setting of DM.

Further pharmacotherapeutic modifications recommended as part of the phase 2 intensification strategy for patients with established CVD or DM are discussed in more detail in the relevant sections below.

Cholesterol Measurement and Management

The 2021 guideline recommendations from the ESC regarding the measurement, monitoring, and management of cholesterol levels focus strongly on the reduction of LDL-C levels as well as reduction in all apolipoprotein B-containing lipoprotein levels. This is motivated by the expanding body of evidence, which has shown an absolute reduction in LDL-C levels to be of benefit in both CVD prevention and overall risk reduction (Amarenco et al. 2020; Flather 2010). Specifically, the latest guidelines encompass key concepts in LDL-C monitoring: that reduced levels of LDL-C over a prolonged period demonstrate a positive-modifying influence on CVD risk regardless of the means of reduction; and that the benefit in lowering these levels is amplified in individuals with higher baseline CVD risk profiles. Data collected from placebo-controlled trials has demonstrated a continued benefit with lower LDL-C levels without a clear lower limit (Flather 2010).

While LDL-C measurements do not feature in SCORE2, total cholesterol and HDL-C levels are input variables within the 10-year total CVD risk calculation. Patients with genetic lipid disorders were not included for analysis during the development of SCORE2 and should not be assessed using this algorithm.

The ESC recommends a two-step model for stratifying and modifying CVD risk in apparently healthy individuals (i.e., those without CVD, DM, CKD, SBP >160 mmHg, or familial hypercholesterolemia). The first step outlines a prevention goal of LDL-C < 2.6 mmol/L for individuals at high CVD risk for those aged ≤75 years. This same target may also be considered, albeit as a class IIB recommendation, for high-risk patients >75 years. The second step intensifies the target LDL-C based on a combination of 10-year calculated risk, additional comorbidities, overall risk–benefit, and ultimately patient preference. This second step targets a stricter LDL-C of <1.8 mmol/L for primary prevention in nondiabetic patients. Furthermore, the 2021 ESC guidelines recommend a treatment LDL-C goal of <1.4 mmol/L and a measured reduction of ≥50% from baseline for secondary prevention among those with established CVD or for primary prevention in diabetic patients with evidence of target organ damage (TOD). Additionally, for those patients who suffer a second vascular event, the latest guideline recommends even more stringent targets of <1.0 mmol/L. Overall, the ESC recommendations have adopted a rationale of lower is better in the management of LDL-C specifically, and that more potent reductions in LDL-C should be encouraged where possible.

Hypertension

The 2021 ESC guidelines have emphasized the paramount importance of BP optimization in CVD prevention, stating that the first goal should be to lower BP below 140/90 mmHg through the use of antihypertensive therapy for all patient demographics where treatment is likely to provide sufficient benefit. This is based on absolute CVD risk, estimated lifetime benefit, and the presence of hypertensive TOD (Sundström et al. 2015; Ettehad et al. 2016). This represents an upgrade from a class IIA to a class I recommendation within the updated 2021 guidelines. Further, more stringent targets are recommended for specific patient subgroups. Once treatment has been established, the goals of SBP reduction are further titrated to 120–130 mmHg for those <65 years of age and to <140 or 130 mmHg if tolerated for those aged ≥65 years (Patel and Group AC 2007; Sundström et al. 2015; Ettehad et al. 2016; Group SR 2015; Williamson et al. 2016). Younger patients may safely achieve an SBP of <120 mmHg with therapy; should this be well-tolerated, but then no further titration is advised.

The measurement of systolic BP plays an important role in the SCORE2 algorithm's estimation of 10-year total CVD risk. Hypertensive patients with rare BP disorders (e.g., primary hyperaldosteronism) were not included in the development of the SCORE2 algorithm, and therefore should not have their CVD risk estimated using this tool.

Although ESC guidelines recognize the logistical difficulties in whole population screening for hypertension, the use of opportunistic screening of patients with identifiable risk factors [e.g., raised body mass index (BMI), smoking, family history of hypertension) remains a grade I recommendation. The confirmation and subsequent grading of hypertension should be based either on repeated office measurements in a controlled setting with standardized methodology, 24-hour ambulatory monitoring, or on repeated home measurements. Office BP measurements should be taken across more than one visit prior to finalizing treatment decisions, with exceptions allowed when the BP measurements are significantly raised such as in grade III hypertension (systolic BP ≥180 or diastolic BP ≥110 mmHg).

Once the diagnosis of hypertension is confirmed, further CVD risk stratification should include screening for evidence of hypertensive TOD. Specifically, this should include renal profiling [in the form of serum creatinine, estimated glomerular filtration rate (eGFR), and urinary albumin:creatinine ratio], electrocardiographic (ECG) screening (with formal echocardiography recommended for those with abnormal ECG tracings or clinical evidence of LV dysfunction), and the use of fundoscopy for patients with a diagnosis of diabetes mellitus or grade II or III hypertension. Potential secondary etiologies of hypertension should also be considered with further investigation when suspected, though the routine measurement of additional biomarkers or vascular imaging is not recommended (Sehestedt et al. 2010; Okin et al. 2004; Perrone-Filardi et al. 2017).

The 2021 ESC guidelines recognize that the cumulative lifetime benefit typically favors SBP reduction even in the setting of younger patients with low 10-year risk profiles. For younger patients with lower CVD risk, it is suggested that the decision

to commence drug therapy should be discussed prior to initiation, specifically with attention toward overall lifetime benefit. Combination therapy has found a greater reception in recent years and now features as a class I recommendation due to a widely displayed inefficacy of monotherapy in BP control, particularly in achieving the stricter goals established in the 2021 guidelines (Wald et al. 2009; MacDonald et al. 2017; Rea et al. 2018; Egan et al. 2012; Salam et al. 2019; Gupta et al. 2017). Indeed, the ESC recommends that combination therapy should be regarded as part of the usual care of hypertension. It is worth noting, however, that antihypertensive monotherapy still retains a place within the guidelines for those either with low-risk grade I hypertension (systolic BP <160 mmHg) or for very old (≥80 years) or frail patients. The goal is to achieve the target BP parameters within 3 months of commencing therapy.

Diabetes Mellitus

Diabetes mellitus (DM) represents a significant independent risk factor for the development of CVD (Selvin et al. 2004). According to the latest 2021 ESC guidelines for CVD prevention, patients with DM should be considered to be high- or very-high-risk populations with further stratification based on evidence of diabetic TOD as well as the presence of additional risk modifiers and comorbidities. Although patients with diagnosed DM were included in both the derivation and calibration of the SCORE2 algorithm, the calculator is not designed or intended for CVD risk estimation for diabetic patients. A number of peer-reviewed CVD risk calculators are available, however, which are tailored specifically for the assessment of CVD risk in patients with DM (e.g., the ADVANCE risk estimation tool) (Kengne et al. 2011; Berkelmans et al. 2019).

The 2021 ESC guidelines propose a two-step treatment algorithm to first establish CVD risk and treatment goals for patients with a diagnosis of diabetes mellitus before moving on to the second step of treatment intensification based on CVD risk re-evaluation, existing comorbidities, and overall patient preference. All patients should engage with lifestyle and dietary modifications, including smoking cessation, aerobic physical exercise of at least moderate intensity, and a low-saturated fat/high-fiber diet. Glycemic control should aim for an HbA1c of <53 mmol/L (<7%) in the majority of patients with DM, though suggested HbA1c targets are stricter (<48 mmol/L, <6.5%) early phase after the diagnosis of DM in persons who are not frail and do not have established CVD. Among frail or elderly patients with DM, HbA1c targets can be relaxed to >53 mmol/L (>7%) on an individual basis in consultation with a physician.

The prevalence of dyslipidemia and its importance in CVD risk reduction for patients with DM remains one of the key aspects of screening, monitoring, and treating this growing patient population. For those patients >40 years of age with DM without evidence of CVD or target organ damage, LDL-C levels of 2.6 mmol/L should be considered; further intensification to levels of 1.8 mmol/L may also be considered. In those where statin monotherapy is not sufficient, the addition of

ezetimibe should be considered. An earlier introduction of statin therapy can be considered before the age of 40 for patients with evidence of target organ damage provided that pregnancy is not being planned; indeed, statin therapy should be avoided for any pre-menopausal women either planning a pregnancy or not on adequate contraception.

Pharmacotherapeutic recommendations for patients with type 2 DM in the 2021 guidelines have adapted to the substantial amount of RCT data released since the publication from the sixth ESC joint committee for CVD prevention in 2016. Metformin remains the recommended first-line agent (as long as it is well tolerated and suitable based on renal function) for type 2 DM patients without evidence of CVD, heart failure, or CKD (Group UPDS 1998). The early commencement of an evidence-supported Sodium/Glucose Cotransporter 2 (SGLT2) inhibitors or Glucagon-like Peptide-1 receptor (GLP1-receptor) agonists is recommended for patients with concomitant T2DM and evidence of CVD (Kristensen et al. 2019; Zelniker et al. 2019; Buse et al. 2020). The use of an SGLT2 inhibitor is now also recommended for those T2DM with a diagnosis of either heart failure or CKD stage II–IIIb or evidence of albuminuria (Heerspink et al. 2020; Perkovic et al. 2019). For those patients with T2DM without evidence of CVD, HF, or CKD, the commencement of an SGLT2 inhibitor or GLP1-receptor agonist may be considered to reduce CVD risk and mortality, though it remains a class IIa recommendation and subject to cost–benefit analysis (Kristensen et al. 2019; Zelniker et al. 2019; Buse et al. 2020).

Although the latest recommendations still employ metformin as first-line therapy for T2DM patients without CVD, HF, or CKD, the option to utilize a risk score and cost–benefit analysis for these patients to determine those who may be better served by either an SGLT2 inhibitor or GLP1-receptor agonist is offered as a class IIa recommendation (Kristensen et al. 2019; Zelniker et al. 2019; Buse et al. 2020).

Unfortunately, therapeutic management for CVD risk reduction in T1DM does not offer the same variety of strong evidence-supported pharmacological options as in T2DM. Key points in CVD prevention in T1DM still focus on improved glycemic control – with a recommended HbA1c range of 48–58 mmol/mol to reduce macrovascular complications and < 53 mmol/mol (<7%) to reduce the incidence of microvascular complications. Unlike in T2DM, metformin is not recommended for the purpose of lowering CVD risk in T1DM patients (Petrie et al. 2017). Conversely, dapagliflozin has recently been approved in the United Kingdom in combination with insulin for the purpose of improving glycemic control in adult T1DM patients with BMI ≥27 kg/m^2 not adequately managed on insulin therapy alone, though this is not yet the case in the United States. The use of SGLT2 inhibitors in T1DM is advised with caution and vigilance due to the increased risk of diabetic ketoacidosis.

Chronic Kidney Disease

The leading cause of morbidity and mortality in patients with CKD is CVD, and CKD represents a unique challenge in CVD prevention with an increased rate of hypertension, dyslipidemia, and DM in comparison to the general population

(Gansevoort et al. 2013). The 2021 ESC guidelines recommend all CKD patients should be assessed for CVD risk as well as monitored for evidence of CKD progression. Estimated eGFR can be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) calculator; evidence and quantification of albuminuria should also be monitored based on urinary albumin:creatinine ratio.

Importantly, the SCORE2 model is not applicable to patients with established CKD. Indeed, many CVD risk calculators aimed at primary prevention exclude CKD from their analyzed cohort. However, according to guidance from the 2021 ESC task force, patients with CKD stage III should qualify as high CVD risk while those with CKD IV or CKD V qualify as very high risk.

Much like other risk factors, a two-step treatment algorithm is suggested for prevention in CKD patients. The first step includes overall CVD risk stratification with targeted prevention goal and treatment initiation before the second step of reassessment and treatment intensification. For those CKD patients with concomitant hypertension, DM, or albuminuria, the addition of a RAAS-inhibiting agent titrated to the highest tolerated dose is recommended. The current ESC guidelines recommend target BP parameters of <130/80 mmHg should be applied to patients with CKD after appropriate treatment intensification; lower BP targets are acceptable provided the patient can tolerate this.

Due to the prevalence of dyslipidemia in the CKD patient cohort, initiation of moderate-intensity statin therapy along with ezetimibe is recommended in all CKD stage III–V patients >50 years of age, excluding those already commenced on dialysis (Baigent et al. 2011; Barylski et al. 2013; Herrington et al. 2016). For those CKD stage V patients already on lipid-lowering therapies at the time of commencing dialysis, the decision to continue therapy should be informed by their CVD risk profile, particularly for those already demonstrating evidence of CVD. Lipid-lowering therapy should not be commenced in those dialysis-dependent CKD patients without evidence of CVD (Fellström et al. 2009; Wanner et al. 2005).

Advice Regarding Antithrombotic Therapy

The 2021 ESC guidelines have balanced a number of contemporaneously published meta-analyses studying the risk versus benefit of aspirin use in primary CVD prevention (McNeil et al. 2018; Group ASC 2018; Gaziano et al. 2018). Prior ESC prevention guidelines provided a class 3 (harm) indication for aspirin in primary prevention. While the overall summation of data for the new 2021 guideline appears to favor ongoing avoidance of the routine use of aspirin, the guideline now acknowledges that there are subgroups of primary prevention adults where benefit may outweigh the bleeding risk. Drawing on the ASCEND trial amongst others, 2021 ESC guidelines state that low-dose aspirin may be considered as part of primary prevention for diabetic patients at high or very high risk of CVD who have no clear contraindication to aspirin (Group ASC 2018; Cosentino et al. 2020).

Summary

The 2021 ESC guideline presents a more nuanced and personalized approach to CVD prevention compared to previous iterations, particularly in the area of risk assessment. With the recent publication of SCORE2 as well as the development of other subgroup-specific risk estimators, clinicians now have a greater array of tools to assist in the planning and optimization of therapy both in primary and secondary prevention. While these models do not represent perfect assessment tools, their accounting for competing comorbidities and the use of more contemporaneous cohorts with appropriate region-specific weighting allows for a more modern approach to risk prediction. Along with the use of more specific risk assessment algorithms, a greater emphasis is being placed on the role of patient education and assisted decision-making, giving the patient a more active role in their own management pathway. This is exemplified in the newly introduced two-step approach to CVD prevention, a unique and very welcome addition to the 2021 guideline that gives the patient an opportunity to decide on the pursuit of a more intensive prevention strategy, based on the balance of CVD risk overall as well as the estimated gain in CVD-free life expectancy from a given therapy. Finally, the 2021 guideline offers more up-to-date insight into disease-specific prevention targets and therapies, with further allowance for the assessment of cost-effective analysis for more novel treatments.

References

Amarenco P, Kim JS, Labreuche J, Charles H, Abtan J, Béjot Y, et al. A comparison of two LDL cholesterol targets after ischemic stroke. N Engl J Med. 2020;382(1):9–19.

Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet. 2011;377(9784):2181–92.

Barylski M, Nikfar S, Mikhailidis DP, Toth PP, Salari P, Ray KK, et al. Statins decrease all-cause mortality only in CKD patients not requiring dialysis therapy—a meta-analysis of 11 randomized controlled trials involving 21,295 participants. Pharmacol Res. 2013;72:35–44.

Berkelmans GF, Gudbjörnsdottir S, Visseren FL, Wild SH, Franzen S, Chalmers J, et al. Prediction of individual life-years gained without cardiovascular events from lipid, blood pressure, glucose, and aspirin treatment based on data of more than 500 000 patients with Type 2 diabetes mellitus. Eur Heart J. 2019;40(34):2899–906.

Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas J-L, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. JAMA. 2006;295(2):180–9.

Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, et al. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol. 2002;156(9):871–81.

Buse JB, Wexler DJ, Tsapas A, Rossing P, Mingrone G, Mathieu C, et al. 2019 update to: management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2020;63(2):221–8.

Collaboration ERF. The Emerging Risk Factors Collaboration: analysis of individual data on lipid, inflammatory and other markers in over 1.1 million participants in 104 prospective studies of cardiovascular diseases. Eur J Epidemiol. 2007;22(12):839–69.

Conroy RM, Pyörälä K, Ae F, Sans S, Menotti A, De Backer G, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003;24(11):987–1003.

Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD). Eur Heart J. 2020;41(2):255–323.

Dorresteijn JA, Visseren FL, Wassink AM, Gondrie MJ, Steyerberg EW, Ridker PM, et al. Development and validation of a prediction rule for recurrent vascular events based on a cohort study of patients with arterial disease: the SMART risk score. Heart. 2013;99(12):866–72.

Egan BM, Bandyopadhyay D, Shaftman SR, Wagner CS, Zhao Y, Yu-Isenberg KS. Initial monotherapy and combination therapy and hypertension control the first year. Hypertension. 2012;59(6):1124–31.

Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016;387(10022):957–67.

Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med. 2009;360(14):1395–407.

Flather M. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet. 2010;376(9753):1670–81.

Force ESCPT. 2021 European guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021.

Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJL, Mann JF, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. Lancet. 2013;382(9889):339–52.

Gaziano JM, Brotons C, Coppolecchia R, Cricelli C, Darius H, Gorelick PB, et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. Lancet. 2018;392(10152):1036–46.

Goff DC, Lloyd-Jones DM, Bennett G, Coady S, D'agostino RB, Gibbons R, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(25 Part B):2935–59.

Group ASC. Effects of aspirin for primary prevention in persons with diabetes mellitus. N Engl J Med. 2018;379(16):1529–39.

Group SR. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015;373(22):2103–16.

Group UPDS. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998;352(9131):854–65.

Gupta P, Patel P, Štrauch B, Lai FY, Akbarov A, Gulsin GS, et al. Biochemical screening for nonadherence is associated with blood pressure reduction and improvement in adherence. Hypertension. 2017;70(5):1042–8.

Hageman S PL, Kaptoge S, de Vries T, Xu Z, Chung R, et al. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. Eur Heart J. 2021;42(25):2439–54.

Heerspink HJ, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou F-F, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383(15):1436–46.

Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, Van Staa T, et al. Data resource profile: clinical practice research datalink (CPRD). Int J Epidemiol. 2015;44(3):827–36.

Herrington W, Emberson J, Mihaylova B, Blackwell L, Reith C, Haynes R, et al. Impact of renal function on the effects of LDL cholesterol lowering with statin-based regimens: a meta-analysis of individual participant data from 28 randomised trials. Lancet Diabetes Endocrinol. 2016;4(10):829.

Jaspers NE, Blaha MJ, Matsushita K, Van Der Schouw YT, Wareham NJ, Khaw K-T, et al. Prediction of individualized lifetime benefit from cholesterol lowering, blood pressure lowering, antithrombotic therapy, and smoking cessation in apparently healthy people. Eur Heart J. 2020;41(11):1190–9.

Kaasenbrood L, Bhatt DL, Dorresteijn JA, Wilson PW, D'Agostino RB Sr, Massaro JM, et al. Estimated life expectancy without recurrent cardiovascular events in patients with vascular disease: the SMART-REACH model. J Am Heart Assoc. 2018;7(16):e009217.

Kengne AP, Patel A, Marre M, Travert F, Lievre M, Zoungas S, et al. Contemporary model for cardiovascular risk prediction in people with type 2 diabetes. Eur J Cardiovasc Prev Rehabil. 2011;18(3):393–8.

Kristensen SL, Rørth R, Jhund PS, Docherty KF, Sattar N, Preiss D, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Diabetes Endocrinol. 2019;7(10):776–85.

Leitsalu L, Haller T, Esko T, Tammesoo M-L, Alavere H, Snieder H, et al. Cohort profile: Estonian biobank of the Estonian genome center, university of Tartu. Int J Epidemiol. 2015;44(4):1137–47.

MacDonald TM, Williams B, Webb DJ, Morant S, Caulfield M, Cruickshank JK, et al. Combination therapy is superior to sequential monotherapy for the initial treatment of hypertension: a double-blind randomized controlled trial. J Am Heart Assoc. 2017;6(11):e006986.

Martin SS, Sperling LS, Blaha MJ, Wilson PW, Gluckman TJ, Blumenthal RS, et al. Clinician-patient risk discussion for atherosclerotic cardiovascular disease prevention: importance to implementation of the 2013 ACC/AHA Guidelines. J Am Coll Cardiol. 2015;65(13):1361–8.

McNeil JJ, Wolfe R, Woods RL, Tonkin AM, Donnan GA, Nelson MR, et al. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. N Engl J Med. 2018;379(16):1509–18.

Mora S, Wenger NK, Cook NR, Liu J, Howard BV, Limacher MC, et al. Evaluation of the pooled cohort risk equations for cardiovascular risk prediction in a multiethnic cohort from the Women's Health Initiative. JAMA Intern Med. 2018;178(9):1231–40.

Okin PM, Devereux RB, Jern S, Kjeldsen SE, Julius S, Nieminen MS, et al. Regression of electrocardiographic left ventricular hypertrophy during antihypertensive treatment and the prediction of major cardiovascular events. JAMA. 2004;292(19):2343–9.

Ollier W, Sprosen T, Peakman T. UK Biobank: from concept to reality. Pharmacogenomics. 2005;6(6):639–46.

Patel A, Group AC. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet. 2007;370(9590):829–40.

Peasey A, Bobak M, Kubinova R, Malyutina S, Pajak A, Tamosiunas A, et al. Determinants of cardiovascular disease and other non-communicable diseases in Central and Eastern Europe: rationale and design of the HAPIEE study. BMC Public Health. 2006;6(1):255. https://doi.org/10.1186/1471-2458-6-255.

Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJ, Charytan DM, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019;380(24):2295–306.

Perrone-Filardi P, Coca A, Galderisi M, Paolillo S, Alpendurada F, de Simone G, et al. Non-invasive cardiovascular imaging for evaluating subclinical target organ damage in hypertensive patients: a consensus paper from the European Association of Cardiovascular Imaging (EACVI), the European Society of Cardiology Council on Hypertension, and the European Society of Hypertension (ESH). Eur Heart J Cardiovasc Imaging. 2017;18(9):945–60.

Petrie JR, Chaturvedi N, Ford I, Brouwers MC, Greenlaw N, Tillin T, et al. Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomised, placebo-controlled trial. Lancet Diabetes Endocrinol. 2017;5(8):597–609.

Piepoli M, Hoes A, Agewall S, Albus C, Brotons C, Catapano A. European Guidelines on CVD prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on CVD Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016;37(29):2315–81.

Pyörälä K, De Backer G, Graham I, Poole-Wilson P, Wood D. Prevention of coronary heart disease in clinical practice: recommendations of the Task Force of the European Society of Cardiology, European Atherosclerosis Society and European Society of Hypertension. Atherosclerosis. 1994;110(2):121–61.

Rea F, Corrao G, Merlino L, Mancia G. Early cardiovascular protection by initial two-drug fixed-dose combination treatment vs. monotherapy in hypertension. Eur Heart J. 2018;39(40):3654–61.

Ricci C, Wood A, Muller D, Gunter MJ, Agudo A, Boeing H, et al. Alcohol intake in relation to non-fatal and fatal coronary heart disease and stroke: EPIC-CVD case-cohort study. BMJ. 2018;361:k934.

Sabanayagam C, Ezzati M, Rao KM, Khalili D, Lehtimaki T, Hajifathalian K, et al. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. Lancet. 2016;387(10027):1513–30.

Salam A, Kanukula R, Atkins E, Wang X, Islam S, Kishore SP, et al. Efficacy and safety of dual combination therapy of blood pressure-lowering drugs as initial treatment for hypertension: a systematic review and meta-analysis of randomized controlled trials. J Hypertens. 2019;37(9):1768–74.

SCORE2-OP working group and ESC Cardiovascular risk collaboration. SCORE2-OP risk prediction algorithms: estimating incident cardiovascular event risk in older persons in four geographical risk regions. Eur Heart J. 2021;42(25):2455–67. https://doi.org/10.1093/eurheartj/ehab312.

Schmermund A, Möhlenkamp S, Stang A, Grönemeyer D, Seibel R, Hirche H, et al. Assessment of clinically silent atherosclerotic disease and established and novel risk factors for predicting myocardial infarction and cardiac death in healthy middle-aged subjects: rationale and design of the Heinz Nixdorf RECALL Study. Am Heart J. 2002;144(2):212–8.

Sehestedt T, Jeppesen J, Hansen TW, Wachtell K, Ibsen H, Torp-Petersen C, et al. Risk prediction is improved by adding markers of subclinical organ damage to SCORE. Eur Heart J. 2010;31(7):883–91.

Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Ann Intern Med. 2004;141(6):421–31.

Simons PCG, Algra A, Van De Laak M, Grobbee D, Van der Graaf Y. Second manifestations of ARTerial disease (SMART) study: rationale and design. Eur J Epidemiol. 1999;15(9):773–81.

Sundström J, Arima H, Jackson R, Turnbull F, Rahimi K, Chalmers J, et al. Effects of blood pressure reduction in mild hypertension: a systematic review and meta-analysis. Ann Intern Med. 2015;162(3):184–91.

Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 European guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42(34):3227–37.

Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. Am J Med. 2009;122(3):290–300.

Wanner C, Krane V, März W, Olschewski M, Mann JF, Ruf G, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med. 2005;353(3):238–48.

Williamson JD, Supiano MA, Applegate WB, Berlowitz DR, Campbell RC, Chertow GM, et al. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged≥ 75 years: a randomized clinical trial. JAMA. 2016;315(24):2673–82.

Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97(18):1837–47.

Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019;393(10166):31–9.

Part II
Traditional Risk Factors

Chapter 4
Hypercholesterolemia

Ali Agha and Christie M. Ballantyne

The direct association between low-density lipoprotein (LDL) cholesterol (LDL-C) and cardiovascular disease (CVD) has been established through abundant and consistent experimental, observational, genetic, and clinical trial data (Borén et al. 2020). However, our understanding and therefore definition of hypercholesterolemia continue to evolve as new data become available through advances in technology (including genetic and imaging approaches) and study design (including additional populations and interventions). At what level should blood cholesterol, and LDL-C in particular, be considered elevated? Randomized clinical trials of progressively efficacious LDL-C–lowering strategies have not identified an LDL-C level below which further LDL-C lowering does not further reduce CVD risk (Giugliano et al. 2017). In addition, complex interactions among risk factors can affect the assessment and interpretation of LDL-C levels in different clinical scenarios even within the spectrum of primary prevention. Accordingly, as reflected in American cholesterol guidelines spanning three decades, the focus of guideline-recommended preventive strategies has shifted from absolute LDL-C level at baseline to include more emphasis on intensity of LDL-C reduction within the context of an individual's overall CVD risk.

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The Role of Low-Density Lipoprotein Cholesterol in the Development and Progression of Cardiovascular Disease

Increased concentrations of circulating LDL and other apoB-containing lipoproteins [such as very low-density lipoprotein (VLDL) remnants and intermediate-density lipoprotein (IDL)] penetrate and are retained in the subendothelial/intimal space, where these particles undergo modifications including oxidation by reactive oxygen species. Endothelial cell phenotypes can be altered in the setting of hypercholesterolemia, hypertension, diabetes, smoking, or hyperglycemia. Endothelial cell phenotypic changes include increased expression of leukocyte adhesion molecules, chemokines, and cytokines, which promote rolling, firm attachment, and transmigration of monocytes into the intimal space. Monocytes then take up modified LDL and differentiate into foamy macrophages and secrete chemoattractants, leading to smooth muscle migration into the intima and changes in the extracellular matrix, with the development of complex plaques over time. As the number and burden of plaque accrues over time, increasing calcium deposition can be detected and quantified by computed tomography (discussed in another chapter). Complex lipid-rich plaques with a high number of macrophages are prone to thinning and rupture of the cap, with acute thrombus formation (Singh et al. 2002; Falk 2006).

Although atherosclerosis is commonly thought to be a disease of the elderly, evidence of atherosclerosis, such as fatty streaks, has been identified among adolescents, showing that the disease process may begin early in life (McGill Jr. et al. 2000). Given that incident CVD increases with increasing LDL cholesterol (LDL-C) concentration as well as duration of exposure, a recent study explored the area under the curve for LDL-C versus age as a possible risk assessment tool. Cardiovascular event risk was associated with not only cumulative prior exposure to LDL-C, but also time course of area accumulation (the slope of the curve). In other words, the same area accumulated at a younger age (as opposed to older age) resulted in the greatest risk increase, further demonstrating the importance of optimal LDL-C control starting at a young age (Domanski et al. 2020). However, individuals at an increased risk of incident CVD events often remain unidentified until late in life, when the atherosclerotic disease process is well underway.

Increasing genetic evidence supports the utility of genetic testing in risk assessment to improve prevention. A recent study including nearly half a million participants in the UK Biobank demonstrated that those with favorable LDL-C genetic scores (above the median, based on 100 exomes known to be associated with lower LDL-C levels) had 14.7 mg/dL lower LDL-C levels and an odds ratio (OR) of 0.73 for major coronary events [95% confidence interval (CI) 0.70–0.75; $P < 0.001$] compared with participants with lower scores (Ference et al. 2019). Additionally, although familial hypercholesterolemia (FH) may be diagnosed clinically (Gidding et al. 2015) (to be discussed later in this chapter), individuals with an identified mutation in *LDLR,* the gene encoding the LDL receptor, have a markedly elevated risk of myocardial infarction (Lee et al. 2019). Furthermore, a prospective study from the Framingham cohort demonstrated that parental premature CVD placed

middle-aged offspring at more than double the risk of a CVD event, suggesting that CVD is a heritable condition. Consistent with this observation, polygenic risk scores have been shown to improve CVD risk stratification (Hadley et al. 2021). These findings demonstrate that genetic testing for pathogenetic variants and polygenic risk scores for LDL-C, FH, and CVD may allow for the early identification of individuals who may benefit from early initiation of lipid-lowering therapy (LLT).

Perhaps the strongest evidence supporting the role of LDL-C in the development and progression of CVD is the reduction in the incidence of major vascular events that can be obtained with the lowering of LDL-C. A meta-analysis including nearly 170,000 patients with a median follow-up of greater than 5 years demonstrated that for each 1-mmol/L (38.7 mg/dL) reduction in LDL-C, there was a stepwise 22% reduction in the incidence of major CVD events (Baigent et al. 2010). Also, the absolute risk reduction for major cardiovascular events with LDL-C reduction was proportional to the baseline risk, which suggests that individuals at greatest risk for future CVD events have the most to gain from LDL-C reduction. However, the benefit of statin therapy to lower LDL-C can even be appreciated among primary prevention patients who are considered "low risk" (i.e., 10-year CVD risk score <5% by the pooled cohort equations). Based on such findings, measurement of a lipid profile that includes total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, and LDL-C has become an essential aspect of cardiovascular risk assessment.

In addition to recommending lifestyle modifications (such as maintaining a heart-healthy diet and exercising frequently), the cornerstone of primary prevention of CVD in both the American Heart Association (AHA)/American College of Cardiology (ACC) (Grundy et al. 2019) and the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) (Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) 2020) cholesterol guidelines is the use of LLT to reduce the levels of atherogenic lipoproteins in the blood. The most notable atherogenic lipoprotein is LDL (Ference et al. 2017). However, clinicians do not routinely measure LDL but use LDL-C as a surrogate measurement for LDL, so reduction in LDL-C is the target of therapy in both sets of guidelines. Assessment of LDL-C levels at baseline is recommended, with additional repeat measurements of LDL-C after initiation and dose adjustment of LLT to determine patient adherence and measure response to treatment (Jia et al. 2019, 2020).

There are multiple methods of measuring LDL-C. Although the gold standard has historically been ultracentrifugation, this test is expensive and time consuming. LDL-C may also be measured directly with homogeneous assays utilizing chemical-based methods. However, these assays are not standardized and may not be reliable in individuals with CVD or lipid disorders (Miller et al. 2010). More commonly, LDL-C levels are estimated based on measurements of total cholesterol, HDL-C, and triglycerides that are obtained with a routine lipid profile. Traditionally, the Friedewald equation has been used to estimate LDL-C (LDL-C = total cholesterol – HDL-C – [triglycerides/5]) (Friedewald et al. 1972). This equation assumes a fixed triglyceride:VLDL ratio of 5:1 but is unreliable at very high triglyceride levels

(>400 mg/dL) and low LDL-C levels (<70 mg/dL). These limitations are important as the incidence of comorbidities associated with elevated triglycerides (including features associated with the metabolic syndrome, to be discussed later in this chapter) is increasing. Furthermore, individuals with CVD or multiple comorbidities who are considered "high risk" are expected to achieve very low levels of LDL-C based on the most recent blood cholesterol guidelines (this is especially true of the current ESC/EAS guidelines), and it is important to measure low concentrations of LDL-C accurately to manage these individuals appropriately. The Martin–Hopkins equation has proven to be a more accurate method of measuring LDL-C than the Friedewald equation in cases of elevated triglycerides and/or low LDL-C because it does not assume a fixed TG:VLDL ratio of 5:1 (Martin et al. 2013). The current AHA/ACC cholesterol guidelines provide a class IIA recommendation for either the direct measurement of LDL or calculation of LDL-C using the Martin–Hopkins equation in individuals with LDL-C < 70 mg/dL. A more recent method of LDL-C estimation developed at the National Institutes of Health (NIH), which does not assume a fixed TG:VLDL ratio either, may be more accurate than either the Friedewald or Martin–Hopkins equations and is reliable even when triglyceride levels are as high as 800 mg/dL (Sampson et al. 2020). Table 4.1 outlines the equations used to estimate LDL-C.

Table 4.1 Methods of estimating low-density lipoprotein cholesterol (LDL-C)

Method of estimation	Equation	Advantages	Disadvantages
Friedewald equation (Friedewald et al. 1972)	LDL-C = TC – HDL-C – (TG/5)	Very simple to calculate LDL-C using total cholesterol and HDL-C	May inaccurately estimate LDL-C in individuals with elevated TG (>400 mg/dL) or low LDL-C (<70 mg/dL)
Martin–Hopkins equation (Martin et al. 2013)	LDL-C = TC – HDL-C – (TG/adjustable factor)	More accurate than Friedewald equation, especially at high TG and low LDL-C (<70 mg/dL); virtually no increased cost compared with Friedewald equation	Less straightforward method of LDL-C calculation compared with Friedewald equation
National Institutes of Health equation (Sampson et al. 2020)	LDL-C = (TC/0.948) – (HDL-C/0.971) – [(TG/8.56) + ([TG × non-HDL-C]/2140) – (TG^2/16100)] – 9.44	More accurate than Friedewald equation or Martin–Hopkins equation at TG as high as 800 mg/dL and low LDL-C (<70 mg/dL); virtually no increased cost compared with Friedewald equation	Less straightforward method of LDL-C calculation compared with Friedewald equation or Martin–Hopkins equation

HDL-C high-density lipoprotein cholesterol, *TC* total cholesterol, *TG* triglyceride

In addition to measurement of LDL-C concentration, determining the size and number of LDL particles is another method for measurement of LDL and may provide useful information in some patients. Individuals with elevated triglycerides, metabolic syndrome, and/or diabetes often have increased small dense LDL (sdLDL) particles, which are associated with increased CVD risk (Williams et al. 2014; Hoogeveen et al. 2014; Hoogeveen and Ballantyne 2021), but may not have a high level of LDL-C because the smaller particles contain less cholesterol. However, LDL particle concentration (LDL-P) has been shown to be a more accurate predictor of CVD risk than LDL-C in individuals with discordant levels of LDL-P and LDL-C (Otvos et al. 2011). Nuclear magnetic resonance (NMR) spectroscopy has been used since the late twentieth century to characterize particle size and concentration (Hoogeveen and Ballantyne 2021). The concentration of each lipoprotein particle is calculated, and particles are classified based on size. An NMR assay by LipoScience (now known as LabCorp) measures lipoprotein particle concentrations and size in 11 lipoprotein subfractions (including three subfractions for LDL), whereas an NMR assay by Nightingale Health measures lipoprotein particle concentrations and size in 14 lipoprotein subfractions (Hoogeveen and Ballantyne 2021; Soininen et al. 2009). Currently, multiple platforms use different software for NMR particle measurement. Lipoprotein concentrations and sizes can also be measured using electrospray differential mobility analysis (also referred to as "ion mobility"), which has been validated against NMR. This method is based on the principle that particles of a given size and charge behave predictably when subjected to an electrical field (Caulfield et al. 2008). However, both NMR and ion mobility involve complex methodology, expensive equipment that is not available in most labs, and proprietary software, and raise major concerns regarding the standardization of lipoprotein subfraction measurements across platforms and laboratories across the globe (Wilson et al. 2021).

The measurement of triglycerides in LDL (LDL-TG) may also be a useful measurement in individuals with conditions associated with elevated triglycerides (to be discussed later in this chapter), as LDL-TG has been shown to be predictive of CVD events (Saeed et al. 2018; Hussain et al. 2022). LDL-TG is usually measured by using ultracentrifugation to isolate LDL in conjunction with an enzyme-based method of quantifying triglycerides (März et al. 2004). More recently, a detergent-based assay for LDL-TG was developed and validated against the more common approach (Ito et al. 2019).

In addition to LDL-C, both the AHA/ACC Multisociety and ESC/EAS guidelines support the assessment of non-HDL-C (total cholesterol – HDL-C) in risk stratification. This may be particularly useful for individuals with elevated triglycerides, in whom accurate estimation of LDL-C may be difficult. Both guidelines also support the measurement of apoB and lipoprotein(a) in risk stratification as apoB-containing lipoproteins are directly involved in the development of CVD (Ference et al. 2017), and lipoprotein(a) has been shown to have a causal association with risk for myocardial infarction (Kamstrup et al. 2009). The ESC/EAS

guidelines recommend measurement of lipoprotein(a) once in everyone and provide specific treatment goals for apoB based on CVD risk (non-HDL-C, lipoprotein(a), and apoB are discussed more extensively in other chapters).

Primary Prevention in High-Risk Groups

Genetic Disorders/Familial Hypercholesterolemia

Aside from traditional CVD risk factors such as age, sex, smoking, hypertension, and diabetes, genetic disorders can also predispose individuals to the development of CVD. Genetic dyslipidemia is a common and treatable cause of CVD (Stitziel and MacRae 2014).

FH is a long-recognized yet underdiagnosed genetic dyslipidemia characterized by severe hypercholesterolemia and greatly increased CVD risk. Heterozygous FH is most often an autosomal-dominant genetic disorder associated with severe elevations of LDL-C (often greater than 190 mg/dL) and a 10- to 17-fold increased risk of atherosclerotic CVD in individuals who are left untreated. Even FH patients who are treated with LLT have an 8- to 14-fold increased risk of developing atherosclerotic CVD, suggesting that these patients are not treated early enough nor aggressively enough (Nordestgaard et al. 2013; Benn et al. 2012). Early identification and treatment of these individuals is of particular importance as the risk of premature coronary heart disease is increased by 20-fold in untreated patients (Hopkins et al. 2011).

FH occurs in approximately 1 in 250 individuals (de Ferranti et al. 2016), with an increased prevalence among those who identify as French Canadians, South African Afrikaners, Finns, Ashkenazi Jews, or Christian Lebanese (Cuchel et al. 2014). Patients with marked elevations in LDL-C may be diagnosed with FH after genetic testing identifies a pathogenic variant of *LDLR*, *APOB,* or *PCSK9* (Sturm et al. 2018; Brown et al. 2020). However, the absence of a causal mutation does not rule out the diagnosis of FH as many individuals with extreme elevations of LDL-C may carry an unidentified FH mutation or have a polygenic inheritance pattern. Therefore, FH is often diagnosed by clinical diagnostic criteria for FH such as the AHA, EAS, Simon Broome, and Dutch Lipid Clinic Network criteria (Gidding et al. 2015; Nordestgaard et al. 2013; Austin et al. 2004; Haase and Goldberg 2012). Patient characteristics that may alert physicians to potential FH are summarized in Table 4.2.

On physical exam, patients with FH may present with tendon xanthomas, the physical exam finding most commonly associated with FH and most often included in the aforementioned diagnostic criteria. Aortic stenosis is also more common in patients with FH compared with the general population and may present as a systolic murmur identified upon auscultation of the heart (Marco-Benedi et al. 2019).

Table 4.2 Characteristics of familial hypercholesterolemia (FH)

Clinical	LDL-C ≥ 190 mg/dL and first-degree relative with similarly elevated LDL-C and or premature CVD
Genetic	Causal mutation in *LDLR*, *APOB*, or *PCSK9*
Family history	First-degree relative with LDL-C ≥ 190 mg/dL, premature coronary heart disease, or causal mutation in *LDLR*, *APOB*, or *PCSK9*

For detailed diagnostic criteria for FH, see American Heart Association, European Atherosclerosis Society, Simon Broome, and Dutch Lipid Clinic Network algorithms (Gidding et al. 2015; Nordestgaard et al. 2013; Austin et al. 2004; Haase and Goldberg 2012)

The AHA/ACC and ESC/EAS cholesterol guidelines both recommend beginning LLT without the calculation of a risk score in patients with LDL-C ≥ 190 mg/dL. The AHA/ACC guidelines recommend initiation of high-intensity statin therapy (i.e., rosuvastatin 20–40 mg daily or atorvastatin 40–80 mg daily) in these individuals; if LDL-C remains ≥100 mg/dL, the addition of other medications, including ezetimibe, proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i), and/or bempedoic acid, should be considered. The ESC/EAS guidelines recommend considering the diagnosis of FH in individuals with LDL-C ≥ 190 mg/dL and suggest treating those with FH and atherosclerotic CVD or another major risk factor aggressively as "very high risk," whereas those with FH but without atherosclerotic CVD or major risk factors are classified as "high risk." Based on its safety profile, statin therapy may be initiated in patients with FH as early as 8–10 years of age (Nordestgaard et al. 2013). Additionally, cascade (family) screening is recommended for family members of individuals diagnosed with FH.

Diabetes and the Metabolic Syndrome

Atherosclerotic CVD is the leading cause of morbidity and mortality in individuals with diabetes (American Diabetes Association 2021), despite advances in prevention (Rawshani et al. 2017). A landmark study by Haffner and colleagues demonstrated that diabetic patients without previous myocardial infarction have as high a risk of myocardial infarction as nondiabetic patients with previous myocardial infarction (Haffner et al. 1998), although this notion has been challenged more recently. Regardless, primary prevention of CVD is essential in the management of diabetic patients, and LLT may be initiated in diabetic patients without calculating a risk score. In diabetic patients aged 40–75 years, the AHA/ACC guidelines recommend treatment with moderate-intensity statin therapy to achieve an LDL-C reduction of ≥30% from baseline, and in those with multiple other risk factors, high-intensity statin therapy to achieve an LDL-C reduction of ≥50% from baseline. Similarly, the ESC/EAS guidelines recommend treating all diabetic patients (except those who are relatively young, newly diagnosed, and with no other CVD risk factors) aggressively with LLT. The American Diabetes Association (ADA)

guidelines recommend moderate-intensity statin therapy in addition to lifestyle therapy in diabetic patients with diabetes aged 40–75 years without atherosclerotic CVD and in diabetic patients aged 20–39 years who have additional CVD risk factors (American Diabetes Association 2021). For higher-risk diabetic patients, particularly those aged 50–70 years or with multiple CVD risk factors, the ADA guidelines recommend high-intensity statin therapy, and in those with estimated 10-year risk ≥20% (by the pooled cohort equations), combination therapy with ezetimibe in addition to maximally tolerated statin therapy to achieve an LDL-C reduction of ≥50%.

The metabolic syndrome represents a group of metabolic abnormalities, including hypertension, central obesity, insulin resistance, and atherogenic dyslipidemia, and is positively associated with both diabetes and CVD (Rochlani et al. 2017). Insulin resistance and obesity are both associated with increased levels of triglycerides. Among individuals with metabolic syndrome, LDL-C may be more accurately measured using the Martin–Hopkins or NIH equation as opposed to the Friedewald equation. Alternatively, CVD risk may also be estimated by using non-HDL-C, which is not influenced by triglyceride levels. It may be useful to measure LDL-P in these individuals as LDL-C may not accurately reflect their high number of atherogenic sdLDL particles.

Excess adipose tissue is also associated with increased levels of cholesteryl ester transfer protein (CETP) (Arai et al. 1994), which mediates the exchange of cholesteryl esters from cholesterol-rich lipoproteins for triglycerides from triglyceride-rich lipoproteins, leading to triglyceride-enriched HDL and LDL particles (Morton 1999). These triglyceride-enriched HDL and LDL particles are substrates for hepatic lipase and lipoprotein lipase, resulting in lower HDL concentrations and more sdLDL (Lagrost et al. 1993) and LDL-TG, all of which are associated with an increased risk of CVD (Williams et al. 2014; Hoogeveen et al. 2014; Hoogeveen and Ballantyne 2021; Saeed et al. 2018; Siddiqi et al. 2015). However, phase 3 clinical trials of several compounds that inhibit CETP failed to reduce CVD events (Tall and Rader 2018). One agent, anacetrapib, showed benefit in a long-term (median 4.1-year follow-up) outcome study (HPS/TIMI-REVEAL Collaborative Group 2017), but this agent was never submitted for approval to regulatory authorities. Although initiation of LLT in diabetic patients aged 40–75 years is widely accepted, targeted approaches to prevent CVD in individuals with features of the metabolic syndrome, including insulin resistance and central adiposity, are still a work in progress.

Conclusion/Future Directions

Hypercholesterolemia, particularly elevated LDL-C, is a major contributor to the development of atherosclerosis. It is important to treat hypercholesterolemia and other CVD risk factors with evidence-based therapies. In the setting of hypercholesterolemia, this primarily involves the identification of those who would benefit from

the initiation of LLT. Measurement of LDL-C can be used as a risk assessment tool and provides clinicians with a "target of therapy" for primary prevention of CVD. Management of hyperlipidemia is of particular importance among high-risk individuals, such as those with FH, diabetes mellitus, and metabolic syndrome.

Considering the high risk of atherosclerotic CVD associated with elevations of LDL-C early in life (Domanski et al. 2020), additional research is needed to understand better the risks versus benefits of initiating LLT in young individuals with hyperlipidemia that is not as extreme as observed in those with FH. Moving forward, genetic testing to identify pathogenic variants and for use in calculating a polygenic risk score could play an important role in identifying individuals who may benefit from early initiation of LLT.

References

American Diabetes Association. 10. Cardiovascular disease and risk management: standards of medical care in diabetes—2021. Diabetes Care. 2021;44:S125–S150.

Arai T, Yamashita S, Hirano K, et al. Increased plasma cholesteryl ester transfer protein in obese subjects. A possible mechanism for the reduction of serum HDL cholesterol levels in obesity. Arterioscler Thromb. 1994;14:1129–36.

Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. Am J Epidemiol. 2004;160:407–20.

Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376:1670–81.

Benn M, Watts GF, Tybjaerg-Hansen A, Nordestgaard BG. Familial hypercholesterolemia in the Danish general population: prevalence, coronary artery disease, and cholesterol-lowering medication. J Clin Endocrinol Metab. 2012;97:3956–64.

Borén J, Chapman MJ, Krauss RM, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2020;41:2313–30.

Brown EE, Sturm AC, Cuchel M, et al. Genetic testing in dyslipidemia: a scientific statement from the National Lipid Association. J Clin Lipidol. 2020;14:398–413.

Caulfield MP, Li S, Lee G, et al. Direct determination of lipoprotein particle sizes and concentrations by ion mobility analysis. Clin Chem. 2008;54:1307–16.

Cuchel M, Bruckert E, Ginsberg HN, et al. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. Eur Heart J. 2014;35:2146–57.

de Ferranti SD, Rodday AM, Mendelson MM, Wong JB, Leslie LK, Sheldrick RC. Prevalence of familial hypercholesterolemia in the 1999 to 2012 United States National Health and Nutrition Examination Surveys (NHANES). Circulation. 2016;133:1067–72.

Domanski MJ, Tian X, Wu CO, et al. Time course of LDL cholesterol exposure and cardiovascular disease event risk. J Am Coll Cardiol. 2020;76:1507–16.

Falk E. Pathogenesis of atherosclerosis. J Am Coll Cardiol. 2006;47:C7–C12.

Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2017;38:2459–72.

Ference BA, Bhatt DL, Catapano AL, et al. Association of genetic variants related to combined exposure to lower low-density lipoproteins and lower systolic blood pressure with lifetime risk of cardiovascular disease. JAMA. 2019;322:1381–91.

Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18:499–502.

Gidding SS, Champagne MA, de Ferranti SD, et al. The agenda for familial hypercholesterolemia: a scientific statement from the American Heart Association. Circulation. 2015;132:2167–92.

Giugliano RP, Pedersen TR, Park JG, et al. Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. Lancet (London, England). 2017;390:1962–71.

Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019;73:3168–209.

Haase A, Goldberg AC. Identification of people with heterozygous familial hypercholesterolemia. Curr Opin Lipidol. 2012;23:282–9.

Hadley T, Agha A, Ballantyne CM. How do we incorporate polygenic risk scores in coronary artery disease risk assessment and management? Curr Atheroscler Rep. 2021;23:28.

Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med. 1998;339:229–34.

Hoogeveen RC, Ballantyne CM. Residual cardiovascular risk at low LDL: remnants, lipoprotein(a), and inflammation. Clin Chem. 2021;67:143–53.

Hoogeveen RC, Gaubatz JW, Sun W, et al. Small dense low-density lipoprotein-cholesterol concentrations predict risk for coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) study. Arterioscler Thromb Vasc Biol. 2014;34:1069–77.

Hopkins PN, Toth PP, Ballantyne CM, Rader DJ, National Lipid Association Expert Panel on Familial Hypercholesterolemia. Familial hypercholesterolemias: prevalence, genetics, diagnosis and screening recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. 2011;5:S9–17.

HPS/TIMI-REVEAL Collaborative Group. Effects of anacetrapib in patients with atherosclerotic vascular disease. N Engl J Med. 2017;377:1217–27.

Hussain A, Sun C, Selvin E, et al. Triglyceride-rich lipoproteins, apolipoprotein C-III, angiopoietin-like protein 3, and cardiovascular events in older adults: Atherosclerosis Risk in Communities (ARIC) study. Eur J Prev Cardiol. 2022;29:e53–64.

Ito Y, Ohta M, Ikezaki H, et al. Development and population results of a fully automated homogeneous assay for LDL triglyceride. J Appl Lab Med. 2019;2:746–56.

Jia X, Al Rifai M, Ramsey DJ, et al. Association between lipid testing and statin adherence in the Veterans Affairs health system. Am J Med. 2019;132:e693–700.

Jia X, Ramsey DJ, Rifai MA, et al. Impact of lipid monitoring on treatment intensification of cholesterol lowering therapies (from the Veterans Affairs Healthcare System). Am J Cardiol. 2020;125:874–9.

Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. JAMA. 2009;301:2331–9.

Lagrost L, Gandjini H, Athias A, Guyard-Dangremont V, Lallemant C, Gambert P. Influence of plasma cholesteryl ester transfer activity on the LDL and HDL distribution profiles in normolipidemic subjects. Arterioscler Thromb. 1993;13:815–25.

Lee S, Akioyamen LE, Aljenedil S, Rivière JB, Ruel I, Genest J. Genetic testing for familial hypercholesterolemia: impact on diagnosis, treatment and cardiovascular risk. Eur J Prev Cardiol. 2019;26:1262–70.

Marco-Benedi V, Laclaustra M, Casado-Dominguez JM, et al. Aortic valvular disease in elderly subjects with heterozygous familial hypercholesterolemia: impact of lipid-lowering therapy. J Clin Med. 2019;8:2209.

Martin SS, Blaha MJ, Elshazly MB, et al. Comparison of a novel method vs the Friedewald equation for estimating low-density lipoprotein cholesterol levels from the standard lipid profile. JAMA. 2013;310:2061–8.

März W, Scharnagl H, Winkler K, et al. Low-density lipoprotein triglycerides associated with low-grade systemic inflammation, adhesion molecules, and angiographic coronary artery disease. Circulation. 2004;110:3068–74.

McGill HC Jr, McMahan CA, Zieske AW, et al. Associations of coronary heart disease risk factors with the intermediate lesion of atherosclerosis in youth. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. Arterioscler Thromb Vasc Biol. 2000;20:1998–2004.

Miller WG, Myers GL, Sakurabayashi I, et al. Seven direct methods for measuring HDL and LDL cholesterol compared with ultracentrifugation reference measurement procedures. Clin Chem. 2010;56:977–86.

Morton RE. Cholesteryl ester transfer protein and its plasma regulator: lipid transfer inhibitor protein. Curr Opin Lipidol. 1999;10:321–8.

Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J. 2013;34:3478–90a.

Otvos JD, Mora S, Shalaurova I, Greenland P, Mackey RH, Goff DC Jr. Clinical implications of discordance between low-density lipoprotein cholesterol and particle number. J Clin Lipidol. 2011;5:105–13.

Rawshani A, Rawshani A, Franzén S, et al. Mortality and cardiovascular disease in type 1 and type 2 diabetes. N Engl J Med. 2017;376:1407–18.

Rochlani Y, Pothineni NV, Kovelamudi S, Mehta JL. Metabolic syndrome: pathophysiology, management, and modulation by natural compounds. Ther Adv Cardiovasc Dis. 2017;11:215–25.

Saeed A, Feofanova EV, Yu B, et al. Remnant-like particle cholesterol, low-density lipoprotein triglycerides, and incident cardiovascular disease. J Am Coll Cardiol. 2018;72:156–69.

Sampson M, Ling C, Sun Q, et al. A new equation for calculation of low-density lipoprotein cholesterol in patients with normolipidemia and/or hypertriglyceridemia. JAMA Cardiol. 2020;5:540–8.

Siddiqi HK, Kiss D, Rader D. HDL-cholesterol and cardiovascular disease: rethinking our approach. Curr Opin Cardiol. 2015;30:536–42.

Singh RB, Mengi SA, Xu YJ, Arneja AS, Dhalla NS. Pathogenesis of atherosclerosis: a multifactorial process. Exp Clin Cardiol. 2002;7:40–53.

Soininen P, Kangas AJ, Würtz P, et al. High-throughput serum NMR metabonomics for cost-effective holistic studies on systemic metabolism. Analyst. 2009;134:1781–5.

Stitziel NO, MacRae CA. A clinical approach to inherited premature coronary artery disease. Circ Cardiovasc Genet. 2014;7:558–64.

Sturm AC, Knowles JW, Gidding SS, et al. Clinical genetic testing for familial hypercholesterolemia: JACC Scientific Expert Panel. J Am Coll Cardiol. 2018;72:662–80.

Tall AR, Rader DJ. Trials and tribulations of CETP inhibitors. Circ Res. 2018;122:106–12.

Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41:111–88.

Williams PT, Zhao XQ, Marcovina SM, Otvos JD, Brown BG, Krauss RM. Comparison of four methods of analysis of lipoprotein particle subfractions for their association with angiographic progression of coronary artery disease. Atherosclerosis. 2014;233:713–20.

Wilson PWF, Jacobson TA, Martin SS, Jackson EJ, Le NA, Davidson MH, Vesper HW, Ballantyne CM, Remaley AT. Lipid measurements in the management of cardiovascular diseases: practical guidelines. A scientific statement from the National Lipid Association Writing Group. J Clin Lipidol. 2021;15:629–48.

Chapter 5
Blood Pressure Control in Primary Care

LaShanda Brown, Jeff D. Williamson, and C. Barrett Bowling

In this chapter, we will first review hypertension prevalence, treatment, and control, also highlighting current clinical practice guideline definitions and their implications for identifying and monitoring hypertension in primary care practice. Next, we describe some considerations for controlling hypertension, focused especially on adults at older ages, the most prevalent group of hypertensives in primary care. Finally, we propose a framework for BP management particularly focused on older adults but that is applicable across the entire adult age spectrum. This framework will consider the aging context as well as the specific steps in hypertension management. Using this framework, we will summarize the existing literature as it relates to four necessary steps in hypertension control: (1) measuring BP, (2) planning and goal setting, (3) treating hypertension, and (4) monitoring BP over time, discussing implementation challenges and opportunities for improving care for adults with hypertension, especially older adults.

Epidemiology

Accurate blood pressure screening and careful management of elevated blood pressure (BP) is perhaps the most important public health activity in the primary care of adults. This is because for many years, including the past decade, elevated BP has

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been the leading cause of death and disability-adjusted life-years worldwide (Lim et al. 2012). In the United States, hypertension accounts for more CVD deaths than any other modifiable CVD risk factor, second only to cigarette smoking as a preventable cause of death for any reason (Danaei et al. 2009). In 23,272 US National Health and Nutrition Examination Survey (NHANES) participants, >50% of deaths from coronary heart disease (CHD) and stroke occurred among individuals with hypertension (Ford 2011). Because of the high prevalence of hypertension and its associated increased risk of CHD, stroke, and end-stage renal disease (ESRD), the population-attributable risk of these outcomes associated with hypertension is high (Ford 2011; Cheng et al. 2014). In the population-based Atherosclerosis Risk in Communities (ARIC) study, 25% of the cardiovascular events (CHD, coronary revascularization, stroke, or HF) were attributable to hypertension. In the Northern Manhattan study, the percentage of events attributable to hypertension was higher in women (32%) than in men (19%) and higher in blacks (36%) than in whites (21%) (Willey et al. 2014). In 2012, hypertension was the second leading assigned cause of ESRD, behind diabetes mellitus (DM), and accounted for 34% of incident ESRD cases in the US population (Saran et al. 2015). Many adult patients with hypertension have other CVD risk factors, and a list of these modifiable and relatively fixed risk factors is provided in Table 5.1. Among US adults with hypertension between 2009 and 2012, 15.5% were current smokers, 49.5% were obese, 63.2% had hypercholesterolemia, 27.2% had DM, and 15.8% had chronic kidney disease [CKD; defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 and/or urine albumin:creatinine ≥300 mg/g] (Egan et al. 2014).

Not only are CVD risk factors common among adults with hypertension, a higher percentage of adults with CVD risk factors have hypertension. For example, 71% of US adults with diagnosed DM have hypertension (Centers for Disease Control and Prevention 2014). In the Chronic Renal Insufficiency Cohort (CRIC), 86% of the participants had hypertension (Muntner et al. 2010). Also, 28.1% of adults with hypertension and CKD in the population-based Reasons for Geographic and Racial Differences in Stroke (REGARDS) study were classified as having resistant hypertension (Tanner et al. 2013). In NHANES 1999–2010, 35.7% of obese individuals had hypertension (Saydah et al. 2014). The presence of multiple CVD risk factors in individuals with hypertension results in high absolute risks for CHD and stroke in this population. For example, among US adults with hypertension between 2009

Table 5.1 Risk factors common in patients with hypertension

Modifiable risk factors[a]
Current cigarette smoking, secondhand smoking
Diabetes mellitus
Dyslipidemia/hypercholesterolemia
Overweight/obesity
Physical inactivity/low fitness
Unhealthy diet

[a]Factors that can be changed and, if changed, may reduce CVD risk

and 2012, 41.7% had a 10-year CHD risk >20%, 40.9% had a risk of 10–20%, and only 18.4% had a risk <10% (Egan et al. 2014). It is important to note that the prevalence of hypertension and the incidence of hypertension-related cardiovascular disease (CVD) increase with older age, making blood pressure (BP) control among older adults an even more important population health goal (Muntner et al. 2018; Benjamin et al. 2019).

Although antihypertensive medications are effective, inexpensive, and recommended by clinical practice guidelines, a large percentage of adults with hypertension have uncontrolled BP (Muntner et al. 2020; Whelton et al. 2018). There are several factors that contribute to poor blood pressure control in primary care, including multiple co-occurring health conditions, often complex combinations of personal and environmental factors, and, in the context of aging, heterogeneity in physical and cognitive function (World Health Organization 2002; Boyd et al. 2019; Tinetti and Fried 2004). Importantly, there are also specific considerations for measuring and treating hypertension that vary by age and comorbidity (Reynolds et al. 2015). An additional contributor has been the differing guidelines for defining and maintaining good blood pressure control by nation and even by professional medical societies within a nation such as the United States.

Guideline Definitions and Treatment Goals

The 2017 American College of Cardiology/American Heart Association (ACC/AHA) Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults classifies BP into one of four categories that applies to all ages: normal, elevated, stage 1, and stage 2 (Whelton et al. 2018). The guideline defines normal BP as systolic BP (SBP) <120 mm Hg and diastolic (DBP) <80 mm Hg. Elevated BP is defined as SBP 120–129 mm Hg and DBP <80 mm Hg. Stage 1 hypertension is defined as SBP 130–139 mm Hg or DBP 80–89 mm Hg, and stage 2 hypertension is defined as SBP ≥140 mm Hg or DBP ≥90 mm Hg. These were based on increasingly larger quantities of observational data and the new categories replaced the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) classification, adding the new category elevated BP, eliminating the pre-hypertension category, and lowering the BP levels for defining stage 1 hypertension (Whelton et al. 2018; Chobanian et al. 2003).

New to these guidelines are recommendations for thresholds to initiate BP-lowering medications linked to BP goals and based on individual CVD risk. Among patients with clinical CVD, guidelines recommend treatment for secondary prevention of CVD events with a BP goal <130 mm Hg/<80 mm Hg. For primary prevention among those without known CVD, guidelines recommend first estimating the 10-year atherosclerotic cardiovascular disease (ASCVD) risk. BP-lowering medications are recommended for goal BP levels of <130 mm Hg/<80 mm Hg in patients with an ASCVD risk of >10%. As 88% of adults over 65 years and 100%

of those over 75 years old have an ASCVD risk of ≥10%, the recommended BP goal for the vast majority of older adults is <130 mm Hg/<80 mm Hg (Whelton et al. 2018). In addition to antihypertensive medication to achieve these goals, the 2017 ACC/AHA guidelines also recommend nonpharmacological interventions including weight loss among those overweight or obese, a heart-healthy diet, sodium restriction, increased physical activity, and reduction in alcohol consumption. These treatment recommendations are the same for adults of all ages.

Prevalence, Treatment, and Control in Primary Care

The prevalence of hypertension increases with age. Most epidemiological studies have used BP ≥140/90 mm Hg to define hypertension. For example, according to an analysis of data from NHANES conducted between 2011 and 2014, the prevalence of hypertension was 10.5%, 29.5%, 52.4%, 63.6%, and 75.1% among US adults 20–44, 45–54, 55–64, 65–74, and ≥75 years old, respectively (Muntner et al. 2018). Applying the 2017 ACC/AHA guideline definition of hypertension as BP ≥130/80 mm Hg classified a higher percentage of US adults as having hypertension (45.6% and 31.9% for 2017 ACC/AHA and JNC7, respectively). However, most of the increased prevalence occurred in younger adults as among those 75 years old and older the difference in those meeting the definition of hypertension (82.3% versus 75.1%) or who would receive recommendations for antihypertensive medications (82.3% versus 78.5%) is small. In the general US population, gender differences in the prevalence of hypertension have also been reported with a higher percentage of men compared to women meeting the definition for hypertension prior to age 65. However, after age 65 years the prevalence of hypertension is higher among women than men (Benjamin et al. 2019).

The percentage of adults with awareness of hypertension and receiving treatment is generally high. Awareness of hypertension, when it was defined as BP ≥140/90 mm Hg, was 67.3%, 79.3%, 85.4%, and 82.1% among US adults 18–44, 45–64, 65–74, and ≥75 years old, respectively (Muntner et al. 2020). Hypertension awareness is more common among those with a usual health-care provider, which may explain in part the higher prevalence of awareness at older ages as older adults often require more frequent interactions with the health-care system. Among those aware they had hypertension, antihypertensive medication use is highest among older adults. Among those who reported awareness, the percentage taking antihypertensive medication were 75.8%, 87.7%, 94.1%, and 96.0% at 18–44, 45–64, 65–74, and ≥75 years old (Muntner et al. 2020).

Even in older adults with hypertension, those most at risk for CVD and brain health complications, the percentage with controlled BP has generally been reported to be less than 50%, even when control was defined as an SBP < 140 mmHg. A recent analysis reported trends in BP control using NHANES calendar periods across nearly two decades (Muntner et al. 2020). Serial cross-sectional surveys took

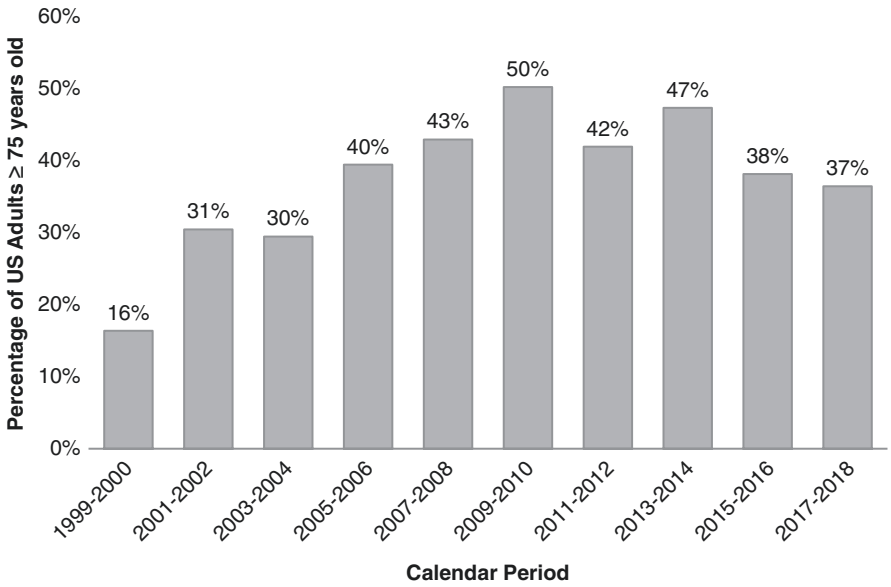

Fig. 5.1 Trends in blood pressure (BP) control among US adults ≥75 years old from the National Health and Nutrition Examination Survey (NHANES). (Source: Muntner et al. 2020)

place over 2-year intervals from 1999–2000 through 2017–2018. Overall, an increasing percentage of adults with controlled BP was seen through 2013–2014, followed by a decrease in calendar periods 2015–2016 and 2017–2018. This trend was also seen among those ≥75 years old (Fig. 5.1). To achieve adequate control (SBP, 130 mmHg), an average of three antihypertensive medications daily is necessary, as shown in the recently completed SPRINT trial.

BP Control and Disabling Conditions

As adults age and prioritize remaining independent in late life, it is important to help them recognize the association between BP control and conditions that impair cognitive and physical function. Uncontrolled BP is a known risk factor for disabling conditions, including stroke, heart failure, and coronary heart disease (Benjamin et al. 2019). Studies have also shown direct associations of hypertension with a decline in cognitive and physical function (Hajjar et al. 2007). For example, BP ≥120/80 mm Hg during midlife was found to be associated with a greater risk of developing dementia in later life (Gottesman et al. 2017). Therefore, a life-course perspective is helpful for understanding the detrimental effects of uncontrolled BP that may accumulate over many years, leading to disability (Yano et al. 2014).

Framework

Without careful attention to prevention in this area from primary care providers, the combination of an aging US population, a decreasing percentage with controlled hypertension, and recommendations for lower BP goals will likely result in an expanding population of older adults with uncontrolled BP who are at risk for CVD events, cognitive and physical disability. Population health efforts to improve BP control often focus on increasing awareness and treatment. However, awareness and treatment have remained high among older adults. An alternative approach may be to recognize specific challenges to BP control among adults. A framework for considering how key steps in BP management occur in the context of common issues as adults age is shown in Fig. 5.2.

Implications of an Aging Population on Treatment Approach

There is compelling evidence that treatment of elevated blood pressures in ambulatory, cognitively normal adults, even those over the age of 80 years, is effective at reducing cardiovascular events, morbidity and mortality, and early dementia [mild cognitive impairment (MCI)] (Williamson et al. 2016; SPRINT MIND Investigators for the SPRINT Research Group et al. 2019). Multiple studies have shown a significant reduction in morbidity and mortality when elevated blood pressures are appropriately treated to goal. Despite the benefits of treating hypertension, medical providers remain reluctant to treat elevated blood pressures in older adults according to current guidelines.

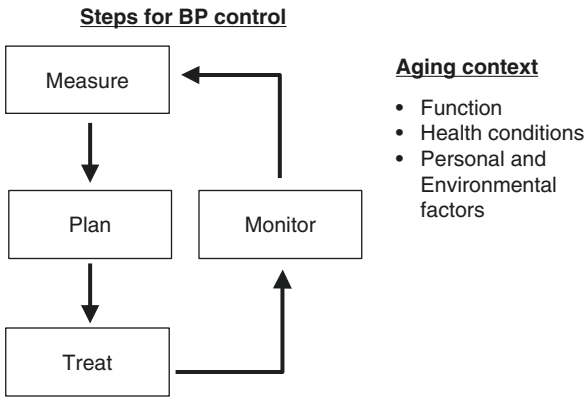

Fig. 5.2 A framework to improve blood pressure (BP) control that considers how key steps in BP management occur in the context of common aging issues

While some conditions have overlapping treatment goals with hypertension, reinforcing the need for treatment (e.g., ACE/ARB among those with hypertension, chronic kidney disease, and diabetes), the presence of multimorbidity may make self-management more complex (Bowling et al. 2017; Hall et al. 2020).

The World Health Organization (WHO) has developed a model that is useful for helping to identify the likelihood of benefit from intense efforts to control BP. The WHO International Classification of Functioning (ICF) model describes four domains that require consideration: (1) function, (2) health conditions (i.e., multimorbidity), (3) personal factors, and (4) environmental factors (World Health Organization 2002; Jette 2006). This model considers the impact of functional limitations and multiple chronic conditions on treatment decisions (Barnett et al. 2012; Tinetti et al. 2012). These include personal factors (such as individual health goals, personal financial resources) and environmental factors (such as the availability of caregivers to assist with complex medication regimens, living situations such as independent living versus nursing home residence). Each of these categories should be incorporated into shared treatment decision-making by the patient and their treatment team. While these considerations may be important regardless of age, the frequency at which these factors interact is known to increase at older ages (Bowling et al. 2019a). For example, persons with limited life expectancy due to such conditions as advanced cancer, dementia, or those residing in nursing homes are less likely to benefit from prioritizing guideline blood pressure control and may even experience harm (Pajewski et al. 2020). This is the rationale for the 2017 AHA/ACC to include a second recommendation for blood pressure control in older adults who have "a high burden of comorbidity and limited life expectancy [where] clinical judgment, patient preference, and a team-based approach to assess risk/benefit is reasonable for decisions regarding intensity of BP lowering and choice of antihypertensive drugs."

Steps in BP Management

There are specific components involved in achieving and sustaining BP control (Table 5.2). This framework acknowledges that the BP *measure* can be affected by the technique, device, and setting in which BP is measured. The *plan* refers to setting a goal BP in the context of the patient and family's overall health goals. *Treatment* refers to the management strategy, including the use of BP-lowering medications, the expected benefits of treatment, and risk for adverse events. Lastly, *monitor* refers to the need for ongoing follow-up to support a patient's ability to sustain BP control over time. Below, we highlight some of the relevant literature for each of these four steps.

Table 5.2 Steps in hypertension control and relevant considerations for older adults

	Description	Relevance and potential limitations in older adults
Measure	Technique, device, setting	Proper technique may be limited by physical and cognitive impairment or geriatric conditions Competing demands for clinical assessments among older adults with multimorbidity (i.e., proper technique a low priority) Higher prevalence of treated white coat hypertension at older age
Plan	Setting goals	Concerns about the generalizability of clinical trial evidence for some older adults Wide range in health goals and willingness to accept tradeoffs between benefits and risks
Treat	Management strategy	Treatment intensification Physical and cognitive impairment may limit management Dependence on caregivers for management support
Monitor	Follow-up over time	Changing life expectancy over time for which BP monitoring may be necessary Intervening health events at older age may affect BP control and treatment goals

Measure

A recent report showed a poor correlation between blood pressures recorded in electronic health records (EHR) compared to BP obtained under a standardized research protocol (Drawz et al. 2020). The greatest portion of the average clinical care readings for patients was usually higher than the research clinic readings, but approximately 20% of the clinical care readings were usually lower than the research clinic measurements (Drawz et al. 2020). Most of these findings can be explained by variations from the AHA Scientific Statement on Measurement of BP in Humans, which describes 6 overall steps and 20 specific instructions for the proper technique to obtain seated BP in the office (Muntner et al. 2019). However, primary care clinicians do not need to tackle all 20 to make a big difference in reducing CVD and disability risks related to hypertension. Large-scale studies have demonstrated that implementing proper BP measurement technique is feasible. Primary care clinic-level challenges are important but manageable and include (1) ensuring a 3- to 5-minute relaxation period, (2) using an automated device to measure BP and not human ascertainment, (3) minimizing talking to the patient during the measurement, (4) ensuring the proper cuff size for obese patients, and (5) removing clothing that impairs accurate measurement at the patient level. These five steps are good examples of how outpatient clinics can overcome clinic- and patient-level barriers to guideline BP care just as they have done in other areas of primary care practice (e.g., blood drawing, laboratory calibration, crash cart maintenance) through putting standardized policies into place. This might also involve an expanded use of home blood pressure monitoring (HBPM) according to an AHA Scientific Statement recommendation for proper technique (Muntner et al. 2019). Concerns about device validation have also been reported (Cohen et al. 2019).

Nevertheless, none of these concerns preclude guideline-based management of consistently elevated blood pressure.

Research has shown differences based on the setting in which BP is measured, an important example being white coat hypertension (Reynolds et al. 2015; Ishikawa et al. 2011). One way to identify white coat hypertension is by using ambulatory blood pressure monitoring (ABPM). In ABPM, a BP monitor is worn for 24 hours and obtains automatic readings in the out-of-office setting (Reynolds et al. 2015). ABPM has been shown to be similarly feasible in older and younger adults (Nesti et al. 2014). Using ABPM, white coat hypertension is defined as having elevated clinic BP without elevated daytime BP on ABPM. An analysis of data from the Jackson Heart Study compared the difference in clinic and daytime SBP among black US adults with hypertension <60 versus ≥60 years old (Tanner et al. 2016). The difference between clinic SBP and daytime SBP was on average higher among those ≥60 years old compared to <60 years old (12 mm Hg higher versus 8 mm Hg higher). The prevalence of white coat hypertension may be greater among special populations of adults. Taken together, these findings suggest that clinic BPs, often poorly measured as part of routine care, may not always reflect the out-of-clinic BP, and this discrepancy should be considered when addressing difficult control BP or poorly tolerated BP control. Given this, primary care clinicians could review their blood pressure measurement approach with the goal to both improve in-clinic measurement and identify patients who may benefit from additional out-of-clinic measurements.

Plan

The plan refers to setting goals for BP control levels. As described above, the guideline-recommended goal BP for the vast majority of older adults is <130 mm Hg/<80 mm Hg. This recommendation is supported by clinical trial evidence, including findings from the Systolic Blood Pressure Intervention Trial (SPRINT), which tested intensive versus standard control (SPRINT Research Group et al. 2015). While the results of SPRINT have been extensively reported, (Supiano and Williamson 2019) it is worth reviewing three findings that are relevant to older adults. First, among the prespecified subgroup of participants ≥75 years old, treating to an SBP goal of <120 mm Hg (intensive control) versus <140 mm Hg (standard control) resulted in and achieved a mean of 123 mmHg and lower rates of fatal and nonfatal CVD events and death (Williamson et al. 2016). This was true in prespecified subgroups in which participants were categorized as fit, less fit, or frail or had a low gait speed and among those ≥80 years old free of cognitive impairment (Pajewski et al. 2020). Second, findings from SPRINT may be generalizable to a large number of ambulatory older adults, including those with frailty. In SPRINT, 31% of participants ≥75 years old were frail, a similar prevalence seen in community-dwelling older adults (Pajewski et al. 2016) Recent work has shown that more than

1/3 of all older adults meet the criteria for blood pressure control with a goal of SBP of 120 mmHg as defined in SPRINT (Bress et al. 2016). Third, findings from the SPRINT MIND study found a lower incidence of mild cognitive impairment (MCI) and the combination of MCI or probable dementia with intensive SBP control (SPRINT MIND Investigators for the SPRINT Research Group et al. 2019). There was no difference seen in the primary outcome of probable dementia, perhaps due to the intervention being terminated early and inadequate follow-up time. However, because maintaining cognitive function is such an important goal in aging, findings of lower risk of MCI are clinically relevant for older adults.

While SPRINT is a landmark study and representative of a large percentage of older adults with hypertension, it is not possible for a randomized trial to be generalizable to all older adults. Therefore, it is important to consider the study exclusions most relevant to older adults when planning BP goals. For example, SPRINT excluded adults residing in nursing homes and those with standing hypotension of <110 mm Hg, type 2 diabetes, prior history of stroke, estimated glomerular filtration rate <20 ml/min/1.73 m^2, dementia, or symptomatic heart failure (SPRINT Research Group et al. 2015). As these conditions are common at older age and may be associated with risk for adverse events, it is not known if intensive SBP control would confer the same benefits for some subgroups of older adults.

Treat

After making plans for BP goals, the next step is to choose a management strategy. This includes both nonpharmacological interventions, such as low sodium diets and weight loss, as well as the use of BP-lowering medications. Several nonpharmacological interventions (weight loss, smoking cessation, limiting alcohol intake, etc.) have additional benefits such as improvement of function and should be considered regardless of the need for antihypertensive medication. The clinician and patient should have an understanding of the expected benefits and potential for risk for adverse events when considering antihypertensive medication initiation or intensification. In general, guideline recommendations for specific antihypertensive medications do not differ by age (Whelton et al. 2018). As the majority of older adults with hypertension are on treatment, treatment decisions less often focus on which antihypertensive medication to initiate, but more on when to intensify treatment by adding medications from other classes. For example, among adults ≥75 years old in SPRINT, 85% of participants in the intensive treatment group and 57% in the standard treatment group required two or more antihypertensive medication classes to achieve the targeted BP goals (mean number 2.8 versus 1.8) (Williamson et al. 2016). The most commonly used antihypertensive medications for both randomization groups were ACE inhibitors/ARBs followed by diuretics and calcium channel blockers. Therefore, it is important to anticipate the need for multiple strategies when treating hypertension.

Another aspect of treatment to consider is the risk for adverse events. Falls are the leading cause of injury and death among older adults (Bergen et al. 2016). While low blood pressure is associated with falls, (Tinetti et al. 2014) no randomized clinical trial, including SPRINT, has ever shown intensive BP treatment to be associated with a higher risk of injurious falls (SPRINT Research Group et al. 2015; Margolis et al. 2014). However, rates of falls have been shown to be lower in trial populations than in observational studies (Tinetti et al. 2014; Deandrea et al. 2010). These findings suggest that the risk for falls should not preclude hypertension treatment for most older adults, but careful titration, short-term monitoring, and addressing multiple fall risk factors should be part of comprehensive hypertension treatment.

Monitor

In practice, clinicians diagnose and treat individuals with hypertension over many visits and patients live with hypertension over many years. As patients age and experience health events, many unrelated to hypertension, these may affect their BP and its control. Therefore, monitoring BP control over time with the goal of sustaining BP control is an important step in hypertension management. Recent studies have shown that sustained BP control is associated with better health outcomes (Bowling et al. 2019b). For example, an analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) linked to Medicare health insurance claims examined the association between sustained SBP control and the progression of multimorbidity, defined by the co-occurrence of up to 14 separate chronic conditions (Bowling et al. 2020). SBP control was categorized as <140 mm Hg at <50%, 50% to <75%, 75% to <100%, and 100% of visits over a 48-month assessment period. Participants with sustained SBP control at a higher percentage of visits had a slower rate of multimorbidity progression and developed multimorbidity when they were 5–10 years older than their counterparts without sustained SBP control. As older adults often consider their overall health when assessing the risks and benefits of treatment, not just the disease-specific outcomes, evidence on reducing multimorbidity could be used to guide patient-centered discussions about monitoring and improving BP control over time.

Implementing This Framework into Primary Care

Understanding the unique challenges and opportunities for BP control in adults may facilitate better implementation of hypertension guidelines in primary care. Opportunities to improve blood pressure control can be considered for each of the four steps described above. For example, for *measure*, primary care clinicians may need to work with clinic staff to develop practical approaches to BP measurement

that are tailored to their clinical settings or accurately obtained BP outside of the clinic. For *plan*, risk stratification tools may be helpful to identify patients for whom guideline-recommended BP is appropriate and shared decision-making tools help align patient goals with BP treatment goals. For *treat*, partnering with pharmacists to use treatment protocols that address polypharmacy, drug–drug, and drug–condition interactions may help reduce adverse events. Finally, for *monitor*, primary care clinicians may want to consider meaningful metrics for sustained BP control that support patient–provider communication and quality improvement.

Conclusions

Elevated blood pressure is the most common risk factor for cardiovascular disease, memory decline, and death encountered in primary care. Nevertheless, despite proven effective and inexpensive treatments, substantial clinical trial evidence on the benefits of treatment, and regularly updated guideline recommendations, a large percentage of adults do not have adequately controlled BP. A framework that recognizes both the broader implications for poorly controlled hypertension and the specific challenges and opportunities for better BP management may be helpful for improving BP control. Implementation of current guidelines in populations of older adults will be improved when barriers to BP measurement, planning, treating, and monitoring are addressed.

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References

Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet. 2012;380(9836):37–43.

Benjamin EJ, Muntner P, Alonso A, et al. American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2019 update: a report from the American Heart Association. Circulation. 2019;139(10):e56–e528.

Bergen G, Stevens MR, Burns ER. Falls and fall injuries among adults aged ≥ 65 years - United States, 2014. MMWR Morb Mortal Wkly Rep. 2016;65(37):993–8.

Bowling CB, Plantinga L, Phillips LS, et al. Association of multimorbidity with mortality and healthcare utilization in chronic kidney disease. J Am Geriatr Soc. 2017;65(4):704–11.

Bowling CB, Deng L, Sakhuja S, Morey MC, Jaeger BC, Muntner P. Prevalence of activity limitations and association with multimorbidity among US adults 50 to 64 years old. J Gen Intern Med. 2019a;34(11):2390–6.

Bowling CB, Davis BR, Luciano A, et al. Sustained blood pressure control and coronary heart disease, stroke, heart failure, and mortality: an observational analysis of ALLHAT. J Clin Hypertens (Greenwich). 2019b;21(4):451–9.

Bowling CB, Sloane R, Pieper C, et al. Association of sustained blood pressure control with multimorbidity progression among older adults. J Am Geriatr Soc. 2020;68(9):2059–66.

Boyd C, Smith CD, Masoudi FA, et al. Decision making for older adults with multiple chronic conditions: executive summary for the American Geriatrics Society guiding principles on the care of older adults with multimorbidity. J Am Geriatr Soc. 2019;67(4):665–73.

Bress AP, Tanner RM, Hess R, Colantonio LD, Shimbo D, Muntner P. Generalizability of SPRINT results to the U.S. adult population. J Am Coll Cardiol. 2016;67(5):463–72.

Centers for Disease Control and Prevention. National diabetes statistics report: estimates of diabetes and its burden in the United States. Atlanta, GA: U.S. Department of Health and Human Services; 2014.

Cheng S, Claggett B, Correia AW, et al. Temporal trends in the population attributable risk for cardiovascular disease: the Atherosclerosis Risk in Communities Study. Circulation. 2014;130(10):820–8.

Chobanian AV, Bakris GL, Black HR, et al. National Heart, Lung, and Blood Institute Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure: National High Blood Pressure Education Program Coordinating Center. The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. JAMA. 2003;289(19):2560–72.

Cohen JB, Padwal RS, Gutkin M, et al. History and justification of a national blood pressure measurement validated device listing. Hypertension. 2019;73(2):258–64.

Danaei G, Ding EL, Mozaffarian D, et al. The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors. PLoS Med. 2009;6(4):e1000058.

Deandrea S, Lucenteforte E, Bravi F, Foschi R, La Vecchia C, Negri E. Risk factors for falls in community-dwelling older people: a systematic review and meta-analysis. Epidemiology. 2010;21(5):658–68.

Drawz PE, Agarwal A, Dwyer JP, et al. Concordance between blood pressure in the systolic blood pressure intervention trial and in routine clinical practice. JAMA Intern Med. 2020;180(12):1655–63.

Egan BM, Li J, Hutchison FN, et al. Hypertension in the United States, 1999 to 2012: progress toward healthy people 2020 goals. Circulation. 2014;130(19):1692–9.

Ford ES. Trends in mortality from all causes and cardiovascular disease among hypertensive and nonhypertensive adults in the United States. Circulation. 2011;123(16):1737–44.

Gottesman RF, Albert MS, Alonso A, et al. Associations between midlife vascular risk factors and 25-year incident dementia in the Atherosclerosis Risk in Communities (ARIC) cohort. JAMA Neurol. 2017;74(10):1246–54.

Hajjar I, Lackland DT, Cupples LA, Lipsitz LA. Association between concurrent and remote blood pressure and disability in older adults. Hypertension. 2007;50(6):1026–32.

Hall RK, Zhou H, Reynolds K, Harrison TN, Bowling CB. A novel approach to developing a discordance index for older adults with chronic kidney disease. J Gerontol A Biol Sci Med Sci. 2020;75(3):522–8.

Ishikawa J, Ishikawa Y, Edmondson D, Pickering TG, Schwartz JE. Age and the difference between awake ambulatory blood pressure and office blood pressure: a meta-analysis. Blood Press Monit. 2011;16(4):159–67.

Jette AM. Toward a common language for function, disability, and health. Phys Ther. 2006;86(5):726–34.
Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2224–60.
Margolis KL, Palermo L, Vittinghoff E, et al. Intensive blood pressure control, falls, and fractures in patients with type 2 diabetes: the ACCORD trial. J Gen Intern Med. 2014;29(12):1599–606.
Muntner P, Anderson A, Charleston J, et al. Hypertension awareness, treatment, and control in adults with CKD: results from the Chronic Renal Insufficiency Cohort (CRIC) study. Am J Kidney Dis. 2010;55(3):441–51.
Muntner P, Carey RM, Gidding S, Jones DW, Taler SJ, Wright JT Jr, Whelton PK. Potential US population impact of the 2017 ACC/AHA high blood pressure guideline. Circulation. 2018;137(2):109–18.
Muntner P, Shimbo D, Carey RM, et al. Measurement of blood pressure in humans: a scientific statement from the American Heart Association. Hypertension. 2019;73(5):e35–66.
Muntner P, Hardy ST, Fine LJ, et al. Trends in blood pressure control among US adults with hypertension, 1999–2000 to 2017–2018. JAMA. 2020;324(12):1190–200.
Nesti N, Pieraccioli M, Mossello E, et al. Tolerability of ambulatory blood pressure monitoring (ABPM) in cognitively impaired elderly. Blood Press. 2014;23(6):377–80.
Pajewski NM, Williamson JD, Applegate WB, for the SPRINT Study Research Group, et al. Characterizing frailty status in the Systolic Blood Pressure Intervention Trial. J Gerontol A Biol Sci Med Sci. 2016;71(5):649–55.
Pajewski NM, Berlowitz DR, Bress AP, et al. Intensive vs standard blood pressure control in adults 80 years or older: a secondary analysis of the Systolic Blood Pressure Intervention Trial. J Am Geriatr Soc. 2020;68(3):496–504.
Reynolds K, Bowling CB, Sim JJ, Sridharan L, Harrison TN, Shimbo D. The utility of ambulatory blood pressure monitoring for diagnosing white coat hypertension in older adults. Curr Hypertens Rep. 2015;17(11):86.
Saran R, Li Y, Robinson B, et al. US Renal Data System 2014 annual data report: epidemiology of kidney disease in the United States. Am J Kidney Dis. 2015;66(1Suppl 1):Svii, S1–305.
Saydah S, Bullard KM, Cheng Y, et al. Trends in cardiovascular disease risk factors by obesity level in adults in the United States, NHANES 1999–2010. Obesity (Silver Spring). 2014;22(8):1888–95.
SPRINT MIND Investigators for the SPRINT Research Group, Williamson JD, Pajewski NM, Auchus AP, et al. Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial. JAMA. 2019;321(6):553–61.
SPRINT Research Group, Wright JT Jr, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015;373(22):2103–16.
Supiano MA, Williamson JD. New guidelines and SPRINT results: implications for geriatric hypertension. Circulation. 2019;140(12):976–8.
Tanner RM, Calhoun DA, Bell EK, et al. Prevalence of apparent treatment-resistant hypertension among individuals with CKD. Clin J Am Soc Nephrol. 2013;8(9):1583–90.
Tanner RM, Shimbo D, Seals SR, et al. White-coat effect among older adults: data from the Jackson Heart Study. J Clin Hypertens (Greenwich). 2016;18(2):139–45.
Tinetti ME, Fried T. The end of the disease era. Am J Med. 2004;116(3):179–85.
Tinetti ME, Fried TR, Boyd CM. Designing health care for the most common chronic condition--multimorbidity. JAMA. 2012;307(23):2493–4.
Tinetti ME, Han L, Lee DS, et al. Antihypertensive medications and serious fall injuries in a nationally representative sample of older adults. JAMA Intern Med. 2014;174(4):588–95.
Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of

Cardiology/American Heart Association task force on clinical practice guidelines. Circulation. 2018;138(17):e426–83.

Willey JZ, Moon YP, Kahn E, et al. Population attributable risks of hypertension and diabetes for cardiovascular disease and stroke in the northern Manhattan study. J Am Heart Assoc. 2014;3(5):e001106.

Williamson JD, Supiano MA, Applegate WB, for the SPRINT Research Group, et al. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged ≥ 75 years: a randomized clinical trial. JAMA. 2016;315(24):2673–82.

World Health Organization. Towards a common language for functioning, disability, and health, ICF, the international classification of functioning, disability and health. Geneva: World Health Organization; 2002.

Yano Y, Ning H, Allen N, et al. Long-term blood pressure variability throughout young adulthood and cognitive function in midlife: the Coronary Artery Risk Development in Young Adults (CARDIA) study. Hypertension. 2014;64(5):983–8.

Chapter 6
Cardiovascular Risk Assessment in Metabolic Syndrome and Diabetes

Nathan D. Wong

Summary

- Cardiovascular diseases, including coronary heart disease, stroke, heart failure, and peripheral arterial disease, along with microvascular disease (retinopathy, neuropathy, and chronic kidney disease), are the principal causes of morbidity and mortality in persons with metabolic syndrome and diabetes.
- Both metabolic syndrome and diabetes are associated with great heterogeneity in cardiovascular disease risk, warranting cardiovascular risk assessment, including global risk scoring and consideration of risk-enhancing factors. Many such persons do not reach high-risk status based on global risk scoring.
- Evaluating subclinical atherosclerosis can also stratify risk in persons with metabolic syndrome and diabetes; persons with significant levels of coronary calcium have coronary heart disease rates 10-fold greater than those without coronary calcium.
- Few persons with metabolic syndrome and diabetes are at recommended targets for all major cardiovascular risk factors, including LDL-cholesterol, blood pressure, HbA1c, nonsmoking status, and body mass index.

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Introduction

The metabolic syndrome (MetS) had its foundations with the original designation of the insulin resistance syndrome (Reaven 1988) and cardiometabolic syndrome (Fagan and Deedwania 1998), but evolved and became a commonly utilized clinical construct in the United States and worldwide with the release of the Third Adult Treatment Panel of the National Cholesterol Education Program in 2001 (National Cholesterol Education Program (NCEP) 2002). The most recent and currently used worldwide definition proposed by the International Diabetes Federation (Alberti et al. 2009) requires three or more of five key risk factors (Table 6.1), including increased waist circumference with specific cutpoints for persons of different ethnic origins (Table 6.2). In addition, if waist circumference is not available, a body mass index of 30 kg/m^2 or greater be substituted and assumed to designate abdominal obesity. With approximately 30 million US adults having type 2 diabetes mellitus (DM) in 2017, given the prevalence of MetS is approximately three times that of DM, approximately 100 million (one-third) US adults are estimated to have MetS (Saklayen 2018). Moreover, with nearly 500 million adults globally having DM, a number expected to increase to 700 million by 2045 (International Diabetes Federation Atlas 2019), one can estimate that approximately 1.5 billion individuals currently have MetS, which will exceed 2 billion by 2045.

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in persons with MetS and DM due principally to coronary heart disease, stroke, heart failure, and peripheral arterial disease (Geiss et al. 1995). While type 2 DM has traditionally been referred to as a coronary heart disease (CHD) risk equivalent, it actually confers great heterogeneity in CHD and CVD risk, which is dependent on many factors, such as the 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. MetS is also accompanied by a wide variation in risk for CVD.

Table 6.1 IDF/IAS/NHLBI/AHA/WHF joint scientific statement on diagnosis of metabolic syndrome (Alberti et al. Circulation 2009) (≥3 criteria required for diagnosis)

Measure	Categorical Cut Points
Elevated waist circumference	Population- and country-specific definitions (see Table 6.2)
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator)	≥150 mg/dL (1.7 mmol/L)
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator)	<40 mg/dL (1.0 mmol/L) in males;<50 mg/dL (1.3 mmol/L) in females
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥130 and/or diastolic ≥85 mm Hg
Elevated fasting glucose‡ (drug treatment of elevated glucose is an alternate indicator)	≥100 mg/dL

Table 6.2 Current recommended waist circumference thresholds for abdominal obesity by different organizations

	Recommended waist circumference threshold for abdominal obesity	
Population	Men	Women
Europid	≥94 cm	≥80 cm
Caucasian	≥94 cm	≥80 cm
	≥102 cm	≥88 cm
United States	≥102 cm	≥88 cm
Canada	≥102 cm	≥88 cm
European	≥102 cm	≥88 cm
Asian (including Japanese)	≥90 cm	≥80 cm
Asian	≥90 cm	≥80 cm
Japanese	≥85 cm	≥90 cm
China	≥85 cm	≥80 cm
Middle East, Mediterranean	≥94 cm	≥80 cm
Sub-Saharan African	≥94 cm	≥80 cm
Ethnic Central and South American	≥90 cm	≥80 cm

[a]Recent AHA/NHLBI guidelines for metabolic syndrome recognize an increased risk for CVD and diabetes at waist-circumference thresholds of ≥94 cm in men and ≥80 cm in women and identify these as optional cut points for individuals or populations with increased insulin resistance

This chapter will briefly review the epidemiology of MetS, DM, and CVD and focus on the role of and strategies for cardiovascular risk assessment in persons with MetS and DM and the status and implications of multiple risk factor control in such persons.

Epidemiology of Metabolic Syndrome, Diabetes, and Cardiovascular Disease

The latest estimates from 2019 indicate that 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; with MetS prevalence approximately three times that of DM (Saklayen 2018), this would translate into approximately 1.5 billion persons globally with MetS, projected to increase to more than 2 billion by 2045. Current annual deaths in the United States due to complications from DM are estimated to be 4.2 million and annual health-care expenditures exceed 750 billion US dollars. 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 (International Diabetes Federation Atlas 2019).

CVD is the most common cause of death among patients with DM, 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 (Geiss

et al. 1995). 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 (Geiss et al. 1995). 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 (Emerging Risk Factors Collaboration 2010). Recent data from a population of 1.9 million persons from the United Kingdom demonstrated that 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 (Shah et al. 2015). 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 that 34–45% have diabetes and another 35–37% have prediabetes, indicating that the vast majority of cardiovascular patients have abnormal glucose tolerance (Conaway and O'Keefe 2006). It has also been shown that upon admission for an acute coronary syndrome approximately 15% of patients are newly diagnosed with T2DM (Conaway et al. 2005) and some two-thirds of patients meeting criteria for DM based on fasting glucose are discharged from the hospital inappropriately undiagnosed for DM (Anselmino et al. 2008).

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 without MetS nor DM, or had MetS, DM without CVD, prior CVD without DM, or with both DM and CVD, with this combination having the greatest risk, warranting such persons to be very high risk (Fig. 6.1) (Malik et al. 2004). In a systematic review and meta-analysis of 43 cohorts involving over 170,000 subjects, Gami et al. (2007) showed MetS without DM to have a relative risk of CVD events and death of 1.78 (95% CI = 1.58–2.00), with a stronger association in women and in those of lower-risk persons, and a relation that remained robust after adjustment for traditional risk factors. Others also have demonstrated a 29% greater risk of CVD events and death in those with MetS and a 68% increased risk in those with DM who also had a prior myocardial infarction (Levantesi et al. 2005).

The Framingham Heart Study long ago demonstrated that diabetes is a stronger risk factor for CVD outcomes in women compared to men. While DM 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 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) (Wilson 2001). 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 (Foley et al. 2005).

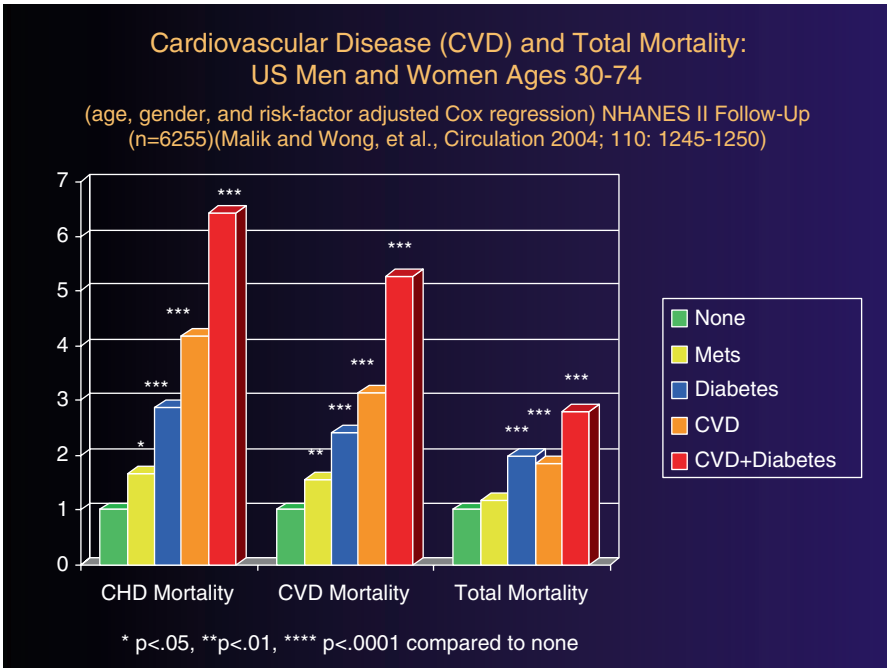

Fig. 6.1 Metabolic syndrome and diabetes in relation to CHD, CVD, and total mortality: US men and women ages 30–74. * $p < 0.05$, ** $p < 0.01$, **** <0.0001 compared to none. (Based on data from Malik et al. 2004)

Global Cardiovascular Risk Assessment in Metabolic Syndrome and Diabetes

The work of Haffner and colleagues (Haffner et al. 1998) 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 (ATP III) of the National Cholesterol Education Program in 2001, which proposed that persons with DM should be treated as aggressively for cholesterol as those with preexisting CHD (National Cholesterol Education Program (NCEP) 2002). While our study in US adults did show that 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, CHD and CVD mortality were observed to be lower among US persons with DM compared to those with prior CVD, questioning the concept of whether DM is a CHD risk equivalent for these end points (Malik et al. 2004). 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 (Bulugahapitiya et al. 2009). Moreover, we have 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) (Wong et al. 2012a) (Fig. 6.2). Most recently, Rana and colleagues showed, among a large registry of DM patients from Kaiser Permanente, that DM patients with a duration of DM of 10 years or more have a risk similar to those with preexisting CHD (Rana et al. 2016). Thus, while those with DM are

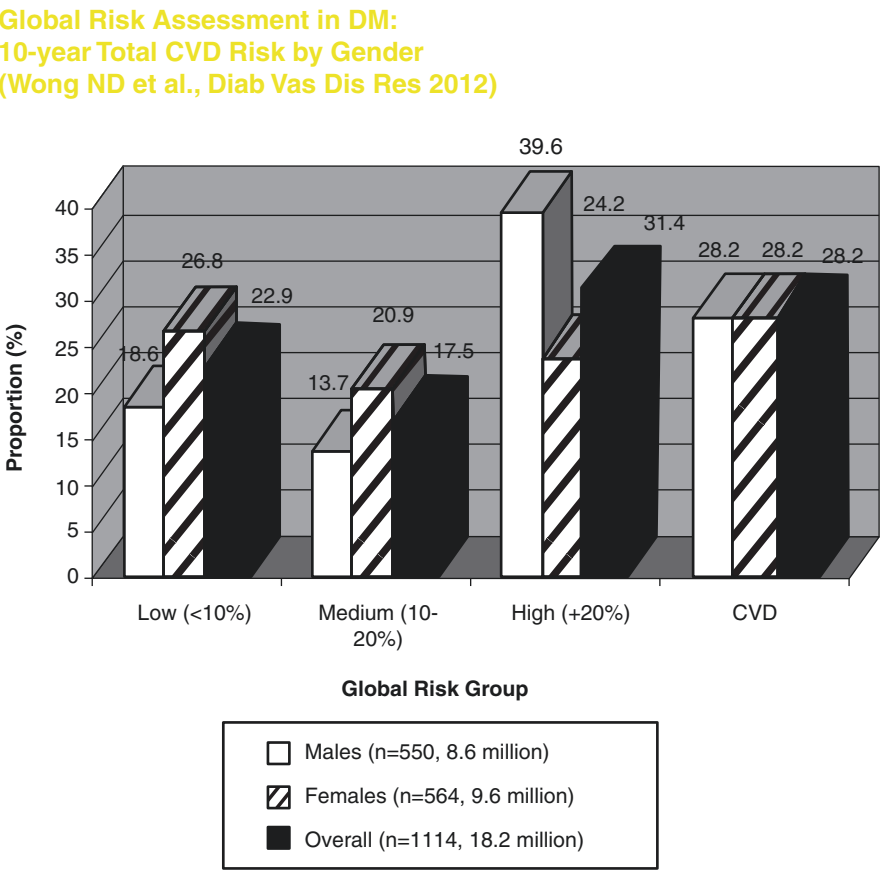

Fig. 6.2 Global risk assessment in DM by gender: 10-year total CVD risk. (Based on data from Wong et al. 2012a)

clearly at higher risk of CVD events than those without DM, some are at clearly higher risk than others, warranting the importance of quantitative risk stratification.

Global risk estimation using risk scoring is the first step in CVD risk assessment. When we examined global risk assessment in US adults in 2003–2004 with MetS utilizing the ATP III definition for MetS, we identified 38.5% of US adults (30.7% of men and 46.9% of women) to be classified as low risk (<6% 10-year risk of CHD), 8.5% (7.9% of men and 9.1% of women) to be moderate risk (6- < 10% 10-year risk), 15.8% (23.4% of men and 7.6% of women) to be at moderately high risk (10–20% 10-year risk), and 37.3% (38.0% of men and 36.5% of women) to be classified as high risk (>20% CHD risk in 10-year or with preexisting CVD) (Hoang et al. 2008). In a more recent but smaller study examining the Framingham risk score in 160 patients with MetS, the highest prevalence of MetS components was found in those classified as low risk, and systolic blood pressure and fasting glucose were the most important determinants of intermediate and high Framingham risk (Jahangiry et al. 2017).

Many traditional and more novel risk factors in persons with DM promote CHD risk. This includes elevated low-density lipoprotein cholesterol (LDL-C), low high-density lipoprotein cholesterol (HDL-C), elevated blood pressure, and elevated triglycerides. In a study of 2693 adults with DM, the UKPDS showed important predictors (of a first CVD event) to include (in order of importance) LDL-C, HDL-C, HbA1c, systolic blood pressure, and cigarette smoking (Turner et al. 1998). In addition, thrombogenic and inflammatory factors promote risk in those with DM and include C-reactive protein, intereukin-1, fibrinogen, and PAI-1, all of which are increased in DM (Biondi-Zoccai et al. 2003). We have also shown in the National Health and Nutrition Examination survey elevated hs-CRP levels to further augment the odds of CVD and peripheral arterial disease in persons with MetS and DM (Malik et al. 2005; Vu et al. 2005). Further, diet, physical activity, tobacco smoking, obesity, and excess alcohol consumption can also influence risk and nonmodifiable factors, including age, sex, and family and personal history of CVD (Pyorala et al. 1994). In the Swedish National Diabetes Register, an increased HbA1c was the strongest predictor of stroke and acute myocardial infarction, and those under age 55 years had the highest excess risk (Rawshani et al. 2018). Patients with type 1 DM are also at risk for ASCVD with HbA1c, albuminuria, duration of DM, systolic blood pressure, and LDL-C to be the strongest predictors of CVD outcomes and death (Rawshani et al. 2019). In those with DM, risk factors frequently cluster together, and among those with hypertension, hyperlipidemia, and obesity, over 35% have two of these factors and another 21% have all three (Suh et al. 2010). The MRFIT study also showed that the risk of mortality varies fourfold (from 31 to 125 per 10,000 person-years) comparing those with DM without risk factors to those who smoke and have elevated cholesterol and blood pressure (Stamler et al. 1993).

In the case of MetS, a central question has been whether its construction as a whole is more important than its parts. In a study examining its role in predicting early-onset clinical CHD, while both MetS and DM were associated with increased odds of early-onset CHD (4.9 and 8.0, respectively), these relationships were attenuated after adjusting for its components (Iribarren et al. 2006). Others show the

number of components of MetS to be important in risk prediction (Knuiman et al. 2009); for instance, while waist circumference, triglycerides, and glucose cutpoints did not predict cardiovascular disease in two large studies, all five components did (Sattar et al. 2008).

Role of Subclinical Atherosclerosis in Risk Stratification for Metabolic Syndrome and Diabetes

Given the modest predictive value of global risk assessment involving standard risk factors in risk stratification for persons with MetS and DM, there has been a significant interest in the role that evaluation of subclinical atherosclerosis, most commonly with carotid ultrasound or coronary calcium, may have in risk assessment of such persons.

In an early study, we showed that among 1823 persons who underwent screening for CAC, those with neither MetS nor DM, MetS, or DM, had a CAC prevalence of 53.5%, 58.8%, and 75.3% ($p < 0.001$), respectively. The prevalence of CAC increased directly with the number of MetS risk factors present (ranging from 34.0% to 58.3% for 0–5 present) ($p < 0.001$) and that compared to neither condition, the risk -adjusted odds for CAC being present was 1.40 (1.05–1.87) and 1.67 (1.12–2.50) in those with MetS or DM, respectively (Wong et al. 2003a). Raggi and colleagues (Raggi et al. 2004) further demonstrated a greater increase in the risk of total mortality with higher CAC scores in those with versus without DM, but that both in those with and without DM, among those with CAC scores of 0, there was a similarly excellent prognosis (long-term survival rates >98%). We further showed in the Multiethnic Study of Atherosclerosis (MESA) that both the prevalence and extent of CAC were lowest in those with neither MetS nor DM, intermediate in those with MetS, and highest in those with DM (prevalences of 45%, 55%, and 62%, respectively) with CAC scores of >400 being present in 8%, 11%, and 17% of subjects, respectively. Common and internal CIMT thicknesses were also significantly greater across these conditions (Malik et al. 2011). While we did not find CIMT continuously or in quartiles to predict CHD or CVD events independently of age, sex, and traditional risk factors, we did find a strong association of CAC with future CHD and CVD event rates in those with MetS and DM, where there was a 10-fold variation in event rates across levels of CAC (Fig. 6.3). 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. In those with MetS, CHD event rates ranged from 0.2% per year to 3.5% per year, respectively. Scores of 100 or higher were associated with event rates of approximately 2% or greater, considered to be the cutpoint for a "CHD risk equivalent." Finally, in a more recent 11-year follow-up of MESA, incident CHD continued to be strongly associated with CAC both in those with and without MetS and DM, and CAC remained importantly predictive after adjusting for diabetes duration, insulin use, and glycemic control (Malik et al. 2017). We have also described the incidence and progression of CAC in persons with MetS and DM (Wong et al.

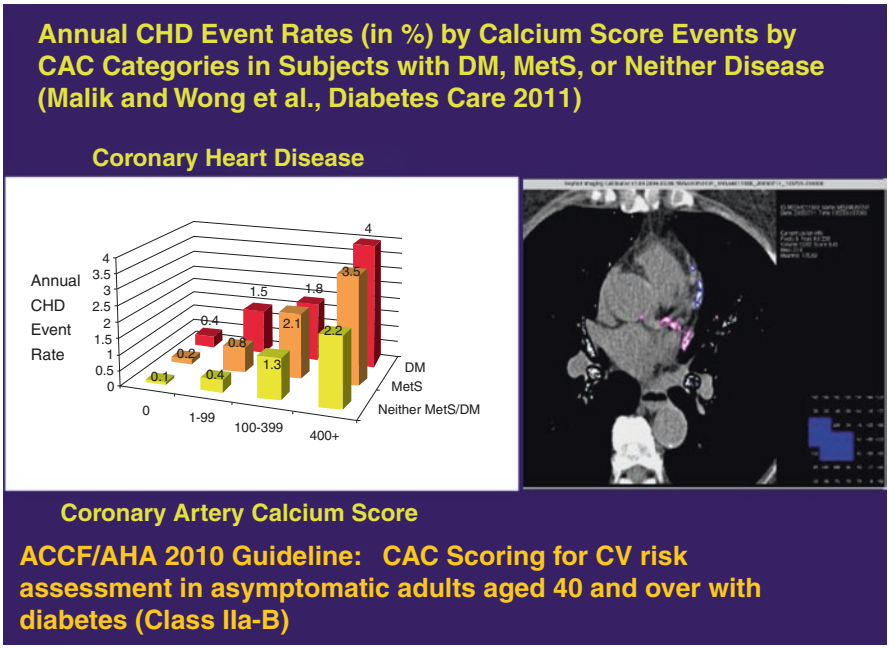

Fig. 6.3 Annual CHD event rates (in %) by calcium score events by CAC categories in subjects with DM, MetS, or neither disease (Malik et al. 2011). (Courtesy of Nathan D. Wong, PhD)

2012b), showing that relative to those with neither MetS nor DM, adjusted relative risks for incident CAC were 1.7 (95% CI: 1.4–2.0), 1.9 (95% CI: 1.4–2.4), and 1.8 (95% CI: 1.4–2.2) (all $p < 0.01$), and absolute differences in mean progression (volume score) were 7.8 (95% CI: 4.0–11.6; $p < 0.01$), 11.6 (95% CI: 2.7–20.5; $p < 0.05$), and 22.6 (95% CI: 17.2–27.9; $p < 0.01$) for those with MetS without DM, DM without MetS, and both DM and MetS, respectively. In addition, progression of CAC predicted CHD events in those with MetS without DM (adjusted hazard ratios of 4.1 [2.0–8.5]) and DM (4.9 [1.3–18.4]) among those in the highest tertile of CAC increase versus no increase. These observations demonstrate the powerful value of CAC scanning for risk stratification both in those with and without MetS and DM, importantly identifying subsets of such persons at highest risk where more aggressive risk factor modification can be recommended.

Risk Prediction Strategies in Metabolic Syndrome and Diabetes

The Adult Treatment Panel III of the National Cholesterol Education Program (National Cholesterol Education Program (NCEP) 2002) as well as the European SCORE algorithms (Conroy et al. 2003) automatically consider those with DM to

be at high risk and do not do a quantitative risk assessment, although the European Society of Cardiology guidelines for dyslipidemia management do place patients with DM into one of several high- or higher-risk categories based on the coexistence of other risk factors or CVD (Mach et al. 2020).

The more recent 2018 AHA/ACC Multisociety Guideline for Management of Blood Cholesterol (Grundy et al. 2019) includes DM as a factor in the Pooled Cohort Risk Calculator for the calculation of 10-year and lifetime ASCVD risk; however, as a binary factor, neither this risk calculator nor the earlier Framingham risk calculators considers other DM-specific factors such as HbA1c or duration of DM, which may preclude precise estimation of ASCVD risk in those with DM. Likewise for risk estimation in those with MetS, these and most other equations are limited by not including factors for waist circumference (or body mass index), glucose, or triglycerides, which are three of the major MetS factors, and thus could also lead to imprecise risk estimation in such individuals. The recent guideline, however, does consider the presence of MetS (three or more of the qualifying factors) to be a risk-enhancing factor in the treatment decision, and specifically in those with DM, the following risk-enhancing factors are indicated to be considered 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 that 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%. Thus, risk assessment in those with DM does have an important role in determining the intensity of treatment.

The recently developed Globorisk score (Ueda et al. 2017), utilizing data from eight large prospective studies, created cardiovascular risk scores for 182 countries based on recalibration from national survey data. While it did include diabetes as one of the factors, like in prior scores, it was treated as a binary factor and the authors noted there was a substantial underestimation of risk.

Based on this need for individualized risk assessment in those with DM, several CVD risk engines for patients with DM have been previously developed (Zhao and Wong 2018; Stevens et al. 2001; Yeboah et al. 2014; Parrinello et al. 2016; Basu et al. 2017; Cederholm et al. 2008; Donnan et al. 2006; Yang et al. 2008), Specifically, the UKPDS risk score (Stevens et al. 2001) (Fig. 6.4), which was derived from the large UKPDS diabetes sample, calculates the 10-year risk of fatal and nonfatal MI and stroke and includes predictors such as duration of DM, HbA1c, and even the presence of atrial fibrillation. Another diabetes risk prediction tool (Yeboah et al. 2014) incorporated newer measures, including high-sensitivity C-reactive protein and coronary calcium, showing it to outperform other risk scores. In the ARIC cohort, a DM-specific score was developed among whites and blacks estimating overall CVD, but not individual CVD end points (Parrinello et al. 2016). Also, from the ACCORD clinical trial cohort, a comprehensive risk scoring system called RECODe (Risk Equations for Complications Of type 2 Diabetes) was developed to predict both microvascular and macrovascular complications (Basu et al. 2017).

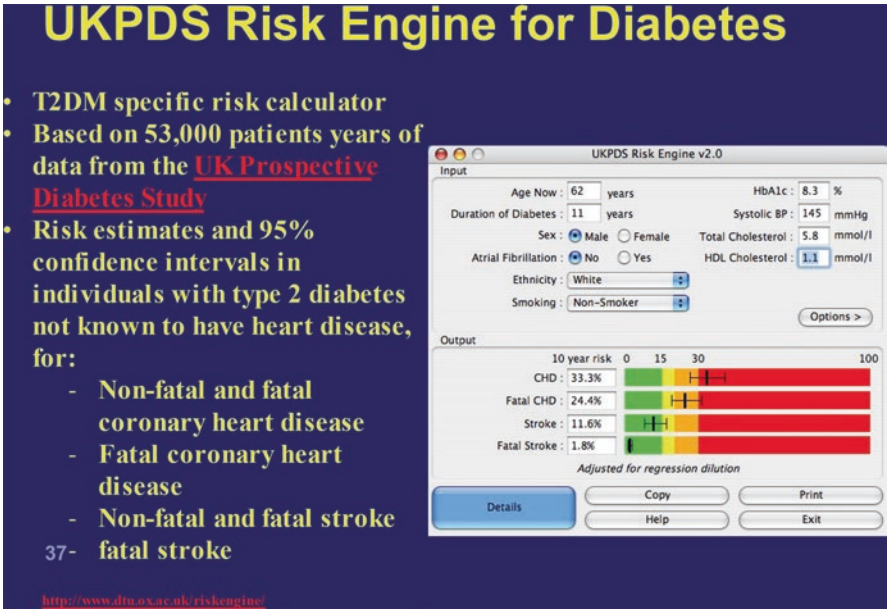

Fig. 6.4 UKPDS risk engine. T2DM-specific risk calculator. Based on 53,000 patient-years of data from the UK Prospective Diabetes Study. Risk estimates and 95% confidence intervals in individuals with type 2 diabetes not known to have heart disease. (http://www.dtu.ox.ac.uk/riskengine (Donnan et al. 2006))

However, neither of these prior scores were derived from a wide range of population-based cohorts, suggesting the need for a more inclusive multicohort risk score developed specifically in patients with DM.

Considering other important comorbidities in DM, we recently developed, from the ACCORD cohort, a 5-year risk score to predict incident atrial fibrillation (AF) using Cox regression with internal validation (Yang et al. 2020). We studied 9240 subjects with DM of which 1.8% developed AF over a median follow-up of 4.9 years. Subjects developing AF were more likely to be male, of white ethnicity and with more obesity and poorer kidney function, but with lower diastolic blood pressure and LDL-C. In the risk prediction model, age, gender, race, body mass index, heart failure, diastolic blood pressure, triglycerides, hemoglobin A1c, duration of DM, serum creatinine, and hypertension medication were included as important predictors.

Evidence for Multiple Risk Factor Control to Reduce Cardiovascular Risk in Metabolic Syndrome and Diabetes

Assessment of cardiovascular risk for persons with MetS and DM has the purpose of identifying those who can best benefit from risk factor interventions to prevent future CHD and CVD events. It is important to understand the extent of

uncontrolled risk factors in persons with MetS and DM and the evidence for the prevention of CHD and CVD events in such persons.

When examining US adults from the National Health and Nutrition Examination Survey, we identified, among those with MetS (but without DM), that among men elevations in waist circumference (81%), blood pressure (84%), triglycerides (85%), and low HDL-C (83%) were prevalent in more than 80% of subjects, followed by LDL-C ≥ 130 mg/dL (58%) and fasting glucose 100–125 mg/dL (22%) (the cut-point used the time the project was conducted). This compared to prevalences in women of 95%, 77%, 73%, 87%, 63%, and 17%, respectively. In that report, we projected that "nominal" management of lipids (LDL-C and HDL-C) and blood pressure could prevent 51% of CHD events in men and 43% in women, whereas "optimal" management could prevent 81% and 82%, respectively (Wong et al. 2003b). In a systematic review, Dunkley et al. (Dunkley et al. 2012) showed, among 16 randomized controlled trials involving 3907 participants with metabolic syndrome, that compared to controls, lifestyle (odds ratio 3.8) and pharmacological interventions (odds ratio 1.6) were superior for reversing metabolic syndrome.

Of major concern, cardiovascular risk factor control in persons with DM remains suboptimal with little improvement over the past decade. A recent report from the US Diabetes Collaborative Registry Analysis of 74,393 US adults with DM (Fan et al. 2019) showed that 74% of patients had HbA1C <7% (<8% if with ASCVD), 40% had blood pressure <130/80 mmHg, 49% had 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, a recent NHANES 2013–2016 (Andary et al. 2019) analysis from our group demonstrated that of adults with DM, 56%, 51%, and 49% were at target for HbA1c, blood pressure, and LDL-C cholesterol, respectively, but only 17% were at target for all three. When nonsmoking (84%) and BMI < 25 kg/m^2 (9%) were factored in, fewer than 10% met 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, while of limited sample size, is among the few that has examined the impact of multiple risk factor control (lipids, blood pressure, glucose, diet, exercise) on cardiovascular and mortality outcomes. The original trial of 7.8 years of follow-up showed a 53% reduction in the composite CVD end point of CVD death, myocardial infarction, stroke, revascularization, and amputation (Gaede et al. 2008), and a further 13-year follow-up report showed mortality to be 40% lower in the intensively treated group (Gæde et al. 2016), suggesting a possible legacy effect beyond the original intervention assignment from the original 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 (Bittner et al. 2015). Finally, in a pooled analysis of more than 2000 subjects with DM without CVD at baseline we conducted from the MESA, Jackson, and Atherosclerosis

Risk in Communities (ARIC) prospective studies (Wong et al. 2016), the more the number of risk factors at target, the lower the CVD and CHD event rates (Fig. 6.5). Those that had HbA1c < 7%, blood pressure <130/80 mmHg, and LDL-C < 100 mg/dl had multivariable-adjusted risks that were 62% lower for CVD events and 60% lower for CHD events, with robust findings also seen in African-Americans who comprised about half of the cohort. Taken together, these data highlight 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 current poor state of risk factor control among US adults with DM.

Conclusions

The prevalence of MetS and DM continues to increase both in the United States and worldwide, further fueling the CVD epidemic. Accurate assessment of CVD risk is warranted in these persons, beginning with global risk assessment and considering the role that additional risk enhancers, as well as assessment of subclinical atherosclerosis, can have in more accurately stratifying risk. While the most

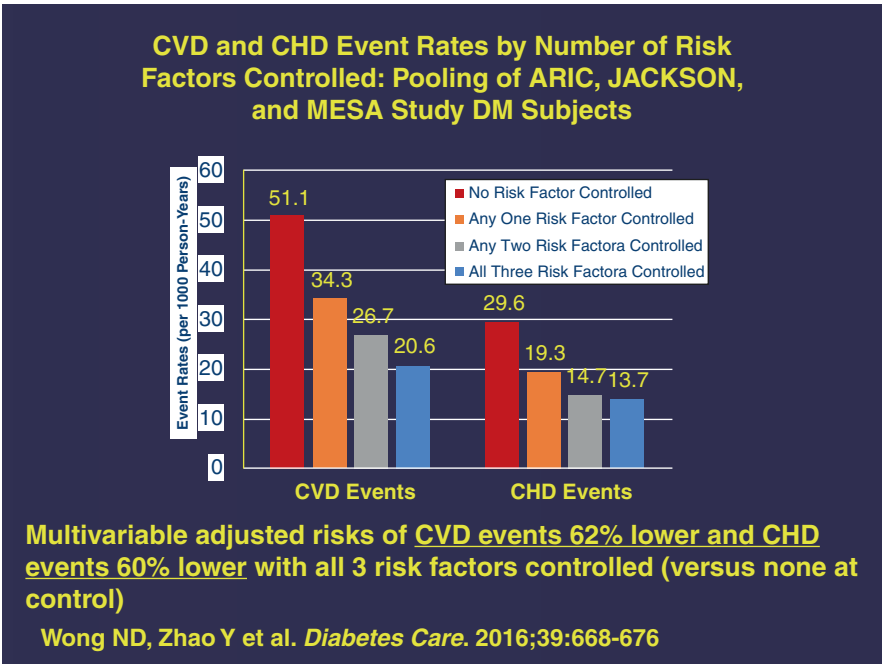

Fig. 6.5 CVD and CHD event rates by the number of risk factors at target among HbA1c, LDL-C, and blood pressure: pooling of ARIC, JACKSON, and MESA study DM subjects (Wong et al. 2016). (Courtesy of Nathan D. Wong, PhD)

aggressive risk factor intervention is warranted for those who also have preexisting CVD, many who have significant risk factors and/or substantial subclinical atherosclerosis (e.g., significant coronary calcium) may be at a similar risk compared to those with preexisting CVD. CVD risk factors remain inadequately controlled in a large proportion of those with MetS and DM, and evidence suggests that multiple risk factor control can prevent half or more of future CVD events. A coordinated multidisciplinary team of health-care providers focusing on the common goal of reducing CVD and other complications in patients with DM is essential.

References

Alberti KG, Eckel RH, Grundy SM, et al. International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120(16):1640–5.

Andary R, Fan W, Wong ND. Control of cardiovascular risk factors among US adults with type 2 diabetes with and without cardiovascular disease. Am J Cardiol. 2019;124(4):522–7.

Anselmino M, Mellbin L, Wallander M, Rydén L. Early detection and integrated management of dysglycemia in cardiovascular disease: a key factor for decreasing the likelihood of future events. Rev Cardiovasc Med. 2008;9(1):29–38.

Basu S, Sussman JB, Berkowitz SA, Hayward RA, Yudkin JS. Development and validation of Risk Equations for Complications Of type 2 Diabetes (RECODe) using individual participant data from randomised trials. Lancet Diabetes Endocrinol. 2017;5(10):788–98.

Biondi-Zoccai GG, Abbate A, Liuzzo G, Biasucci LM. Atherothrombosis, inflammation, and diabetes. J Am Coll Cardiol. 2003;41(7):1071–7.

Bittner V, Bertolet M, Barraza Felix R, et al. Comprehensive cardiovascular risk factor control improves survival: the BARI 2D trial. J Am Coll Cardiol. 2015;66(7):765–73.

Bulugahapitiya U, Siyambalapitiya S, Sithole J, Idris I. Is diabetes a coronary risk equivalent? Systematic review and meta-analysis. Diabet Med. 2009;26:142–8.

Cederholm J, Eeg-Olofsson K, Eliasson B, et al. Risk prediction of cardiovascular disease in type 2 diabetes: a risk equation from the Swedish National Diabetes Register. Diabetes Care. 2008;31(10):2038–43.

Conaway DG, O'Keefe JH. Frequency of undiagnosed and untreated diabetes mellitus in patients with acute coronary syndromes. Expert Rev Cardiovasc Ther. 2006;4(4):503–7.

Conaway DG, O'Keefe JH, Reid KJ, Spertus J. Frequency of undiagnosed diabetes mellitus in patients with acute coronary syndrome. Am J Cardiol. 2005;96(3):363–5.

Conroy RM, Pyörälä K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003;24(11):987–1003. https://doi.org/10.1016/s0195-668x(03)00114-3.

Donnan PT, Donnelly L, New JP, Morris AD. Derivation and validation of a prediction score for major coronary heart disease events in a U.K. type 2 diabetic population. Diabetes Care. 2006;29(6):1231–6.

Dunkley AJ, Charles K, Gray LJ, Camosso-Stefinovic J, Davies MJ, Khunti K. Effectiveness of interventions for reducing diabetes and cardiovascular risk in people with metabolic syndrome: systematic review and mixed treatment comparison meta-analysis. Diabetes Obes Metab. 2012;1:616–25.

Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010;375(9733):2215–22.

Fagan TC, Deedwania PC. The cardiovascular dysmetabolic syndrome. Am J Med. 1998;105(1A):77S–82S. https://doi.org/10.1016/s0002-9343(98)00216-2. PMID: 9707273.

Fan W, Song Y, Inzucchi SE, et al. Composite cardiovascular risk factor target achievement and its predictors in US adults with diabetes: the Diabetes Collaborative Registry. Diabetes Obes Metab. 2019;21(5):1121–7.

Foley RN, Murray AM, Li S, et al. Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. J Am Soc Nephrol. 2005;16(2):489–95.

Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med. 2008;358(6):580–91.

Gæde P, Oellgaard J, Carstensen B, et al. Years of life gained by multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: 21 years follow-up on the Steno-2 randomised trial. Diabetologia. 2016;59(11):2298–307.

Gami AS, Witt BJ, Howard DE, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. J Am Coll Cardiol. 2007;49:403–14.

Geiss LS, Herman WH, Smith PJ. Mortality in non-insulin-dependent diabetes. In: Diabetes in America. 2nd ed. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health; 1995:233–257. NIH Publication No. 95–1468.

Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines [published correction appears in J Am Coll Cardiol. 2019;73(24):3237–41. J Am Coll Cardiol. 2019;73(24):e285–e350.

Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med. 1998;339(4):229–34.

Hoang KC, Ghandehari H, Lopez VA, Barboza MG, Wong ND. Global coronary heart disease risk assessment of individuals with the metabolic syndrome in the US. Diabetes Care. 2008;31:1405–9.

2019 International Diabetes Federation Atlas. https://www.diabetesatlas.org/upload/resources/material/20200106_152211_IDFATLAS9e-final-web.pdf.

Iribarren C, Go AS, Husson G, et al. Metabolic syndrome and early-onset coronary artery disease: is the whole greater than its parts? J Am Coll Cardiol. 2006;8:1800–7.

Jahangiry L, Farhangi MA, Rezaei F. Framingham risk score for estimate of 10-years of cardiovascular diseases risk in patients with metabolic syndrome. J Health Popul Nutr. 2017;36:1–6.

Knuiman MW, Hung J, Divitini ML, Davis TM, Beilby JP. Utility of the metabolic syndrome and its components in the prediction of incident cardiovascular disease: a prospective cohort study. Eur J Cardiovasc Prev Rehabil. 2009;16:235–41.

Levantesi G, Macchia A, Marfisi R, et al. Metabolic syndrome and risk of cardiovascular events after myocardial infarction. J Am Coll Cardiol. 2005;6:277–83.

Mach F, Baigent C, Catapano AL, et al. ESC Scientific Document Group, 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: the task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). Eur Heart J. 2020;41(1):111–88. https://doi.org/10.1093/eurheartj/ehz455.

Malik S, Wong ND, Franklin SS, et al. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. Circulation. 2004;110(10):1245–50.

Malik S, Wong ND, Franklin S, Pio J, Fairchild C, Chen R. Cardiovascular disease in U.S. patients with metabolic syndrome, diabetes, and elevated C-reactive protein. Diabetes Care. 2005;28(3):690–3.

Malik S, Budoff MJ, Katz R, et al. Impact of subclinical atherosclerosis on cardiovascular disease events in individuals with metabolic syndrome and diabetes: the multi-ethnic study of atherosclerosis. Diabetes Care. 2011;34(10):2285–90.

Malik S, Zhao Y, Budoff M, et al. Coronary artery calcium score for long-term risk classification in individuals with type 2 diabetes and metabolic syndrome from the Multi-ethnic Study of Atherosclerosis. JAMA Cardiol. 2017;2:1332–40.

National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002;106(25):3143–421. PMID: 12485966.

Parrinello CM, Matsushita K, Woodward M, Wagenknecht LE, Coresh J, Selvin E. Risk prediction of major complications in individuals with diabetes: the Atherosclerosis Risk in Communities Study. Diabetes Obes Metab. 2016;18(9):899–906.

Pyorala K, De Backer G, Graham I, Poole-Wilson P, Wood D. Prevention of coronary heart disease in clinical practice. Recommendations of the Task Force of the European Society of Cardiology, European Atherosclerosis Society and European Society of Hypertension. Eur Heart J. 1994;15:1300–31.

Raggi P, Shaw LJ, Berman DS, Callister TQ. Prognostic value of coronary artery calcium screening in subjects with and without diabetes. J Am Coll Cardiol. 2004;43(9):1663–9.

Rana JS, Liu JY, Moffet HH, Jaffe M, Karter AJ. Diabetes and prior coronary heart disease are not necessarily risk equivalent for future coronary heart disease events. J Gen Intern Med. 2016;31(4):387–93.

Rawshani A, Rawshani A, Franzén S, et al. Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2018;379(7):633–44.

Rawshani A, Rawshani A, Sattar N, et al. Relative prognostic importance and optimal levels of risk factors for mortality and cardiovascular outcomes in type 1 diabetes mellitus. Circulation. 2019;139(16):1900–12.

Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes. 1988;37(12):1595–607. https://doi.org/10.2337/diab.37.12.1595. PMID: 3056758.

Saklayen MG. The global epidemic of the metabolic syndrome. Curr Hypertens Rep. 2018;20:12.

Sattar N, McConnachie A, Shaper AG, et al. Can metabolic syndrome usefully predict cardiovascular disease and diabetes? Outcome data from two prospective studies. Lancet. 2008;371:1927–35.

Shah AD, Langenberg C, Rapsomaniki E, et al. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1·9 million people. Lancet Diabetes Endocrinol. 2015;3(2):105–13.

Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care. 1993;16(2):434–44.

Stevens RJ, Kothari V, Adler AI, Stratton IM, United Kingdom Prospective Diabetes Study (UKPDS) Group. The UKPDS risk engine: a model for the risk of coronary heart disease in type II diabetes (UKPDS 56). Clin Sci (Lond). 2001;101(6):671–9.

Suh DC, Choi IS, Plauschinat C, Kwon J, Baron M. Impact of comorbid conditions and race/ethnicity on glycemic control among the US population with type 2 diabetes, 1988–1994 to 1999–2004. J Diabetes Complications. 2010;24(6):382–91.

Turner RC, Millns H, Neil HA, et al. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). BMJ. 1998;316(7134):823–8.

Ueda P, Woodward M, Lu Y, et al. Laboratory-based and office-based risk scores and charts to predict 10-year risk of cardiovascular disease in 182 countries: a pooled analysis of prospective cohorts and health surveys. Lancet Diabetes Endocrinol. 2017;5(3):196–213. https://doi.org/10.1016/S2213-8587(17)30015-3. Epub 2017 Jan 24. PMID: 28126460; PMCID: PMC5354360.

Vu JD, Vu JB, Pio JR, Malik S, Franklin SS, Chen RS, Wong ND. Impact of C-reactive protein on the likelihood of peripheral arterial disease in United States adults with the metabolic syndrome, diabetes mellitus, and preexisting cardiovascular disease. Am J Cardiol. 2005;96(5):655–8.

Wilson PW. Diabetes mellitus and coronary heart disease. Endocrinol Metab Clin North Am. 2001;30(4):857–81.

Wong ND, Sciammarella MG, Polk D, et al. The metabolic syndrome, diabetes, and subclinical atherosclerosis assessed by coronary calcium. J Am Coll Cardiol. 2003a;41:1547–53.

Wong ND, Pio JR, Franklin SS, L'Italien GJ, Kamath TV, Williams GR. Preventing coronary events by optimal control of blood pressure and lipids in patients with the metabolic syndrome. Am J Cardiol. 2003b;91:1421–6.

Wong ND, Glovaci D, Wong K, Malik S, Franklin SS, Wygant G, Iloeje U. Global cardiovascular disease risk assessment in United States adults with diabetes. Diab Vasc Dis Res. 2012a;9(2):146–52.

Wong ND, Nelson JC, Granston T, et al. Metabolic syndrome, diabetes, and incidence and progression of coronary calcium: the Multiethnic Study of Atherosclerosis study. JACC Cardiovasc Imaging. 2012b;5(4):358–66.

Wong ND, Zhao Y, Patel R, et al. Cardiovascular risk factor targets and cardiovascular disease event risk in diabetes: a pooling project of the Atherosclerosis Risk in Communities Study, Multi-Ethnic Study of Atherosclerosis, and Jackson Heart Study. Diabetes Care. 2016;39(5):668–76.

Yang X, So WY, Kong AP, et al. Development and validation of a total coronary heart disease risk score in type 2 diabetes mellitus. Am J Cardiol. 2008;101(5):596–601.

Yang P, Zhao Y, Wong ND. Development of a risk score for atrial fibrillation in adults with diabetes mellitus (from the ACCORD study). Am J Cardiol. 2020;125(11):1638–43.

Yeboah J, Erbel R, Delaney JC, et al. Development of a new diabetes risk prediction tool for incident coronary heart disease events: the Multi-Ethnic Study of Atherosclerosis and the Heinz Nixdorf Recall Study. Atherosclerosis. 2014;236(2):411–7.

Zhao Y, Wong ND. The evolving cardiovascular disease risk scores for persons with diabetes mellitus. Curr Cardio Rep. 2018;20(12):126.

Chapter 7
Primary Prevention: Smoking

Donna Polk

Introduction

Tobacco use is the leading preventable cause of disease and death worldwide and accounts for over 6 million deaths annually (GBD 2015 Tobacco Collaborators 2017). In the United States, over 480,000 Americans die each year due to tobacco use (Burden of Cigarette Use in the US/data and statistics-CDC n.d.). Smokers not only have higher rates of respiratory and cardiovascular disease, and cancer, it is estimated that their life span is shortened by over a decade (Jha et al. 2013). The risk of adverse cardiovascular outcomes is related to tobacco exposure, including secondhand smoke, so efforts at cessation should be a top priority for all health-care providers as should be policies aimed at reducing exposure.

While the overall percent of cigarette smokers in the United States continues to decline, there continues to be significant differences in tobacco use based on age, sex, race/ethnicity, and socioeconomic status. In addition, with the increase in the use of e-cigarettes there has been a shift toward younger users of noncombustible tobacco products such as e-cigarettes. Estimates of overall tobacco product use by US adults are 50.6 million or 20.8% of the population with cigarette users accounting for 14% of users, e-cigarette users (4.5%), cigar (3.6%), smokeless tobacco (2.4%), and pipes (1.0%) (Cornelius et al. 2019). Of the over 34 million (14%) estimated cigarette smokers in 2019, 15.3% were male and 12.7% female (Burden of Cigarette Use in the US/data and statistics-CDC n.d.). Individuals aged 18–24 years were least likely to smoke (8%), followed by adults over the age of 65 (8.2%). Over the past 15 years, there has been a greater reduction in the prevalence of smoking among Hispanics (16.2% to 8.8%) and non-Hispanic blacks (21.5% to

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14.9%). Groups where the prevalence was higher than the national average included American Indians/Alaska Natives, veterans and military service members, people living with HIV, and individuals with mental health conditions or those with disabilities. Predictors of cigarette use also included education level achieved, sexual orientation, household income, and marital status. E-cigarette users were more likely to be younger with 24.5% of users aged 18–24 and 49.3% aged 25–44 years. In 2015 when 3.5% of the US population reported e-cigarette use within the past 30 days, 11.3% of high-school students and 4.3% of middle-school students reported use during the same period (Jamal et al. 2017). While most e-cigarette users were former cigarette smokers (39.5%), 23.6% of users were never smokers and over half (56%) of those were under the age of 24, highlighting a concerning trend (Cornelius et al. 2019).

Smoking and Cardiovascular Risk

Tobacco use is a major modifiable risk factor in the development of atherosclerosis, myocardial infarction, and mortality after revascularization, and the risk of recurrent events, including death, can be reduced through smoking cessation and continued abstinence (Doll et al. 1994; Hasdai et al. 1997). Current smokers have an increased risk of myocardial infarction (OR 2.87, 95% CI 2.58–3.19) (Yusuf et al. 2004), double the risk of stroke (Thun et al. 2013), and three times the risk of premature cardiovascular death compared with those that never smoked (Thomson et al. 2020). Cardiovascular risk is higher in those using smokeless tobacco as well and highest in those that use both cigarettes and smokeless tobacco. Not surprisingly, the risk is greatest in those who began smoking at an early age. This risk, however, can be reduced significantly with smoking cessation especially prior to the age of 40 (Jha et al. 2013; Thomson et al. 2020). Smoking cessation has been associated with increased survival of up to a decade (US Department of Health and Human Services 2014).

The risk of cardiovascular morbidity and mortality because of tobacco use is evident at every level of exposure. This elevated risk appears to be dose related and is present not just in long-term high-dose smokers but is seen at all levels of cigarette use and exposure, including secondhand smoke (Law and Wald 2003). The risk of stroke is increased even with smoking a single cigarette daily (Hackshaw et al. 2018). Exposure to secondhand smoke can cause sudden infant death syndrome, respiratory and ear infections, worsen asthma, as well as coronary heart disease, stroke, and cancer in nonsmokers (US Department of Health and Human Services 2014). Secondhand smoke in nonsmokers increases the risk of heart disease [1.31 (95% CI 1.21–1.41)] and stroke [1.25 (95% CI 1.12–1.38)] (Barnoya and Glantz 2005; Oono et al. 2011). Tobacco use is also associated with a higher risk of other cardiovascular diseases, including peripheral artery disease, abdominal aortic aneurysm, arrhythmias, including atrial fibrillation and ventricular arrhythmias, as well as the risk of heart failure. Eliminating the effects of tobacco combustion decreases some

of the risks of cigarette smoking, but the hemodynamic, atherosclerotic, and metabolic effects still persist. Electronic cigarettes have been associated with increased inflammation, oxidative stress, platelet aggregation, and endothelial dysfunction, which are all associated with atherosclerotic progression (Middlekauff 2020).

Smoking cessation reduces cardiovascular morbidity and mortality in individuals with and without cardiovascular disease. In patients admitted with acute ischemic syndrome, quitting smoking was associated with an odds ratio of 0.57 (95% CI 0.36–0.89) of myocardial infarction (Chow et al. 2010). In those with left ventricular dysfunction who stopped smoking, there was a 40% reduction in all-cause mortality and a 30% reduction of death, recurrent myocardial infarction, or heart failure hospitalization (Shah et al. 2010). Even a reduction in the amount smoked can lead to improvement in outcomes with an 18% reduction in mortality post MI for every reduction of five cigarettes smoked in the long-term follow-up of post-MI patients (Gerber et al. 2009). The benefits of smoking cessation begin almost immediately with improvements in hemodynamics and platelet activation within hours to days of stopping tobacco use (US Department of Health and Human Services 2014). The cardiovascular risk associated with smoking declines over time after cessation and at 5 years is similar to the risk for nonsmokers for those with less than 20 pack-year history of smoking. It takes nearly 10–15 years for the risk to subside for heavy smokers (US Department of Health and Human Services 2014; Ahmed et al. 2015; Duncan et al. 2019). The benefit of smoking cessation is evident at all ages, with or without cardiovascular disease and with any amount of smoking. Patients should be reminded that it is never too late to benefit from smoking cessation.

Pathophysiology

Cardiovascular risk is increased by cigarette smoking via effects of both nicotine and the combustible effects of tobacco, including increased carbon monoxide, free radicals, carbonyls, reactive oxygen species, and particulate matter, as well as reduced monocyte-derived endothelial progenitor cells. This occurs with directly inhaled smoke from the primary user as well as from side stream smoke emitted from the burning tobacco product and exhaled smoke. The increased risk occurs through a variety of mechanisms, including, endothelial dysfunction, vasomotor effects, inflammatory effects, hypercoagulability and thrombosis, adverse effects on lipids and insulin resistance, as well as arrhythmogenesis (Fig. 7.1). Endothelial dysfunction is characteristic of coronary artery disease and can occur when nitrous oxide is reduced as a result of acute, chronic, or passive exposure to tobacco smoke (Kalio et al. 2010; Johnson et al. 2010). Smoking cessation can reverse this endothelial dysfunction. Acutely, cigarette smoke can cause vasospasm and subsequent cardiovascular events. Its other hemodynamic effects include increased blood pressure, heart rate, and oxygen demand. This, coupled with reduced oxygen delivery because of competing carboxyhemoglobin, can cause an oxygen supply/demand mismatch and associated symptoms such as angina.

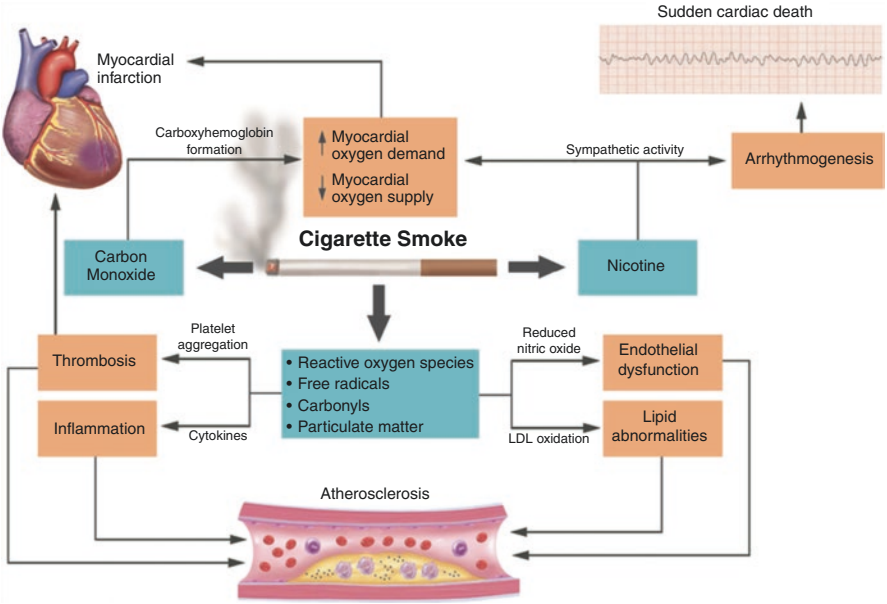

Fig. 7.1 Mechanisms by which smoking causes cardiovascular disease. The major components of cigarette smoke that contribute to cardiovascular disease include nicotine, carbon monoxide, reactive oxygen species, free radicals, carbonyls (such as acrolein), and particulate matter (Kalkhoran et al. 2018)

Exposure to cigarette smoke can cause a reduction in the thrombolytic ability during an acute coronary event. This occurs as platelets become activated and exhibit increased aggregation, fibrinogen levels increase, and endothelial cells produce less tissue plasminogen activator and plasminogen activator inhibitor-1 and therefore alter the thrombotic/lytic balance, thus increasing the risk of acute ischemic events. Active cigarette exposure increases the risk of stent thrombosis post-percutaneous coronary intervention (Hasdai et al. 1997; Haddock et al. 2003; Chen et al. 2012). Inflammation also plays a key role in the increased cardiovascular risk associated with tobacco use. Measured levels of inflammatory markers such as C-reactive protein, tumor necrosis factor, and interleukin-6 and 1β (Barbieri et al. 2011; Jefferis et al. 2010; Asthana et al. 2010) are seen in smokers and those exposed to secondhand smoke.

Cardiometabolic changes occur with tobacco use and include detrimental effects on lipids, including increasing low-density lipoprotein (LDL), triglyceride levels, and decreasing high-density lipoprotein levels (Gepner et al. 2011). Smoking causes proatherogenic changes in LDL, resulting in increased oxidized particles that are more likely to be incorporated into plaque. Smoking cessation can improve these measures, in particular improving HDL levels.

Smoking Cessation

Smoking cessation leads to decreased morbidity and mortality of a variety of smoking-related illnesses, including cardiovascular disease. Most smokers (69%) want to quit tobacco use, and many have attempted at least once to stop smoking, more than half within the past year (Babb et al. 2017). Many smokers make many attempts to quit, and ultimately many are able to quit with an estimated 60% of US smokers who have ever smoked are able to quit (Jamal et al. 2018). Smoking cessation efforts should include an understanding of the smoker's interest and willingness to quit, knowledge of the methods including behavioral and pharmacologic to assist quitting, as well as an understanding of the barriers to quitting and staying quit. Individuals who smoke must be ready to quit, and identification of their readiness to quit is critical in assisting with a successful quit attempt. Prochaska's Stages of Change theory gives a framework for understanding the challenges of smoking cessation. There are five stages of change: precontemplation, contemplation, preparation, action, and maintenance (Prochaska et al. 1992). Smokers who are in the precontemplation stage are not likely to quit in the next six months, and thus provides the health-care provider an opportunity to provide additional information to help move them to precontemplation. Each subsequent encounter provides an additional opportunity to help them toward the action stage. Those at the contemplation stage have been thinking about quitting within the next six months, so time spent focusing on specific motivators, goals, as well as resources can help these smokers move to action. Those at the preparation stage have often tried to quit within the last year and are actively thinking about quitting. They may have changed their behavior and have cut down on the amount they are smoking. If not, they may be receptive to this as a tool to help move them toward the action stage. Those at the action stage can set a quit date, discuss barriers to quit, and how to solve them or preempt them such as making the house smoke free, as well as access tools such as pharmacological therapy, to aid in their quit attempt. It is important to understand the challenges and barriers for the smoker to help them have a plan to succeed. For example, if the house has other smokers, banning smoking in the living space can help the smoker quit and stay quit. For those who have quit before, asking why they restarted can be helpful for them to identify the triggers and anticipate them to improve their chances of success and avoid relapse. Assessing smoking status and assisting with cessation is the key to successful cessation. This includes asking about smoking and documenting this at each health-care visit.

Despite the increased advice to quit smoking from health professionals, only four out of nine adult smokers who saw a health professional in the past year were advised to quit smoking (US Department of Health and Human Services 2014). Even fewer were provided the tools, including medication or counseling, to assist them in quitting. Even brief advice to quit is important, but the stronger the advice to quit smoking, the more likely smokers are to quit. The USPSTF recommends using the 5A to assist smokers (Fig. 7.2). Health-care providers should ask, advise, assess, assist, and arrange for follow-up to assist smokers in their efforts to quit

tobacco use. Directly asking about smoking at each encounter will help identify active tobacco users. Spending time advising to quit and assessing the willingness to quit are the next steps. Advising to quit and providing resources such as behavioral and pharmacological and resources like quit lines should be the next step. Advice that is directed at the individual's own risks and discussion of the benefits of quitting can help motivate individuals to quit. Assessing dependence on tobacco, in addition to willingness to quit, is the next important step. Those that use tobacco daily and are heavier tobacco users will benefit from pharmacological therapy. Assessing tobacco dependence such as nicotine dependence can help predict success and allow for early follow-up for those at an increased risk of recidivism. Those that have the highest nicotine dependence are characterized by smoking soon after awakening in the morning higher cigarette use. Assisting the quit attempt and arranging follow-up keeping smokers accountable can assist with successful quit efforts. If smokers are not ready to quit, then utilizing the 5R approach can be helpful to move them toward being ready to quit. These include relevance, risks, rewards, roadblocks, and repetition to help motivate the smoker to quit (Fig. 7.3).

1. **Ask** - Identify and document tobacco use status for every patient at every visit. (You may wish to develop your own vital signs sticker, based on the sample below).
2. **Advise** - In a clear, strong, and personalized manner, urge every tobacco user to quit.
3. **Assess** - Is the tobacco user willing to make a quit attempt at this time?
4. **Assist** - For the patient willing to make a quit attempt, use counseling and pharmacotherapy to help him or her quit. (See Counseling Patients To Quit and pharmacotherapy information in this packet).
5. **Arrange** - Schedule followup contact, in person or by telephone, preferably within the first week after the quit date.

Fig. 7.2 The 5 As of smoking cessation. (www.ahrq.gov/sites/default/files/wysiwyg/professionals/clinicians-providers/guidelines-recommendations/tobacco/5steps.pdf). https://www.ahrq.gov/

1. **Relevance** - Encourage the patient to indicate why quitting is personally relevant.
2. **Risks** - Ask the patient to identify potential negative consequences of tobacco use.
3. **Rewards** - Ask the patient to identify potential benefits of stopping tobacco use.
4. **Roadblocks** - Ask the patient to identify barriers or impediments to quitting.
5. **Repetition** - The motivational intervention should be repeated every time an unmotivated patient has an interaction with a clinician. Tobacco users who have failed in previous quit attempts should be told that most people make repeated quit attempts before they are successful.

Fig. 7.3 The 5 R's of smoking cessation (https://www.ahrq.gov/sites/default/files/wysiwyg/professionals/clinicians-providers/guidelines-recommendations/tobacco/5rs.pdf). https://www.ahrq.gov/

Behavioral Interventions

Behavioral Interventions include cognitive therapy, motivational interviewing, acceptance and commitment therapy, and contingency management and monetary incentives (US Department of Health and Human Services 2014), and effectiveness is often dose dependent and can be enhanced with pharmacological therapies. Those that are in the contemplation or planning stages should be targeted for intervention. Understanding the barriers to quitting and staying quit is instrumental in helping smokers quit. Brief (less than 20 minute) sessions can improve quit rates, and more intensive interventions such as greater than 20-minute sessions with additional follow-up further increase quit rates at 6 months (Patnode et al. 2021; Black et al. 2020). In a meta-analysis, interventions delivered by a person were more effective than written interventions (Black et al. 2020). A Cochrane review of behavioral interventions found that telephone counseling, group counseling, and individually delivered smoking cessation counseling improved quit rates compared to usual care (Hartmann-Boyce et al. 2021). The success of interventions such as telephone counseling is enhanced in a dose-dependent manner (Matkin et al. 2019). In a Cochrane Systematic Review, there was the strongest evidence for any type of counseling and guaranteed financial incentives (Hartmann-Boyce et al. 2019). More modest evidence and need for further study were noted for automated text messages-based support, text messaging, email, delivery by lay health advisor, and tailored Internet-based interventions to improve quit rates (Hartmann-Boyce et al. 2019). The use of incentives improves long-term quit rates even after the incentive has ended, including in pregnant women (Notley et al. 2019). The addition of exercise to smoking cessation support and hypnotherapy did not appear to improve quit rates. Interventions such as gamification via mobile applications have improved the motivation to quit (Rajani et al. 2021). Initial small studies have yielded heterogeneous results, and overall meta-analysis suggests that mobile applications may not be as effective a tool in general for smoking cessation (Cobos-Campos et al. 2020). However, in those aged 18–24, personalized test message interventions, sustained quit-and-win contests, and multiple behavior interventions such as for tobacco and alcohol were most effective (Villanti et al. 2020). Several studies are ongoing and will add to the current literature.

Expanding opportunities for health behavior change, including smoking cessation, through technology and mobile-based interventions is an additional resource for smokers that can improve quit rates and can be used in combination with other interventions such as pharmacological therapy. Quit rates can be enhanced by an additional 10–20% with the addition of behavioral support to pharmacological therapies (Hartmann-Boyce et al. 2019).

Pharmacological Therapies

Nicotine Replacement

Nicotine replacement has long been the foundation of smoking cessation interventions. It comes in a variety of formulations, including gum, patches, lozenges, nasal spray, and inhalers (Table 7.1). Nicotine acts centrally on the nicotinic cholinergic receptors within the brain in 2–8 seconds from inhalation. In addition to the sympathomimetic effects of nicotine that result in the release of catecholamines that affect the cardiovascular system, including heart rate and blood pressure, nicotine causes the release of neurotransmitters, including dopamine, serotonin, and γ-aminobutyric acid (GABA). This quick activation of central nicotine receptors contributes to the addictive nature of nicotine. Withdrawal symptoms include irritability, restlessness, changes in mood, insomnia difficulty concentrating, and weight gain. Nicotine replacement therapy should be used with caution in individuals with recent (less than 2 weeks) myocardial infarction, angina, serious arrhythmia, or those who are pregnant or breastfeeding. Nicotine replacement therapies such as transdermal patches provide a lower level of nicotine to help mitigate withdrawal symptoms. The use of two forms of nicotine replacement therapy such as a basal amount from a patch in conjunction with scheduled and breakthrough gum, for example, can increase quit rates over each one individually.

Nicotine patches are available in escalating doses and take 6–8 hours to reach steady state. The highest doses should be used for the heaviest smokers to prevent withdrawal symptoms. Most formulations should be removed at bedtime to prevent side effects such as insomnia and vivid dreams. Faster peak concentrations

Table 7.1 Highlights of recommended pharmacotherapy tobacco treatment

Treatment	Dosing		Precautions
NRT			
Patch	21 mg, 14 mg, or 7 mg	Starting dose: 21 mg for ≥10 CPD; 14 mg for <10 CPD	Local irritation possible; avoid with skin disorders; may remove for sleep if needed
Gum	2 mg or 4 mg	Starting dose: 4 mg if first tobacco use is ≤30 min after waking; 2 mg if first tobacco use is >30 min after waking; maximum of 20 lozenges or 24 pieces of gum/day Chew and park gum	Hiccups/dyspepsia possible; avoid food or beverages 15 min before and after use
Lozenge	2 mg or 4 mg		
Nasal spray	10 mg/mL	Starting dose: 1–2 doses/h (1 dose = 1 spray each nostril); maximum of 40 doses/day	Local irritation possible; avoid with nasal or reactive airway disorders
Oral inhaler	10-mg cartridge	Starting dose: puff for 20 min/cartridge every 1–2 h; maximum 16 cartridges/day	Cough possible; avoid with reactive airway disorders

Modified (Arnett et al. 2019)

(20–60 minutes) can be achieved with gum, lozenges, or an oral inhaler. It is important to instruct patients regarding the proper use of nicotine replacement gum. It should be chewed for a few seconds until they feel tingling, then put the gum in their cheek and every few minutes chewed for a few seconds. Chew traditional gum and can therefore develop side effects that cause them to discontinue its use such as jaw discomfort, headache and nausea. Lozenges should be allowed to dissolve for 20–30 minutes and should not be chewed. This can cause dyspepsia. Each of these formulations comes in escalating doses, and higher doses should be used in the heaviest tobacco users. To improve quit rates, nicotine replacement regardless of the form should be scheduled several times per day. The quickest onset and the one most similar to smoking a cigarette is the nasal spray, which has its peak serum concentration in 4–15 minutes. Because of this, it can be the most addicting. There is also an oral inhaler that is available and comes with removable cartridges that can be puffed for about 20 minutes. The maximum dose is 16 cartridges per day. Those with reactive airways disease should avoid both the inhaler and nasal spray. In general, all forms of nicotine replacement therapy increase quit rates over placebo by 50–60% (Kalkhoran et al. 2018; Lindson et al. 2019) and as much as an additional 36% increase with the use of long-acting patch plus short-acting nicotine replacement (Arnett et al. 2019).

Electronic cigarettes (ECs) can be effective for smoking cessation as compared to placebo and have similar quit rates to nicotine replacement therapy. A meta-analysis of the effectiveness of electronic cigarettes in smoking cessation found that pooled evidence showed trend for potential of EC's as smoking cessation tool but given the quality of the data could not make conclusive recommendation (Grabovac et al. 2021). Currently, there is no long-term data regarding the long-term effects of electronic cigarettes, and the USPSTF has concluded that there is insufficient evidence of their use as a smoking cessation tool in adults.

Bupropion

Bupropion, a monocyclic antidepressant, had been effective in smoking cessation. It works centrally by partial nicotinic receptor-blocking activity and by inhibiting dopamine reuptake. It should be started 7–14 days prior to the quit date. The initial dose is 150 mg extended release daily for 3 days, and then the dose should be increased to twice daily for a 12-week course but may be extended for up to 6 months. Because of the increased risk of seizure, it should not be used in those with a history of seizure, stroke, severe brain injury, brain tumor; in individuals with anorexia nervosa or bulimia; or in those who use other medications that can lower the seizure threshold. It should be used with caution with class 1C antiarrhythmics, antidepressants, antipsychotics, and beta-blockers that utilize the CYP2D6 enzyme. It is contraindicated in patients on monoamine oxidase inhibitors. Side effects include insomnia, dry mouth, headache, anxiety, and nausea. The use of sustained release bupropion can increase quit rates significantly over nicotine patch at

12 months (30.3% vs. 16.4%), and the quit rate was further enhanced with the combination of bupropion and nicotine patch (35.5%) (Jorenby et al. 1999).

Varenicline

Varenicline works centrally as a partial agonist for α4β2 nicotinic acetylcholine receptor subtypes where its agonist activity increases the release of dopamine and its binding blocks nicotine. Combination of actions on these receptors work centrally to reduce cravings and withdrawal symptoms and in those that choose to smoke, reduce the immediate pleasure associated with smoking a cigarette. It is first-line therapy for smoking cessation but should be used in lower doses in those with renal disease or who are on dialysis. Varenicline should be started at least 7 days prior to the quit date. The initial dose is 0.5 mg daily for 3 days, and then twice daily for four additional days. The maintenance dose is 1 mg twice daily for up to 6 months. Side effects include vivid dreams and nausea. In a more recent review of patients taking varenicline, there has been no increased risk of cardiovascular or neuropsychiatric events as compared to bupropion or nicotine replacement therapy (Anthenelli et al. 2019). Varenicline is more effective than placebo and bupropion and as effective as a combination nicotine replacement therapy; therefore, varenicline and combination nicotine replacement therapy are considered first line for smokers (Cahill et al. 2013; Mills et al. 2012).

Second-Line Therapies

Clonidine and nortriptyline are second-line agents for those who have contraindications or cannot tolerate bupropion or varenicline. Clonidine is a selective alpha-adrenergic receptor agonist with central nervous system effects. Traditionally used as an antihypertensive, it has been more recently used to minimize the side effects of withdrawal. Nortriptyline is a tricyclic antidepressant that has been used in smoking cessation. It was shown to be superior to placebo but did not increase quit rates when used in conjunction with nicotine replacement therapy. There are several therapies that have the potential for expanding the tools available to help patients quit smoking. Cystine is available in Europe and is a partial agonist for the alpha 4 beta2 subtype of the nicotinic acetylcholine receptor. Additional potential future medications include N-acetylcysteine, acetylcholinesterase inhibitors, and baclofen, which works centrally at the GABA receptors.

Opportunities for Intervention

Identifying tobacco users at every interaction with the health-care system is critical in promoting the cessation of tobacco use. Figure 7.4 shows a pathway for tobacco cessation treatment that provides decision points for initial engagement with

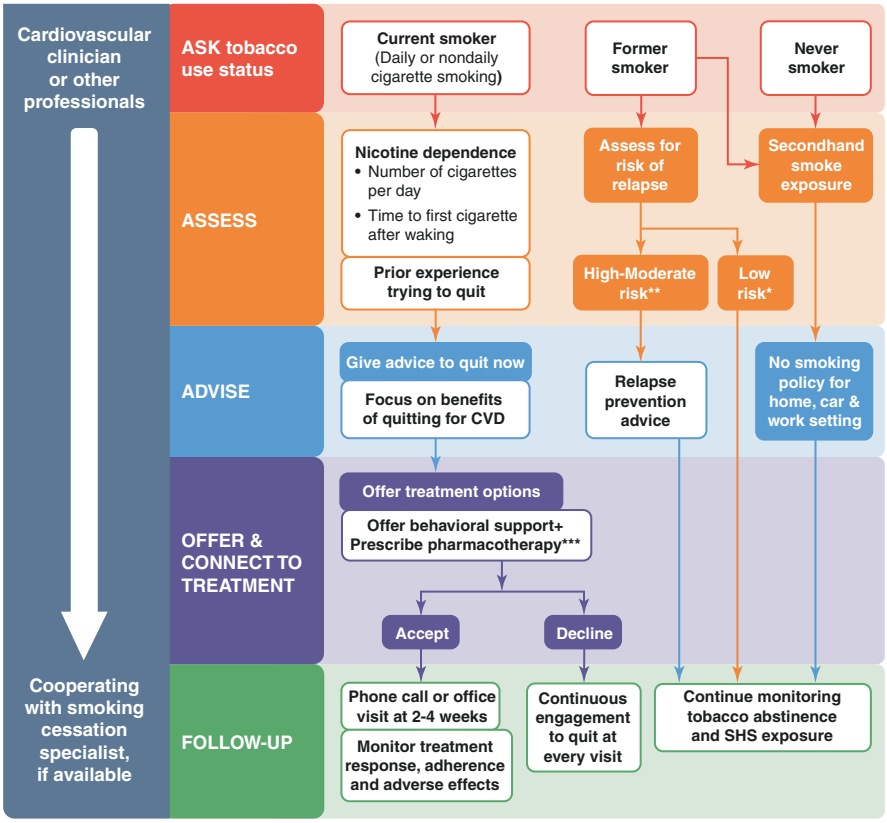

Fig. 7.4 Pathway for tobacco cessation (Barua et al. 2018)

smoking cessation to relapse prevention and the reduction of exposure to secondhand smoke to reduce the burden of cardiovascular disease attributable to tobacco use and exposure. It highlights the importance of continuous engagement to promote tobacco cessation. System changes are important for identifying smokers and providing them with the resources available to quit tobacco use. In the outpatient setting, including tobacco and nicotine use as one of the vital signs has been shown to improve cessation. Identifying smokers at the time of hospitalization and providing post-discharge strategies for smoking cessation can increase quit rates when coupled with outpatient follow-up (26% vs. 15% at 6 months) (Reid et al. 2015). Cardiac rehabilitation offers a unique setting for smoking cessation interventions, and in a meta-analysis 53% of cardiac rehabilitation participants were successful in smoking cessation (Sadeghi et al. 2015). Those programs that provided a comprehensive intervention, including exercise, education, and targeted smoking cessation,

had the highest quit rates. With the high rate of relapse, a multipronged approach that includes policies that promote cessation, systemic identification of smokers, as well as varied treatment options to help smokers quit and stay smoke free, is needed.

References

Ahmed AA, Patel K, Nyaku MA, Kheirbek RE, Bittner V, et al. Risk of heart failure and death after prolonged smoking cessation: role of amount and duration of prior smoking. Circ Heart Fail. 2015;8(4):694–701.

Anthenelli RM, Gaffney M, Benowitz NL, West R, McRae T, Russ C, Lawrence D, St Aubin L, Krishen A, Evins AE. Predictors of neuropsychiatric adverse events with smoking cessation medications in the randomized controlled EAGLES trial. J Gen Intern Med. 2019;34(6):862–70.

Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, Michos ED, Miedema MD, Muñoz D, Smith SC Jr, Virani SS, Williams KA Sr, Yeboah J, Ziaeian B. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Circulation. 2019;140(11):e596–646. https://doi.org/10.1161/CIR.0000000000000678. Epub 2019 Mar 17. Erratum in: Circulation. 2019;140(11):e649–e650. Erratum in: Circulation. 2020;141(4):e60. Erratum in: Circulation. 2020 Apr 21;141(16):e774. PMID: 30879355; PMCID: PMC7734661.

Asthana A, Johnson HM, Piper ME, Fiore MC, Baker TB, et al. Effects of smoking intensity ad cessation on inflammatory markers in a larger cohort of active smokers. Am Heart J. 2010;160:458–63.

Babb S, Malarcher A, Schauer G, Asman K, Jamal A. Quitting smoking among adults—United States, 2000–2015. Morb Mortal Wkly Rep. 2017;65(52):1457–64.

Barbieri SS, Zacchi E, Amadio P, Gianellini S, Mussoni L, Weksler BB, Tremoli E. Cytokines present in smokers' serum interact with smoke components to enhance endothelial dysfunction. Cardiovasc Res. 2011;90(3):475–83.

Barnoya J, Glantz SA. Cardiovascular effects of secondhand smoke: nearly as large as smoking. Circulation. 2005;111:2684–98.

Barua RS, Rigotti NA, Benowitz NL, Cummings KM, Jazayeri MA, Morris PB, Ratchford EV, Sarna L, Stecker EC, Wiggins BS. 2018 ACC expert consensus decision pathway on tobacco cessation treatment: a report of the American College of Cardiology task force on clinical expert consensus documents. J Am Coll Cardiol. 2018;72(25):3332–65. https://doi.org/10.1016/j.jacc.2018.10.027.

Black N, Johnston M, Michie S, Hartmann-Boyce J, et al. Behaviour change techniques associated with smoking cessation in intervention and comparator groups of randomized controlled trials: a systemic review and meta-regression. Addiction. 2020;115:2008–20.

Burden of Cigarette Use in the US/data and statistics-CDC. https://www.cdc.gov › tobacco › data_statistics.

Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database Syst Rev. 2013;2013(5):CD009329. https://doi.org/10.1002/14651858.CD009329.pub2. PMID: 23728690; PMCID: PMC8406789.

Chen T, Li W, Wang Y, Xu B, Guo J. Smoking status on outcomes after percutaneous coronary intervention. Clin Cardiol. 2012;35(9):570–4.

Chow CK, Jolly S, Rao-Melachini P, Fox KA, Arand SS, et al. Associate of diet, exercise, and smoking modification with risk of early cardiovascular events after acute coronary syndromes. Circulation. 2010;121:750–8.

Cobos-Campos R, de Lafuente AS, Apiñaniz A, Parraza N, Llanos IP, Orive G. Effectiveness of mobile applications to quit smoking: systematic review and meta-analysis. Tob Prev Cessat. 2020;6:62.

Cornelius ME, Wang TW, Jamal A, Loretan CG, Neff LJ. Tobacco product use among adults-United States, 2019. MMWR Morb Mortal Wkly Rep. 2019;69:1736–42.

Doll R, Peto R, Wheatley K, Gray R, Sutherland I. Mortality in relation to smoking: 40 years' observations on male British doctors. BMJ. 1994;309:901–11.

Duncan MS, Freiberg MS, Greevy RA Jr, Kundu S, Vasan RS, Tindle HA. Association of smoking cessation with subsequent risk of cardiovascular disease. JAMA. 2019;322(7):642–50.

GBD 2015 Tobacco Collaborators. Smoking prevalence and attributable disease burden in 195 countries and territories, 1990–2015; a systemic analysis from the Global Burden of Disease Study 2015. Lancet. 2017;389:1885–906.

Gepner AD, Piper ME, Johnson HM, Fiore MC, Baker TB, Stein JH. Effects of smoking and smoking cessation on lipids and lipoproteins: outcomes from a randomized clinical trial. Am Heart J. 2011;161(1):145–51.

Gerber Y, Rosen LJ, Goulbourt U, Benyamini Y, Drory Y, Israel Study Group on First Acute Myocardial Infarction. Smoking status and long-term survival after first acute myocardial infarction a population-based cohort study. J Am Coll Cardiol. 2009;54(25):2382–7.

Grabovac I, Oberndorfer M, Fischer J, Wiesinger W, Haider S, Dorner TE. Effectiveness of electronic cigarettes in smoking cessation: a systematic review and meta-analysis. Nicotine Tob Res. 2021;23(4):625–34.

Hackshaw A, Morris JK, Boniface S, Tang JL, Milenkovic D. Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports. BMJ. 2018;360:j5855.

Haddock CK, Poston WS, Taylor JE, Conard M, Spertus J. Smoking and health outcomes after percutaneous coronary intervention. Am Heart J. 2003;145(4):652–7.

Hartmann-Boyce J, Hong B, Livingstone-Banks J, Wheat H, Fanshawe TR. Additional behavioural support as an adjunct to pharmacotherapy for smoking cessation. Cochrane Database Syst Rev. 2019;6(6):CD009670. https://doi.org/10.1002/14651858.CD009670.pub4.

Hartmann-Boyce J, Livingstone-Banks J, Ordóñez-Mena JM, Fanshawe TR, Lindson N, Freeman SC, Sutton AJ, Theodoulou A, Aveyard P. Behavioural interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database Syst Rev. 2021;1:CD013229. https://doi.org/10.1002/14651858.CD013229.pub2.

Hasdai D, Garratt KN, Grill DE, Lerman A, Holmes DR Jr. Effect of smoking status on the long-term outcomes after successful percutaneous coronary revascularization. NEJM. 1997;336:755–61.

https://www.ahrq.gov/sites/default/files/wysiwyg/professionals/clinicians-providers/guidelines-recommendations/tobacco/5rs.pdf.

Jamal A, Gentzke A, Hu SS, Cullen KA, Apelberg BJ, et al. Tobacco use among middle and high school students – United States, 2011–2016. MMWR Morb Mortal Wkly Rep. 2017;66:597–603.

Jamal A, Phillips E, Gentzke AS, Homa DM, Babb SD, King BA, Neff LJ. Current cigarette smoking among adults—United States, 2016. Morb Mortal Wkly Rep. 2018;67(2):53.

Jefferis BJ, Lowe GD, Welsh P, Rumley A, Lawlor DA, Ebrahim S, Carson C, Doig M, Feyerabend C, McMeekin L, Wannamethee SG. Secondhand smoke (SHS) exposure is associated with circulating markers of inflammation and endothelial function in adult men and women. Atherosclerosis. 2010;208(2):550–6.

Jha P, Ramasundarahettige C, Landsman V, Rostron B, Thun M, et al. 21st-century hazards of smoking and benefits of cessation in the United States. N Engl J Med. 2013;368:341–50.

Johnson HM, Gossett LK, Piper ME, Aeschlimann SE, Korcarz CE, et al. Effects of smoking and smoking cessation on endothelial function: 1-year outcomes from a randomized clinical trial. J Am Coll Cardiol. 2010;55(18):1988–95.

Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hughes AR, Smith SS, Muramoto ML, Daughton DM, Doan K, Fiore MC, Baker TB. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. N Engl J Med. 1999;340(9):685–91.

Kalio K, Jokinen E, Saarien M, Hamalainen M, Volanen I, et al. Arterial intima-media thickness, endothelial function, and apolipoproteins in adolescents frequently exposed to tobacco smoke. Circ Cardiovasc Qual Outcomes. 2010;3:196–203.

Kalkhoran S, Benowitz NL, Rigotti NA. Prevention and treatment of tobacco use: JACC health promotion series. JACC. 2018;72:1030–45.

Law MR, Wald NJ. Environmental tobacco smoke and ischemic heart disease. Prog Cardiovasc Dis. 2003;46:31–8.

Lindson N, Chepkin SC, Ye W, Fanshawe TR, Bullen C, Hartmann-Boyce J. Different doses, durations and modes of delivery of nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev. 2019;4(4):CD013308.

Matkin W, Ordóñez-Mena JM, Hartmann-Boyce J. Telephone counselling for smoking cessation. Cochrane Database Syst Rev. 2019;5(5):CD002850. https://doi.org/10.1002/14651858.CD002850.pub4.

Middlekauff HR. Cardiovascular impact of electronic-cigarette use. Trends Cardiovasc Med. 2020;30(3):133–40.

Mills EJ, Wu P, Lockhart I, Thorlund K, Puhan M, Ebbert JO. Comparisons of high-dose and combination nicotine replacement therapy, varenicline, and bupropion for smoking cessation: a systematic review and multiple treatment meta-analysis. Ann Med. 2012;44(6):588–97.

Notley C, Gentry S, Livingstone-Banks J, Bauld L, Perera R, Hartmann-Boyce J. Incentives for smoking cessation. Cochrane Database Syst Rev. 2019;7(7):CD004307. https://doi.org/10.1002/14651858.CD004307.pub6. PMID: 31313293; PMCID: PMC6635501.

Oono IP, Mackay DF, Pell JP. Meta-analysis of the association between secondhand smoke exposure and stroke. J Public Health. 2011;33:496–502.

Patnode CD, Henderson JT, Melnikow J, et al. Interventions for tobacco cessation in adults, including pregnant women: an evidence update for the U.S. Preventive Services Task Force [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2021 Jan. (Evidence Synthesis, No. 196.) Chapter 2, Methods. Available from: https://www.ncbi.nlm.nih.gov/books/NBK567061/.

Prochaska JO, DiClemente CC, Norcross JC. In search of how people change. Applications to addictive behaviors. Am Psychol. 1992;47(9):1102–14.

Rajani NB, Mastellos N, Filippidis FT. Impact of gamification on the self-efficacy and motivation to quit of smokers: observational study of two gamified smoking cessation mobile apps. JMIR Serious Games. 2021;9(2):e27290.

Reid ZZ, Regan S, Kelley JH, Streck JM, Ylioja T, Tindle HA, Chang Y, Levy DE, Park ER, Singer DE, Carpenter KM. Comparative effectiveness of post-discharge strategies for hospitalized smokers: study protocol for the Helping HAND 2 randomized controlled trial. BMC Public Health. 2015;15(1):1–2.

Sadeghi R, Mokhber N, Mahmoudi LZ, Asgharipour N, Seyfi H. A systematic review and meta-analysis on controlled treatment trials of metacognitive therapy for anxiety disorders. J Res Med Sci. 2015;20(9):901–9.

Shah AM, Pfeffer MA, Hartley LH, Moye LA, Gersh BJ, et al. Risk of all-cause of all-cause mortality, recurrent myocardial infarction, and heart failure hospitalization associated with smoking status following myocardial infarction with left ventricular dysfunction. Am J Cardiol. 2010;106(7):911–6.

Thomson G, Eberson J, Lacey B, Peto R, Woodward M, et al. Childhood smoking ,adult cessation, and cardiovascular mortality: prospective study of 390,000 US adults. J Am Heart Assoc. 2020;9(21):e018431. https://doi.org/10.1161/JAHA.120.018431. Epub 2020 Oct 28. PMID: 33108954; PMCID: PMC7763404.

Thun MJ, Carter BD, Feskanich D, Freedman ND, Prentice R, et al. 50- year trends in smoking related mortality in the United States. NEJM. 2013;368:351–64.

US Department of Health and Human Services. The health consequences of smoking-50 years of progress: a report of the surgeon general. US 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.

Villanti AC, West JC, Klemperer EM, Graham AL, Mays D, Mermelstein RJ, Higgins ST. Smoking-cessation interventions for U.S. young adults: updated systematic review. Am J Prev Med. 2020;59(1):123–36.

www.ahrq.gov/sites/default/files/wysiwyg/professionals/clinicians-providers/guidelines-recommendations/tobacco/5steps.pdf https://www.ahrq.gov/.

Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study) case-control study. Lancet. 2004;364:937–52.

Chapter 8
At the Heart of the Matter: Obesity and Its Interplay with Preventive Cardiology

Jessica Bartfield, Alex Bonnecaze, and Jamy Ard

Scope of Obesity

Among adults in the United States, it is now more common to have an abnormally high body mass index (BMI) than a normal BMI. Obesity prevalence rates, specifically, increased at an alarming rate over the past 30–40 years, reaching a high of about 42% (Carroll et al. 2017). Obesity affects adults aged 40–59 years old to a greater extent, and a disproportionate number of non-Hispanic blacks (49.6%) and Hispanics (44.8%) (Carroll et al. 2017). It is considered an epidemic, connected to over 200 medical complications, and officially recognized as a disease, yet few health-care providers understand the complexity and chronicity of this disease. This chapter aims to briefly review the scope of obesity, describe its relationship with primary prevention of cardiovascular disease, highlight the current options for obesity treatment, and discuss the future directives of this dynamic field of medicine.

How is obesity defined? In its simplest terms, obesity occurs when a person has an excessively high amount of fat mass in relation to fat-free mass. However, the vast majority of health-care providers are not routinely measuring patients' body

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composition to diagnose and/or treat obesity. Rather, the BMI (weight in kilograms/height in meters squared) remains the most common method used to determine a patient's weight category. If the BMI is over 25 kg/m^2, a patient is considered to have overweight status. Once the BMI is over 30 kg/m^2, a patient is considered to have obesity. Although easy to calculate and convenient for clinical use, using the BMI to define obesity and assess metabolic disease risk raises a few concerns. The BMI fails to consider age, race, gender, or fat distribution, all of which affect risk assessment of obesity and cardiovascular disease risk. Especially for patients with BMI < 35 kg/m^2, waist circumference offers a stronger predictive value of metabolic disease risk by identifying those with excessive central adiposity (waist circumference > 88 cm or 35 in. for females and > 102 cm or 40 in. for males) (Bennasar-Veny et al. 2013; Sahakyan et al. 2015). In fact, metabolic syndrome, a significant risk factor for future cardiovascular disease, includes abnormal waist circumference, but not weight or BMI, as one of its five criteria.

What causes obesity? From a simplistic perspective, an energy imbalance where energy intake exceeds energy expenditure. Far too often, health-care providers incorrectly attribute this solely to lifestyle choices or behaviors, such as eating patterns or exercise. Certainly these two behaviors significantly impact one's weight, but the multifactorial etiologies of obesity reach far beyond just these two lifestyle factors. Hormonal, psychological, genetic, environmental, and physiological factors, to name a few, can all negatively influence weight (Fig. 8.1). Unfortunately, health-care providers often promote weight gain unknowingly by prescribing weight-inducing medications (der Valk et al. 2019). Finally, sleep strongly influences weight gain, with data suggesting that short sleep duration is associated with 1.3–1.5 odds ratio for obesity (Wu et al. 2014; Cappuccio et al. 2008).

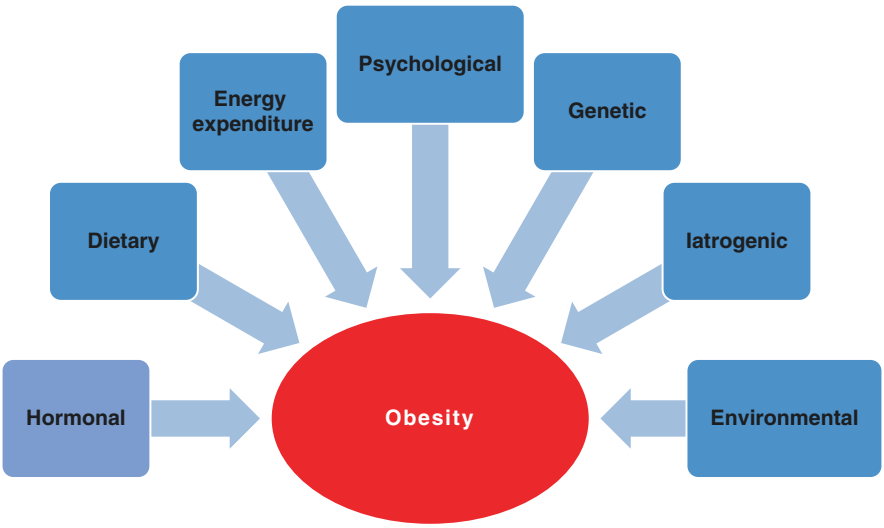

Fig. 8.1 Multifactorial causes of obesity

Furthermore, despite common presumptions, eating behaviors and movement are not just a simple matter of "willpower" or "self-discipline." Appetite regulation involves multiple different central signals [pro-opiomelanocortin (POMC), cocaine- and amphetamine-regulated transcript (CART), dopamine, norepinephrine (NE)] and peripheral signals [leptin, ghrelin, glucagon-like peptide-1 (GLP-1)] that increase or decrease intake (Berthoud et al. 2020). Unfortunately, dysregulation of several of these appetite-regulating signals can occur because of any of the aforementioned influences of body weight. Couple this dysregulation with a food environment replete with inexpensive, highly palatable, energy-dense foods and environments that encourage sedentary behavior rather than movement, and a positive energy imbalance is almost inevitable.

Clinicians treating patients with obesity need to recognize this complexity and avoid simplifying it to "diet and exercise" in order to deliver better patient care and help patients manage expectations for weight management. As discussed later in this chapter, the response to nearly all obesity treatments remains highly variable. Identifying potential contributors to previous or current weight gain allows for more tailored, effective treatment.

Links Between Obesity and Cardiovascular Disease

Cardiovascular disease leads to an average of 2353 deaths every day, more than any other disease (Virani et al. 2020). Obesity impacts both the structure and function of the cardiovascular system. Examples include increased carotid intima thickness, increased left ventricular hypertrophy, and diminished arterial elasticity. Patients with obesity often either have a greater cardiovascular disease burden or face an increased cardiovascular disease risk (Srinivasan et al. 1996; Singh et al. 2010). Previously, the connection between cardiovascular disease and obesity was thought to be dependent on other risk factors such as dietary patterns, hypertension, impaired glycemic control, or dyslipidemia. More recent data, however, emphasizes that obesity contributes to cardiovascular disease independent of other risk factors (Bereson 2005; Hall et al. 2002).

Excess adipose tissue does not simply serve as a reservoir of stored energy, but rather actively secretes a number of different adipokines, influences inflammatory markers, and alters critical hormones such as leptin and insulin (Recinella et al. 2020; Landecho et al. 2019). This endocrine activity of adipose tissue at the cellular level creates a state of inflammation and immune dysregulation in the body. Three influences that deserve particular attention with regard to cardiovascular disease include adiponectin, omentin-1, and leptin.

Adiponectin, the most commonly expressed adipokine, correlates negatively with obesity. Highly beneficial, this adipokine alters many different signaling pathways (interleukin-10, tumor necrosis factor-alpha) and reduces the vascular inflammatory response. The paucity of adiponectin in patients with obesity, therefore, negatively impacts endothelial cells, macrophages, and smooth muscle cells. Within

the vasculature walls, there is a loss of differentiation, a loss of endothelial cell migration with a simultaneous increased proliferation and migration of smooth muscle cells, and an increase in pro-inflammatory mediators from macrophages, among other changes. These effects culminate in the initiation of atherogenesis and vascular disease (Lau et al. 2017). Not surprisingly, much lower levels of plasma adiponectin exist in patients with coronary artery disease when compared to healthy patients. Very low levels of plasma adiponectin (<4.0 ug/mL) are associated with increased coronary artery disease prevalence and complexity of coronary lesions. In certain patient populations, this remained significant even after adjustment for other known risk factors such as tobacco use, BMI, and hypertension (Kumada et al. 2003). Interestingly, adiponectin is also expressed in adult cardiomyocytes, with known involvement in protecting against myocardial ischemia and reperfusion injury (Wang et al. 2010). Research suggests that either low levels of adiponectin or adiponectin resistance links type 2 diabetes with more severe ischemic heart disease morbidity and mortality, but a complete understanding of this has yet to materialize (Basu et al. 2007).

Similarly, circulating levels of omentin-1 correlate negatively with obesity and coronary artery disease. Through influences on anti-inflammatory cytokines and key signaling pathways, omentin-1 promotes vasorelaxation, reduces proliferation of vascular smooth muscle cells, and increases endothelial cell survival (Lau et al. 2017). Studies have shown a negative association of omentin-1 levels with carotid intima media thickness and the prevalence, as well as the severity of coronary artery disease, in patients with metabolic syndrome (Shibata et al. 2011; Shang et al. 2011).

Finally, the influence of leptin potentially mediates the relationship between obesity and coronary artery disease. Discovered in 1994, leptin acts on the hypothalamus to decrease appetite, increase thermogenesis, and activate the sympathetic nervous system. Thus, it was presumed that an increase in leptin would yield weight loss (Misra and Garg 1996; Lonnqvist 1996). However, this has not been true for most patients with obesity. Patients with obesity not only have higher levels of leptin, but also have dysfunctional leptin; better understood as resistance to leptin's appetite and weight regulation effects (Seufert 2004). Further studies identified leptin receptors on the heart, vascular smooth muscle cells, and endothelial cells. In cell culture, leptin increases smooth muscle proliferation and migration, increases oxidative stress, and pro-thrombotic platelet aggregation, all of which lead to endothelial dysfunction, atherogenesis, and ultimately cardiovascular disease. Although many studies support associations of high leptin levels with congestive heart failure, acute myocardial infarction, and left ventricular hypertrophy, there has been some variability in results when controlled for obesity (Singh et al. 2010). A study by the National Health and Examination Survey supports an independent connection between leptin and cardiovascular disease as it found higher leptin levels increased the risk for myocardial infarction and stroke for both men (OR 2.41; CI 1.20–4.93) and women (OR 4.26; 95% CI 1.75–10.73), regardless of traditional cardiovascular

risk factors and obesity (Considine et al. 1996). Finally, the inflammatory actions of leptin increase C-reactive protein production by the liver and perpetuate endothelial cell dysfunction (Knudson et al. 2008). This, coupled with the known increased sympathetic nervous system activity from leptin, can lead particularly to hypertension and other cardiac diseases.

Assessment of the Patient with Obesity

History

As with any other disease, the main goal of assessment is to determine disease severity and complexity and recommend an appropriate intensity of treatment. Asking patients for permission to discuss weight is an essential first step. If the patient agrees, a few key points of the history can yield valuable information. Reviewing a detailed weight history with the patient to identify the onset of weight gain and the highest and lowest adult weights reveals the lifelong weight trajectory. The relationship of weight gain to life events such as puberty, stress, pregnancy, emotional trauma, illness, and medication use should be noted. This not only allows the patient to reflect upon their prior challenges with obesity, but also provides the clinician with essential information that assists the treatment. A family history specific to obesity and early-onset cardiovascular disease should also be obtained.

A review of past medical history for obesity-related comorbidities allows for further risk determination of morbidity and mortality. Common complications include hypertension, congestive heart failure (CHF), coronary artery disease (CAD), cerebrovascular disease, nonalcoholic fatty liver disease (NAFLD), hyperlipidemia, type 2 diabetes, and obstructive sleep apnea (OSA) (Jensen et al. 2014). Calculating a baseline 10-year atherosclerotic cardiovascular disease (ASCVD) score using the Pooled Cohort equations defines cardiovascular risk in those without established ASCVD and LDL levels between 70 and 198 mg/dL (Lloyd-Jones et al. 2019).

A review of current eating behaviors provides crucial insight into weight gain and helps guide more specific counseling for behavior change. This ideally should include timing of meals, daily eating habits, who shops for food at home, consumption of sugar-sweetened beverages (SSBs), frequency of fast food/takeout meals, and financial concerns with food consumption.

Reviewing prior attempts at weight loss reveals patients' previous success and challenges. Previous attempts at specific diets, exercise, use of weight loss medications or supplements, and commercial or medical weight management programs should be reviewed. Identifying both successful and unsuccessful strategies helps to better craft a treatment plan.

Physical Exam

Waist circumference (measured at the iliac crest) of over 40 inches in men and over 35 inches in women is associated with an increased risk of cardiovascular events and type 2 diabetes (Wang et al. 2005). Abdominal adipose distribution is correlated with dyslipidemia, endothelial dysfunction, and vascular inflammation (Berg and Scherer 2005). The presence of an elevated waist circumference is strongly associated with increased visceral adipose mass (Neeland et al. 2019).

A prior study of over 1000 adults found 63% of men with obesity and 22% of women with obesity to have OSA (Tufik et al. 2010). Given the high prevalence of OSA in this population, performing the STOP-BANG questionnaire may help determine which patients warrant further evaluation (Chung et al. 2013, 2016). Those identified to be at risk for OSA should be promptly referred for polysomnography.

Hypertension is one of the most prevalent complications of obesity, affecting approximately 42.5% of patients (Wang and Wang 2004). Obesity-related hypertension is the result of multiple factors, including increased sympathetic activity, increased renin–angiotensin–aldosterone system (RAAS) activity, and insulin resistance (Landsberg et al. 2013). Hypertensive individuals are 2–3 times more likely than normotensive individuals to suffer a cardiovascular event (Lewington et al. 2002). Aggressive management of hypertension, via pharmacological and lifestyle interventions, is warranted in all patients with obesity.

The presence of a dorsocervical adipose pad, supraclavicular fullness, violaceous striae, facial fullness, and easy bruising can be seen in glucocorticoid excess (Cushing's syndrome). This condition is often accompanied by hypertension, osteoporosis, and type 2 diabetes. If glucocorticoid excess is suspected, a thorough review of medications should be performed to exclude iatrogenic Cushing's syndrome. Oral, intra-articular, inhaled, and even topical formulations of glucocorticoids can result in Cushing's syndrome. If no exogenous glucocorticoid exposure is identified, endogenous hypercortisolism should be excluded.

The presence of tendinous xanthomas, xanthelasmas, corneal arcus, and lipemia retinalis should raise suspicion for severe dyslipidemia. Xanthomas are generally only seen in severe hypercholesterolemia and strongly suggest a genetic disorder such as familial hypercholesterolemia. Further assessment with the Dutch Lipid Criteria may be of use in determining the likelihood of familial hypercholesterolemia (Nordestgaard et al. 2013) .

Review of Medications

Medications should be reviewed to identify obesogenic ones. Common weight-promoting medications include beta-blockers, insulin, sulfonylureas (SUs), thiazolidinediones (TZDs), first-generation antihistamines, antipsychotics, hormonal

contraceptives, and antidepressants (Ness-Abramof and Apovian 2005). Patients on multiple weight-promoting medications would benefit from referral to obesity medicine specialists. Occasionally weight-neutral alternatives can be utilized or more intensive treatment can overcome the challenge of weight-promoting medications.

Beta-blockers (with the exception of carvedilol) promote weight gain through multiple mechanisms, including decreased metabolic rate, decreased β-receptor-mediated thermogenesis, decreased thermogenic response to food intake, and increased lethargy (Astrup et al. 1989; Kunz et al. 2000). The summation of these effects has been estimated to result in a decreased total energy expenditure of 5–10% per day. A meta-analysis of 273 prior studies found patients being treated with beta-blockers gained anywhere from 1 to 3.5 kg (Sharma et al. 2001). They are also well known to cause hypertriglyceridemia via impaired carbohydrate metabolism, in addition to causing lowered HDL cholesterol (Black 1991). While many patients have absolute indications for beta blockade, opting for non-weight-promoting alternatives in those that do not require them (such as ACE-inhibitors or ARBs) is essential.

Many patients with obesity and type 2 diabetes are on regimens consisting of insulin and/or SUs and TZDs such as pioglitazone. When possible, discontinuing these medications in favor of glucagon-like peptide-1 (GLP-1) agonists and/or sodium/glucose cotransporter-2 (SGLT2) inhibitors, which promote weight loss and suggested reduction in cardiovascular risk, is preferred (Gerstein et al. 2019; Zelniker et al. 2019). Among the current GLP-1 agonists, dulaglutide appears to have the best data for primary cardiovascular prevention. The REWIND trial demonstrated that dulaglutide was effective for both secondary prevention [number needed to treat (NNT) 18] and primary prevention (NNT 72) among patients with type 2 diabetes (Gerstein et al. 2019). Current studies have not shown evidence of primary cardiovascular prevention with SGLT2 inhibitors; however, strong evidence exists for secondary cardiovascular prevention with these agents (Zelniker et al. 2019).

Obesity-Related Complications: Metabolic, Mechanical, and Psychosocial

Screening for and treating complications of obesity that are known to increase cardiovascular disease risk helps to mitigate this risk, assess the severity of obesity, and guide referral and intensity of obesity treatment. The initial assessment of the patient with obesity should include the following workup and screening.

Metabolic Complications

Initial lab workup should include a lipid profile, thyroid-stimulating hormone (TSH), hemoglobin A1c, fasting blood glucose, and a comprehensive metabolic panel. This will allow for diagnosis of underlying dyslipidemias, overt thyroid

dysfunction, pre-diabetes/diabetes, evidence of renal dysfunction, and potential abnormalities in liver function tests.

Mechanical

Patients with obesity are at increased risk of degenerative osteoarthritis, gastroesophageal reflux (GERD), obstructive sleep apnea (OSA), obesity hypoventilation syndrome (OHS), and congestive heart failure (CHF) (Garvey et al. 2016). A review of systems should include symptoms of joint pain, reflux, daytime somnolence and sleep abnormalities, edema, dyspnea on exertion, and paroxysmal nocturnal dyspnea. Identifying these conditions will allow for appropriate referral to respective specialists for treatment.

Psychosocial

Psychosocial complications among patients with obesity include depression, anxiety, poor self-esteem, substance abuse, eating disorders, and body image disorders (Kwarteng et al. 2017; Rubino et al. 2020). While some patients may be hesitant to disclose such issues, they should be gently discussed by the clinician in order to facilitate referral to appropriate behavioral health resources. Questions may include current or past issues such as binge eating, purging, emotional eating, history of substance abuse, or psychiatric diagnoses.

Treatment of the Patient with Obesity

Behavior Modifications

Dietary Patterns

Ideal dietary strategies for weight loss and cardiovascular health have been studied and debated endlessly. Ultimately, the most effective dietary approach is the one that creates an energy deficit and that the patient can adhere to over the long term (De Jonge et al. 2012; Gardner et al. 2016). Most guidelines suggest the goal of creating a 500–750 kcal deficit per day for effective weight loss and suggest using calorie targets of 1200, 1500, or 1800 kcal per day to achieve this for most patients (Jensen et al. 2014).

Simple, specific, and proven recommendations that providers can use when counseling patients include food journaling and using meal replacements (portion controlled shakes, bars, frozen meals, etc.). Putting foods in areas out of sight

(drawers, cabinets, pantries) rather than out in the open (desktops, countertops, etc.) can be an easy and effective strategy for stimulus control. Avoiding sugar-sweetened beverages (SSBs) and ultraprocessed foods generally results in overall lower caloric intake. An randomized control trial found that patients on a diet of ultraprocessed foods consumed an average of 500 kcal more per day compared to patients randomized to a diet of unprocessed foods (Hall et al. 2019).

A plethora of dietary strategies for weight loss constantly bombard patients, most of which have very little evidence. Several popular dietary strategies include veganism, vegetarianism, ketogenic diets, intermittent fasting, and the Mediterranean diet. While there is fierce debate about the superiority of these diets, each will produce weight loss if the plan creates a net caloric deficit. Current evidence also suggests cardiovascular benefits with some and risks with others, as detailed below.

Plant-based diets have been associated with up to a 40% reduction in CAD and 29% reduction in cerebrovascular disease (Kwok et al. 2014). A caloric deficit is often easier to achieve given the amount of satiating high-fiber vegetables consumed. Adequate daily protein intake may be challenging for strict vegans, relying primarily on legumes, soy, and nuts as sources of amino acids.

The Mediterranean diet involves a high intake of nuts, olive oil, vegetables, fruits, and a limited intake of lean animal proteins such as fish and chicken. Red meats, processed foods, and dairy are generally avoided. The PREDIMED trial involved 7447 patients at high cardiovascular risk who were randomized to either a Mediterranean diet with supplemental olive oil, a Mediterranean diet with supplemental nuts, or a control diet involving low fat. Both Mediterranean diets appeared beneficial for primary prevention of cardiovascular events at 5 years, with a combined hazard ratio of 0.77 compared to those on a low-fat diet (Estruch et al. 2018).

Low and very low carbohydrate diets continue to gain popularity and are associated with significant weight loss. While high-density lipoproteins (HDL) tend to increase and triglycerides generally decrease, a variable LDL response may be seen. Generally, higher saturated fat consumption is correlated with a greater LDL increase (Kirkpatrick et al. 2019). A recent 8-year prospective study revealed that patients on low-carbohydrate/high-fat diets were more likely to develop coronary artery calcium progression. The authors further discussed that this effect was only seen in those replacing carbohydrates with animal fat, potentially contributing to increased vascular inflammation (Gao et al. 2020).

Physical Activity

Exercise and physical activity play a pivotal role in optimizing cardiovascular health and weight management. While exercise is often emphasized for active weight loss, it actually plays a much more crucial role in maintaining weight loss (Donnelly et al. 2004). Without appropriate caloric restriction, increases in exercise alone generally do not result in significant weight loss.

Many patients may hesitate to begin an exercise program. Consistency should be stressed over the initial duration or intensity of exercise. Furthermore, patients may

find increasing daily steps and reducing sedentary time a more appealing and achievable goal. Activity trackers may help motivate patients and increase accountability, both of which translate into effective behavior change (Wang et al. 2017). Utilizing online fitness videos and resistance bands at home creates an alternative for the patient with obesity who may find public gyms intimidating.

Sleep

Poor sleep patterns should be identified and addressed. In particular for primary prevention of cardiovascular disease, symptoms of sleep apnea need to be reviewed. The STOP-BANG score and Epworth sleep score are examples of proven tools to help providers know when to refer patients for polysomnography and sleep medicine. Other sleep disturbances that limit both quantity and quality of sleep (i.e., screen time, vasomotor symptoms, restless leg syndrome, nocturia) should be addressed as sleep impacts both cardiovascular disease risk and obesity (Dashti et al. 2015; Lao et al. 2018).

Stress Management

Chronic stress affects most patients to some degree. Assessment of the patient's stress levels and stress-coping mechanisms provides vital information regarding other habits that induce obesity and cardiovascular health. For example, weight gain would be expected in someone reporting they frequently cope with stress by overeating. The involvement of a behavioral therapist benefits patients by helping them develop healthier outlets for stressors.

Antiobesity Pharmacotherapy

Current guidelines (Apovian et al. 2015) support the use of antiobesity medications (AOMs) in patients with a BMI $\geq$ 30 kg/m^2 or a BMI $\geq$ 27 kg/m^2 with an obesity-related comorbidity, such as type 2 diabetes. These medications can help control symptoms, improve weight loss response, and help patients more consistently adhere to necessary changes in dietary intake required for weight loss and maintenance of weight loss. A prior prospective study found that combined therapy with lifestyle modification and AOM resulted in 12.1 kg weight loss over 1 year compared to 5.0 kg lost with AOM alone (Wadden et al. 2005). A goal of 5% weight loss over 3 months is typically used; if efficacy/benefit is not seen after 3 months, discontinuation of the medication and transitioning to an alternative AOM should be considered (Fujioka et al. 2016). Table 8.1 describes the current FDA-approved antiobesity medications.

Table 8.1 Medications approved by the US Food and Drug Administration for obesity treatment (Micromedex® (electronic version) 2020)

Drug (brand name)	Mechanism of action	Most common side effects	Contraindications *All AOMs contraindicated in pregnancy and breastfeeding	Relative cost
Phentermine 8 mg (Lomaira) 15 mg 30 mg/37.5 mg (Adipex)	Works centrally to increase norepinephrine release, sympathomimetic, appetite suppression	Dry mouth Increased irritability, agitation Elevated heart rate and blood pressure Insomnia	Uncontrolled hypertension Open-angle glaucoma Uncontrolled hyperthyroidism Uncontrolled anxiety History of cardiovascular disease Structural heart disease History of drug abuse MAO inhibitor use within 14 days	$
Phendimetrazine (Bontril) 17.5–35 mg taken twice a day 105 mg extended release taken once daily	Works centrally to increase norepinephrine and dopamine release, sympathomimetic, Appetite suppression	Dry mouth Agitation Insomnia Elevated blood pressure and heart rate	Uncontrolled hypertension Open-angle glaucoma Uncontrolled hyperthyroidism Uncontrolled anxiety History of cardiovascular disease Structural heart disease History of drug abuse	$
Diethylpropion (Tenuate) 25 mg taken up to three times per day 75 mg extended release taken once daily	Works centrally to increase norepinephrine and dopamine release, sympathomimetic, Appetite suppression	Dry mouth Constipation Nausea Dyspepsia Insomnia Elevated blood pressure and/or heart rate	Uncontrolled hypertension Open-angle glaucoma Uncontrolled hyperthyroidism Uncontrolled anxiety History of cardiovascular disease Structural heart disease History of drug abuse Heart murmur	$

(continued)

Table 8.1 (continued)

Drug (brand name)	Mechanism of action	Most common side effects	Contraindications *All AOMs contraindicated in pregnancy and breastfeeding	Relative cost
Orlistat (Xenical)* 120 mg taken three times per day with meals containing fat *Alli only FDA approved over-the-counter weight loss medication 60 mg taken three times per day with meals containing fat	Inhibits pancreatic and gastric lipase, reducing the amount of dietary fat absorbed	Increased stool frequency and urgency Flatus with discharge Fatty diarrhea	Cholestasis Chronic malabsorption syndromes	$$
Phentermine and topiramate extended release (Qsymia) 3.75 mg/23 mg once daily 7.5 mg/46 mg once daily 11 mg/69 mg once daily 15 mg/92 mg once daily	Works centrally to increase norepinephrine release and gamma-amino butyric acid release, appetite suppression	Dry mouth Paresthesias Constipation Taste changes Insomnia Dizziness	Uncontrolled hypertension Open-angle glaucoma Uncontrolled hyperthyroidism Uncontrolled anxiety History of cardiovascular disease Structural heart disease History of drug abuse MAO inhibitor use within 14 days	$$$
Bupropion/naltrexone (Contrave) 8 mg/90 mg tablets; two tablets taken twice a day	Inhibits norepinephrine and dopamine reuptake, blocks opioid receptor, appetite suppression	Nausea Vomiting Constipation Headache Insomnia Flushing	MAO inhibitor use within 14 days ESRD Uncontrolled hypertension Seizure disorder or history Bulimia Anorexia Opioid use or dependence	$$$

Table 8.1 (continued)

Drug (brand name)	Mechanism of action	Most common side effects	Contraindications *All AOMs contraindicated in pregnancy and breastfeeding	Relative cost
Liraglutide (Saxenda) 3 mg subcutaneous injection once a day	Activates glucagon-like peptide (GLP-1) receptor, appetite suppression	Nausea Dyspepsia Diarrhea Constipation Fatigue	Medullary thyroid cancer history or family history of medullary thyroid cancer Multiple endocrine neoplasia syndrome type 2 Pancreatitis history Suicidal ideation or treatment	$$$$

Phentermine

Phentermine is a sympathomimetic medication that primarily works to reduce appetite. It is the oldest, least-expensive, and most widely prescribed antiobesity medication, but currently only FDA-approved for short-term use. Contraindications include CHF, coronary artery disease, arrhythmias, uncontrolled hypertension, uncontrolled hyperthyroidism, monoamine-oxidase inhibitor (MAOI) use, glaucoma, and pregnancy. Commonly experienced side effects include insomnia, constipation, and dry mouth. While it has classically been prescribed at doses of 37.5 mg daily, doses as low as 7.5 mg daily combined with lifestyle changes were found to result in weight loss of greater than 5% at 28 weeks (Aronne et al. 2013). It is now available in an 8 mg scored tablet. Utilizing lower doses allows for decreased risk of adverse events while maximizing efficacy. For patients without contraindications, it continues to be an effective and affordable agent for weight loss.

Phentermine/Topiramate ER (Qsymia)

In individual drug efficacy studies, phentermine/topiramate ER has the highest average weight loss among the currently available AOMs (head-to-head trials of the current FDA-approved antiobesity medications have not been done). It works centrally to reduce appetite. A 28-week randomized controlled trial found that patients achieved −8.5% and 9.2% weight loss with phentermine 7.5 mg/topiramate ER 46 mg and phentermine 15 mg/topiramate ER 92 mg, respectively (Aronne et al. 2013). In addition to the contraindications to phentermine use, it should be avoided

in patients with metabolic acidosis, glaucoma, or pregnancy. Teratogenicity and review of contraceptive strategies should be discussed in women of childbearing age. Commonly experienced side effects include paresthesias and dry mouth. Topamax often causes dysgeusia, which can help patients decrease or eliminate sugar-sweetened beverage use, particularly sodas. An important cost consideration to clinicians is that there is no generic alternative for Qsymia, and many insurers (such as Medicare) do not cover AOMs. In these situations, referral to an obesity medicine specialist for medication management may be helpful.

Naltrexone/Bupropion (Contrave)

Naltrexone/bupropion works to decrease central appetite and inhibit food cravings. In particular, it helps patients with significant emotional eating or strong hedonistic responses to foods. Contraindications include current opioid use, seizure disorder, and uncontrolled hypertension. The presence of bupropion makes this an attractive option for patients who may also be trying to attempt smoking cessation. Unfortunately, like Qsymia, a generic alternative does not exist and many insurance companies may not cover these medications, making cost difficult for patients.

Liraglutide 3.0 mg (Saxenda)

While the GLP-1 agonist liraglutide at lower doses is frequently used for the management of type 2 diabetes (Victoza), liraglutide 3.0 mg is approved for obesity treatment. For most patients, this medication markedly improves satiety, allowing for a reduction in calorie intake and thus substantial weight loss. Contraindications include history of pancreatitis or a family history of medullary thyroid cancer or multiple endocrine neoplasia 2 (MEN2) syndrome. The most common side effects are generally nausea and dyspepsia, but the slow-dose titration of this medication (typically 5 weeks until maximum dose reached) allows for better management of any side effects. Patients with prediabetes or DM2 are also excellent candidates for this medication. In DM2 patients who may already be on a GLP-1 agonist, changing them to liraglutide 3.0 mg generally provides additional glycemic benefits while more strongly promoting weight loss.

Bariatric Surgery

Bariatric surgery should be considered for patients with BMI $\geq$40 kg/m^2 and those with BMI $\geq$35 kg/m^2 with an obesity-related comorbidity (Jensen et al. 2014). Surgical options include gastric banding, vertical sleeve gastrectomy (VSG), Roux-En-Y gastric bypass (RYGB), and bilio-pancreatic diversion with duodenal switch (BPD-DS). A meta-analysis including 22,094 patients undergoing bariatric surgery

demonstrated a mean excess body weight loss (EBWL) of 61.2%, remission of diabetes in 76.8%, resolution of hypertension in 61.7%, and improved or resolved OSA in 83.6% (Buchwald et al. 2004). Mortality of surgery was also noted to be low for those undergoing restrictive procedures (0.1%), gastric bypass (0.5%), and BPD-DS (1.1%) in centers with experienced bariatric surgeons. A 2019 retrospective cohort study comparing bariatric surgery vs. medical management of patients with type 2 diabetes and obesity found a significant reduction in major adverse cardiovascular events (MACE) (31% vs. 48%) and all-cause mortality (7.8% absolute risk reduction) among those undergoing surgery (Aminian et al. 2019). A prospective trial of Swedish patients with obesity found that those undergoing bariatric surgery were significantly less likely to suffer initial cardiovascular events compared to the non-surgical cohort (hazard ratio 0.67) (Sjöström et al. 2012). A caveat to this data is that 68.1% of patients undergoing bariatric surgery received the vertical banded gastroplasty, which is now rarely done.

Prior to undergoing bariatric surgery, patients should be properly evaluated and treated for existing behavioral disorders and counseled extensively on post-bariatric care and potential complications. Lifelong care is critical to help maintain post-bariatric surgery lifestyle habits that maintain weight loss and monitor for nutritional deficiencies. Clinicians caring for bariatric surgical patients should carefully monitor weight changes and ensure that patients avoid nonsteroidal anti-inflammatories (NSAIDs), tobacco, and excess alcohol. Table 8.2 summarizes the four types of bariatric surgeries.

Table 8.2 Bariatric surgery for the management of obesity

Procedure	Mechanism of action	Benefits	Potential complications	Average EBWL
Laparoscopic gastric banding	An adjustable inflatable band is placed around the upper portion of the stomach, restricting food intake.	Early satiety Very low risk for vitamin deficiencies Reversible, adjustable	Band slippage or erosion Foreign body reaction Over-tightening can result in inability to eat or drink, risk esophageal dysmotility or dilation	40–50%
Vertical sleeve gastrectomy (VSG)	80% of the stomach is removed, resulting in significant restriction.	Early satiety No bypass or foreign objects involved Lower risk of complications when compared to RYGB and BPD-DS	Not reversible Vitamin deficiencies (B12, iron, vitamin D, calcium, folate) Potential worsening of GERD	>50%

(continued)

Table 8.2 (continued)

Procedure	Mechanism of action	Benefits	Potential complications	Average EBWL
Roux-En-Y gastric bypass (RYGB)	The stomach is divided to create a small pouch, while the first portion of the small intestine is divided and reattached distally. This results in both restriction and malabsorption.	Early satiety May increase energy expenditure Favorable improvement in gut hormones Improvement of GERD	Anastomotic leak or ulcer Vitamin deficiencies (fat-soluble vitamins, B vitamins, iron, calcium, zinc, copper). Dumping syndrome, post-bariatric surgery hypoglycemia	60%
Bilio-pancreatic diversion with duodenal switch (BPD-DS)	Involves the creation of a stomach pouch and bypassing the first ¾ of the small intestine via diversion. Results in restriction and > 70% reduction in fat absorption.	Results in the greatest weight loss of all bariatric procedures Improved satiety Significant improvement in type 2 diabetes and other metabolic diseases	Highest rate of complications and mortality of all bariatric surgeries More severe vitamin deficiencies (fat-soluble vitamins, B vitamins, iron, calcium, folate, zinc, copper). Steatorrhea	70% (or greater)

Data from the American Society for Metabolic and Bariatric Surgery (ASMBS)
EBWL excess body weight loss

Challenges and Barriers of Obesity Treatment

Despite the advancements in understanding obesity as a disease, the development of more effective therapies, and more obesity medicine specialists trained to provide treatment, few patients receive appropriate care. Reasons for this include patients' perspectives of obesity treatment and clinicians' perspectives of obesity treatment, time, and cost. A recent survey of American adults found that the vast majority (80%) regard obesity to be the most serious health issue, ahead of diabetes and heart disease. Furthermore, over half of Americans name heart disease as the most severe consequence of obesity (Rosenthal et al. 2017).

However, many Americans with obesity lack awareness of weight status, viewing themselves as overweight instead of having obesity, or having mild obesity rather than severe obesity (Mello et al. 2006). This likely dampens any need or sense of urgency to seek medical attention or treatment. Furthermore, even when they do recognize the need for treatment, Americans often turn to the commercial weight

loss industry and self-directed attempts at dietary changes and exercise rather than seeking professional medical care. Unfortunately, despite appreciating the dire effects of obesity, many Americans consider obesity treatments beyond diet and exercise more risky and less safe (Rosenthal et al. 2017).

Surveys of physician practices, similarly, have found that less than half of patients with obesity are informed of their status and even fewer received formal counseling or active treatment (Rosenthal et al. 2017; Mello et al. 2006; Evans-Hoeker et al. 2014; Bleich et al. 2011). A recent prospective study among primary care providers found more encouraging rates of obesity diagnosis and discussion, but persistent gaps in the delivery of treatment, particularly beyond diet and exercise counseling (Galuska et al. 1999; Hite et al. 2019). Although time remains the most commonly cited barrier among primary care physicians, low comfort levels with more intensive obesity treatment, such as pharmacotherapy or bariatric surgery, significantly impede appropriate care.

Underutilization of these therapies, therefore, remains high. Estimates suggest that only 2–3% of patients eligible for antiobesity pharmacotherapy receive it compared to 85% of patients with diabetes receiving antidiabetes pharmacotherapy (Thomas et al. 2016; Saxon et al. 2019).

Despite the increased prevalence of obesity, weight bias and stigmatization remain another challenge to successful treatment. It is well established that patients with obesity experience more social isolation and discrimination in multiple settings, including the workplace and health care (Rubin 2019; Giel et al. 2010). More concerning, both implicit and explicit weight bias infiltrate different types of healthcare providers (doctors, nurses, dietitians) across a number of different medical fields, including primary care, endocrinology, cardiology, and even obesity medicine (FitzGerald and Hurst 2017; Kaplan et al. 2018).

Fortunately, these challenges are surmountable (see Fig. 8.2). Ongoing efforts to better educate physicians earlier and more frequently about obesity diagnosis and treatment will improve comfort levels and diminish bias. The increased specialized education and training of physicians and surgeons in obesity medicine and bariatric surgery will allow both primary care providers and specialists to more easily refer patients for expert care, overcoming both time and comfort-level barriers.

Despite an estimated annual medical cost of about $149.4 billion, the coverage for obesity treatment remains significantly limited, particularly when compared to other chronic diseases (Cawley and Meyerhoefer 2012). Based on studies of state employee health insurance plans, from 2009 to 2017 there was an increase in coverage of both pharmacotherapy and bariatric surgery. Unfortunately, 27 states still do not cover pharmacotherapy and 7 states still do not cover bariatric surgery (Jannah et al. 2018). Reimbursement for obesity treatment, including nutritional counseling, varies widely among private insurers. The recent decision by Medicare to reimburse primary care physicians for intensive behavioral treatment of obesity offers some hope, but still ignores the need for coverage of evidence-based, specialized interdisciplinary care and antiobesity medications (Batsis and Bynum 2016; Government Accountability Office 2019). Ongoing advocacy efforts aim to reduce this financial burden to both patients and providers.

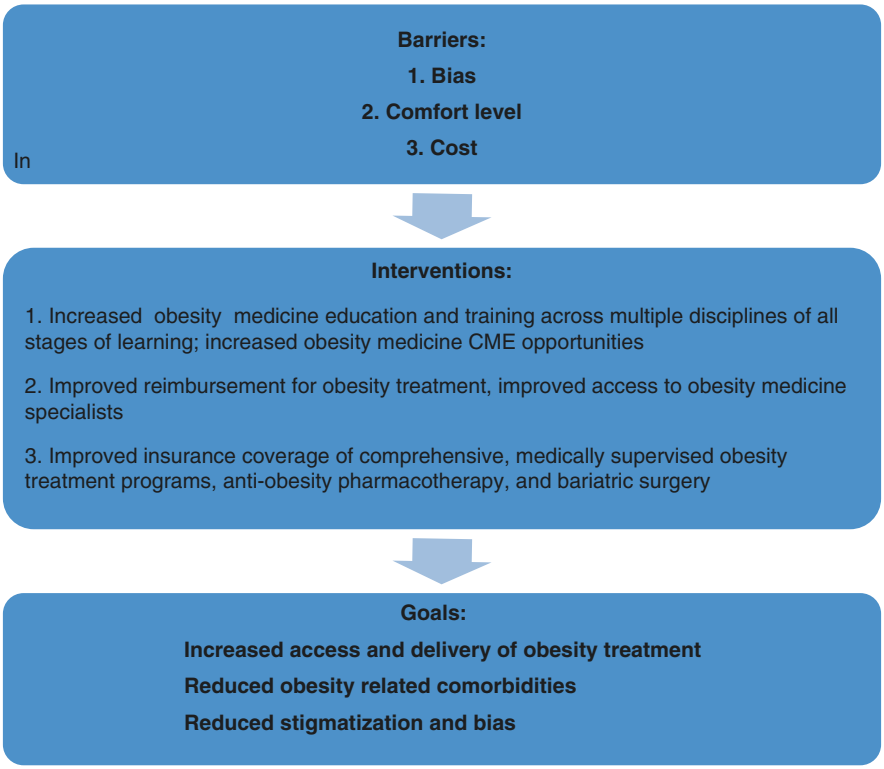

Fig. 8.2 Overcoming barriers to obesity treatment

Conclusion

Primary prevention of cardiovascular disease requires both successful identification of risk factors and intervention to reduce them. Obesity may arguably be the most common and powerful risk factor for cardiovascular disease. Not only does obesity contribute to other known risk factors such as hypertension and type 2 diabetes, it directly causes vascular inflammation and endothelial damage through adipokines and other hormonal alterations.

Fortunately, science has dramatically advanced the understanding of obesity pathophysiology and energy balance, leading to a greater number of treatments to better manage this chronic disease. Yet these treatments are only effective if actually delivered. Clinicians need to move beyond just "diet and exercise" and offer more comprehensive, targeted treatment strategies or refer patients to a specialist who can.

While no cure exists for obesity, more treatments for successful long-term management of this disease continue to emerge, such as devices and additional pharmacotherapy. Future directives that create a greater depth of treatment options and explore the heterogeneity of treatment responses will allow for said targeted

strategies. Increased attention to combination therapies and advancements in long-term weight loss maintenance can be expected in the future as well.

The future looks bright for managing obesity and thus improving the primary prevention of cardiovascular disease.

References

Aminian A, Zajichek A, Arterburn DE, Wolski KE, Brethauer SA, Schauer PR, et al. Association of metabolic surgery with major adverse cardiovascular outcomes in patients with type 2 diabetes and obesity. JAMA. 2019;322:1271.

Apovian CM, Aronne LJ, Bessesen DH, McDonnell ME, Murad MH, Pagotto U, et al. Pharmacological management of obesity: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2015;100(2):342–62.

Aronne LJ, et al. Evaluation of phentermine and topiramate versus phentermine/topiramate extended-release in obese adults. Obesity. 2013;21(11):2163–71. https://doi.org/10.1002/oby.20584.

Astrup A, Simonsen L, Bülow J, Madsen J, Christensen NJ. Epinephrine mediates facultative carbohydrate-induced thermogenesis in human skeletal muscle. Am J Phys. 1989;257(3 Pt 1):E340–5.

Basu R, Pajvani UB, Rizza RA, Scherer PE. Selective down-regulation of the high molecular weight form of adiponectin in hyperinsulinemia and type 2 diabetes: differential regulation from nondiabetic subjects. Diabetes. 2007;56:2174–7.

Batsis JA, Bynum JPW. Uptake of the centers for medicare and medicaid obesity benefit: 2012–2013. Obesity. 2016;24(9):1983–8. https://doi.org/10.1002/oby.21578.

Bennasar-Veny M, Lopez-Gonzalez AA, Tauler P, Cespedes ML, Vicente-Herrero T, Yañez A, Tomas-Salva M, Aguilo A. Body adiposity index and cardiovascular health risk factors in Caucasians: a comparison with the body mass index and others. PLoS One. 2013;8(5):e63999. https://doi.org/10.1371/journal.pone.0063999. PMID: 23734182; PMCID: PMC3667028

Bereson GS. Obesity-a critical issue in preventive cardiology: the Bogalusa Heart Study. Prev Cardiol. 2005;8:234–41.

Berg AH, Scherer PE. Adipose tissue, inflammation, and cardiovascular disease. Circ Res. 2005;96(9):939–49.

Berthoud H-R, et al. The obesity epidemic in the face of homeostatic body weight regulation: what went wrong and how can it be fixed? Physiol Behav. 2020;222:112959. https://doi.org/10.1016/j.physbeh.2020.112959.

Black HR. Metabolic considerations in the choice of therapy for the patient with hypertension. Am Heart J. 1991;121(2 Pt 2):707–15.

Bleich SN, et al. Physician practice patterns of obesity diagnosis and weight-related counseling. Patient Educ Couns. 2011;82(1):123–9. https://doi.org/10.1016/j.pec.2010.02.018.

Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, et al. Bariatric surgery: a systematic review and meta-analysis. JAMA. 2004;292(14):1724–37.

Cappuccio FP, Taggart FM, Kandala NB, Currie A, Peile E, Stranges S, Miller MA. Meta-analysis of short sleep duration and obesity in children and adults. Sleep. 2008;31(5):619–26. https://doi.org/10.1093/sleep/31.5.619. PMID: 18517032; PMCID: PMC2398753

Carroll CM, Fryar CD, Ogden CL. Prevalence of obesity among adults and youth: United States, 2015–1016. NCHS Data Brief. 2017;288:1–8.

Cawley J, Meyerhoefer C. The medical care costs of obesity: an instrumental variables approach. J Health Econ. 2012;31:219–30.

Chung F, Yang Y, Liao P. Predictive performance of the STOP-Bang score for identifying obstructive sleep apnea in obese patients. Obes Surg. 2013;23(12):2050–7.

Chung F, Abdullah HR, Liao P. STOP-Bang questionnaire. Chest. 2016;149(3):631–8.
Considine RV, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med. 1996;334(5):292–5. https://doi.org/10.1056/NEJM199602013340503.
Dashti HS, Scheer FA, Jacques PF, Lamon-Fava S, Ordovás JM. Short sleep duration and dietary intake: epidemiologic evidence, mechanisms, and health implications. Adv Nutr. 2015;6(6):648–59.
De Jonge L, Bray GA, Smith SR, Ryan DH, de Souza RJ, Loria CM, et al. Effect of diet composition and weight loss on resting energy expenditure in the POUNDS LOST study. Obesity. 2012;20(12):2384–9.
der Valk V, Eline S, et al. A comprehensive diagnostic approach to detect underlying causes of obesity in adults. Obes Rev. 2019;20(6):795–804. https://doi.org/10.1111/obr.12836.
Donnelly JE, Smith B, Jacobsen DJ, Kirk E, Dubose K, Hyder M, et al. The role of exercise for weight loss and maintenance. Best Pract Res Clin Gastroenterol. 2004;18(6):1009–29.
Estruch R, Ros E, Salas-Salvadó J, Covas M-I, Corella D, Arós F, et al. Primary prevention of cardiovascular disease with a mediterranean diet supplemented with extra-virgin olive oil or nuts. N Engl J Med. 2018;378(25):e34.
Evans-Hoeker EA, et al. Healthcare provider accuracy at estimating women's BMI and intent to provide counseling based on appearance alone. Obesity. 2014;22(3):633–7. https://doi.org/10.1002/oby.20301.
FitzGerald C, Hurst S. Implicit bias in healthcare professionals: a systematic review. BMC Med Ethics. 2017;18(1):19. https://doi.org/10.1186/s12910-017-0179-8.
Fujioka K, O'Neil PM, Davies M, Greenway F, Lau DCW, Claudius B, Skjøth TV, Jensen CB, Wilding JPH. Early weight loss with liraglutide 3.0 mg predicts 1-year weight loss and is associated with improvements in clinical markers. Obesity. 2016;24(11):2278–88. https://doi.org/10.1002/oby.21629. PMID: 27804269; PMCID: PMC5129670.
Galuska DA, et al. Are health care professionals advising obese patients to lose weight? JAMA. 1999;282(16):1576–8. https://doi.org/10.1001/jama.282.16.1576.
Gao J-W, Hao Q-Y, Zhang H-F, Li X-Z, Yuan Z-M, Guo Y, et al. Low-carbohydrate diet score and coronary artery calcium progression: results from the CARDIA study. Arterioscler Thromb Vasc Biol 2020 41;491;10.1161/ATVBAHA120314838.
Gardner CD, Offringa LC, Hartle JC, Kapphahn K, Cherin R. Weight loss on low-fat vs. low-carbohydrate diets by insulin resistance status among overweight adults and adults with obesity: a randomized pilot trial. Obesity. 2016;24(1):79–86.
Garvey WT, Mechanick JI, Brett EM, Garber AJ, Hurley DL, Jastreboff AM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. Endocr Pract. 2016;22(Suppl 3):1–203.
Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet Lond Engl. 2019;394(10193):121–30.
Giel KE, et al. Weight bias in work settings – a qualitative review. Obes Facts. 2010;3(1):33–40. https://doi.org/10.1159/000276992.
Government Accountability Office. Obesity Drugs [GAO-19-577]. Aug 2019. https://www.gao.gov/products/GAO-19-577.
Hall JE, Crok ED, Jones DW, Wofford MR, Dubbert PM. Mechanisms of obesity associated cardiovascular and renal disease. Am J Sci. 2002;324:127–37.
Hall KD, Ayuketah A, Brychta R, Cai H, Cassimatis T, Chen KY, et al. Ultra-processed diets cause excess calorie intake and weight gain: an inpatient randomized controlled trial of Ad libitum food intake. Cell Metab. 2019;30(1):67–77.e3.
Hite A, et al. An exploration of barriers facing physicians in diagnosing and treating obesity. Am J Health Promot. 2019;33(2):217–24. https://doi.org/10.1177/0890117118784227.

Jannah N, et al. Coverage for obesity prevention and treatment services: analysis of medicaid and state employee health insurance programs. Obesity. 2018;26(12):1834–40. https://doi.org/10.1002/oby.22307.

Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Circulation. 2014;129(25 Suppl 2):S102–38.

Kaplan LM, Golden A, Jinnett K, et al. Perceptions of barriers to effective obesity care: results from the national ACTION study. Obesity (Silver Spring). 2018;26:61–9.

Kirkpatrick CF, Bolick JP, Kris-Etherton PM, Sikand G, Aspry KE, Soffer DE, et al. Review of current evidence and clinical recommendations on the effects of low-carbohydrate and very-low-carbohydrate (including ketogenic) diets for the management of body weight and other cardiometabolic risk factors: a scientific statement from the National Lipid Association Nutrition and Lifestyle Task Force. J Clin Lipidol. 2019;13(5):689–711.e1.

Knudson JD, et al. Leptin and mechanisms of endothelial dysfunction and cardiovascular disease. Curr Hypertens Rep. 2008;10(6):434–9. https://doi.org/10.1007/s11906-008-0082-2.

Kumada M, Kihara S, Sumitsuji S, Kawamoto T, Matsumoto S, Ouchi N, et al. Association of hypoadkiponectinemia with coronary artery disease in men. Arterioscler Thromb Vasc Biol. 2003;23:85–9.

Kunz I, Schorr U, Klaus S, Sharma AM. Resting metabolic rate and substrate use in obesity hypertension. Hypertens Dallas Tex 1979. 2000;36(1):26–32.

Kwarteng JL, et al. Independent effects of neighborhood poverty and psychosocial stress on obesity over time. J Urban Health. 2017;94(6):791–802. https://doi.org/10.1007/s11524-017-0193-7.

Kwok CS, Umar S, Myint PK, Mamas MA, Loke YK. Vegetarian diet, seventh day adventists and risk of cardiovascular mortality: a systematic review and meta-analysis. Int J Cardiol. 2014;176(3):680–6.

Landecho MF, et al. Relevance of leptin and other adipokines in obesity-associated cardiovascular risk. Nutrients. 2019;11(11):2664. https://doi.org/10.3390/nu11112664.

Landsberg L, Aronne LJ, Beilin LJ, Burke V, Igel LI, Lloyd-Jones D, et al. Obesity-related hypertension: pathogenesis, cardiovascular risk, and treatment–a position paper of the Obesity Society and The American Society of Hypertension. Obesity. 2013;21(1):8–24.

Lao XQ, Liu X, Deng H-B, Chan T-C, Ho KF, Wang F, et al. Sleep quality, sleep duration, and the risk of coronary heart disease: a prospective cohort study with 60,586 adults. J Clin Sleep Med JCSM. 2018;14(1):109–17.

Lau WB, et al. Role of adipokines in cardiovascular disease. Circ J. 2017;81(7):920–8. https://doi.org/10.1253/circj.CJ-17-0458.

Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet Lond Engl. 2002;360(9349):1903–13.

Lloyd-Jones DM, Braun LT, Ndumele CE, Smith SC, Sperling LS, Virani SS, et al. Use of risk assessment tools to guide decision-making in the primary prevention of atherosclerotic cardiovascular disease. J Am Coll Cardiol. 2019;73(24):3153–67.

Lonnqvist F. The obese (ob) gene and its product leptin: a new route towards obesity treatment in man? J Med. 1996;89:327–32.

Mello MM, et al. Obesity–the new frontier of public health law. N Engl J Med. 2006;354(24):2601–10. https://doi.org/10.1056/NEJMhpr060227.

Micromedex® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com/. Cited 914/2020.

Misra A, Garg A. Leptin: its receptor and obesity. J Investig Med. 1996;44:540–8.

Neeland IJ, Ross R, Després J-P, Matsuzawa Y, Yamashita S, Shai I, et al. Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: a position statement. Lancet Diabetes Endocrinol. 2019;7(9):715–25.

Ness-Abramof R, Apovian CM. Drug-induced weight gain. Drugs Today Barc Spain 1998. 2005;41(8):547–55.
Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J. 2013;34(45):3478–90.
Recinella L, et al. Adipokines: new potential therapeutic target for obesity and metabolic, rheumatic, and cardiovascular diseases. Front Physiol. 2020;11:578966. https://doi.org/10.3389/fphys.2020.578966.
Rosenthal RJ, et al. Obesity in America. Surg Obesity Rel Dis. 2017;13(10):1643–50. https://doi.org/10.1016/j.soard.2017.08.002.
Rubin R. Addressing medicine's bias against patients who are overweight. JAMA. 2019;321(10):925–7. https://doi.org/10.1001/jama.2019.0048.
Rubino F, et al. Joint international consensus statement for ending stigma of obesity. Nat Med. 2020;26(4):485–97. https://doi.org/10.1038/s41591-020-0803-x.
Sahakyan KR, et al. Normal-weight central obesity: implications for total and cardiovascular mortality. Ann Intern Med. 2015;163(11):827–35. https://doi.org/10.7326/M14-2525.
Saxon DR, Iwamoto SJ, Mettenbrink CJ, et al. Antiobesity medication use in 2.2 million adults across eight large health care organizations: 2009–2015. Obesity. 2019;27(12):1975–81. https://doi.org/10.1002/oby.22581.
Seufert J. Leptin effects on pancreatic beta-cell gene expression and function. Diabetes. 2004;53(suppl 1):S152–8.
Shang F-J, et al. Serum omentin-1 levels are inversely associated with the presence and severity of coronary artery disease in patients with metabolic syndrome. Biomarkers. 2011;16(8):657–62. https://doi.org/10.3109/1354750X.2011.622789.
Sharma AM, Pischon T, Hardt S, Kunz I, Luft FC. Hypothesis: beta-adrenergic receptor blockers and weight gain: a systematic analysis. Hypertension. 2001;37(2):250–4.
Shibata R, et al. Association of a fat-derived plasma protein omentin with carotid artery intima-media thickness in apparently healthy men. Hypertens Res. 2011;34(12):1309–12. https://doi.org/10.1038/hr.2011.130.
Singh M, Bedi US, Singh PP, Arora R, Khosla S. Leptin and the clinical cardiovascular risk. Int J Cardiol. 2010;140:266–71.
Sjöström L, Peltonen M, Jacobson P, Sjöström CD, Karason K, Wedel H, et al. Bariatric surgery and long-term cardiovascular events. JAMA. 2012;307(1):56–65.
Srinivasan SR, Bao W, Wattigney WA, et al. Adolescent overweight is associated with adult overweight and related multiple cardiovascular risk factors. The Bogalusa Heart Study. Metabolism. 1996;45:235–40.
Thomas CE, Mauer EA, Shukla AP, Rathi S, Aronne LJ. Low adoption of weight loss medications: a comparison of prescribing patterns of antiobesity pharmacotherapies and SGLT2s. Obesity. 2016;24(9):1955–61. https://doi.org/10.1002/oby.21533.
Tufik S, Santos-Silva R, Taddei JA, Bittencourt LRA. Obstructive sleep apnea syndrome in the Sao Paulo Epidemiologic Sleep Study. Sleep Med. 2010;11(5):441–6.
Virani SS, Alonso A, Benjamin E, et al. Heart disease and stroke statistics—2020 update: a report from the American Heart Association. Circulation. 2020;141:e139–e59628. https://doi.org/10.1161/CIR.0000000000000757.
Wadden TA, Berkowitz RI, Womble LG, Sarwer DB, Phelan S, Cato RK, et al. Randomized trial of lifestyle modification and pharmacotherapy for obesity. N Engl J Med. 2005;353(20):2111–20.
Wang Y, Wang QJ. The prevalence of prehypertension and hypertension among US adults according to the new joint national committee guidelines: new challenges of the old problem. Arch Intern Med. 2004;164(19):2126–34.
Wang Y, Rimm EB, Stampfer MJ, Willett WC, Hu FB. Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men. Am J Clin Nutr. 2005;81(3):555–63.

Wang Y, Lau WB, Gao E, Tao L, Yuan Y, Li R, et al. Cardiomyocyte-derived adiponectin is biologically active in protecting against myocardial ischemia-reperfusion injury. Am J Physiol Endocrinol Metab. 2010;298:E663–70.

Wang Y, et al. A systematic review of application and effectiveness of mhealth interventions for obesity and diabetes treatment and self-management. Adv Nutr. 2017;8(3):449–62. https://doi.org/10.3945/an.116.014100.

Wu Y, Zhai L, Zhang D. Sleep duration and obesity among adults: a meta-analysis of prospective studies. Sleep Med. 2014;15(12):1456–62. https://doi.org/10.1016/j.sleep.2014.07.018. Epub 2014 Sep H

Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Lond Engl. 2019;393(10166):31–9.

Part III
Risk Enhancers

Chapter 9
Family History of Premature Atherosclerotic Cardiovascular Disease

Amit Khera and Ezimamaka Ajufo

Introduction

Familial aggregation of atherosclerotic cardiovascular disease (ASCVD) has been recognized for at least a century. Some of its earliest descriptions come from pedigrees of familial hypercholesterolemia (FH). In these families, the high incidence of premature and non-premature coronary events was linked to markedly elevated cholesterol levels, providing seminal evidence for the causal relationship between elevated cholesterol and ASCVD (Boas et al. 1948). Early twin studies corroborated and quantified the familial predilection to ASCVD even in the absence of severe hypercholesterolemia (Marenberg et al. 1994). Families share known and unknown genetic and environmental factors that place them at increased risk of cardiovascular disease. Recognizing the breadth of information it captures, family history of ASCVD has become a key component of cardiovascular risk assessment.

A central question is what comprises a "positive" family history of premature ASCVD. There are several areas of ambiguity and inconsistency in family history definitions across studies and guidelines. The major ASCVD guidelines define premature ASCVD rather broadly, including coronary, cerebrovascular, and peripheral arterial events occurring before the age of 55 in men and 65 in women (Cardiovascular disease: risk assessment and reduction, including lipid modification 2020; Piepoli et al. 2016; Grundy et al. 2019; Arnett et al. 2019). However, the vast majority of epidemiological family history studies take coronary artery disease (CAD) into

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account, fewer take cerebrovascular disease (CVD) into account, and very few consider peripheral arterial disease (PAD). Moreover, prematurity is defined with a threshold that ranges from 50 to 65 in the family history literature. In most guideline recommendations, family history is considered a binary measure – either positive or negative. Relatedness is specified in some (usually only first-degree relatives), (Cardiovascular disease: risk assessment and reduction, including lipid modification 2020) but is missing in many guidelines (Grundy et al. 2019; Arnett et al. 2019). Similarly, there is considerable variability in the categorization of family history measures in the literature. Many studies define family history of premature ASCVD as a dichotomous measure insensitive to family size, number, and relatedness of affected relatives and relative characteristics. However, some studies define family history as a continuous variable that takes into account the key characteristics ignored by dichotomous family history measures (Li et al. 2000; Ciampi et al. 2001). It is useful to keep this variability in mind when reviewing the recommendations and evidence base for implementing family history of ASCVD in cardiovascular risk assessment.

In this chapter, we review the epidemiology of family history of premature ASCVD, the proposed mechanisms that underlie familial clustering of cardiovascular risk, and recommendations for implementing family history of ASCVD into clinical practice. In addition, following the analytic framework laid out by the Centers for Disease Control and Prevention Office of Public Health Genomics for evaluating evidence about genetic and related tests (Yoon et al. 2003), we discuss the analytic and clinical validity, and clinical utility of collecting a family history of ASCVD in clinical practice, and touch on relevant ethical, legal, and social considerations.

Epidemiology of Family History of Premature ASCVD

Prevalence of Family History of Premature Cardiovascular Disease

The reported prevalence of family history of premature ASCVD ranges from 10% to 40% in cohorts from the general population (Lloyd-Jones et al. 2004a; Philips et al. 2007; Moonesinghe et al. 2019; Hunt et al. 1986) based on how family history of premature ASCVD is defined, and the geographic origin and prevalence of CAD in the population in question. Using the nationally representative National Health and Nutrition Examination Survey (NHANES) sample of US adults from 2007 to 2014, the prevalence of a family history of CAD in any first-degree relative before the age of 50 in the United States was estimated at 12–13% (Moonesinghe et al. 2019). In another population-based US sample of adult offspring free of ASCVD at baseline from the Framingham Heart Study, the prevalence of a parental history of ASCVD before the age of 55 in a father or 65 in a mother was ~40% (Lloyd-Jones et al. 2004a). There does not seem to be appreciable variation in the prevalence of family history of ASCVD by race/ethnicity and socioeconomic status, (Li et al. 2000; Williams et al. 2001) but the impact of age and sex is somewhat unclear. In NHANES, the prevalence

of family history of CAD increased in a graded fashion with age from 9% in those aged 20–39 up to 15% in those aged ≥60 (Moonesinghe et al. 2019). However, in an independent sample of >15,000 adults free of ASCVD at baseline from Eastern Finland, the opposite trend was observed (26%, 23%, and 17% in age groups 30–39, 40–49, and 50–59) (Jousilahti et al. 1996a). Similarly, in some reports, family history of ASCVD has been reported more frequently in women than men (Moonesinghe et al. 2019; Jousilahti et al. 1996a) but not in others (Williams et al. 2001).

Due to its prevalence and associated risk, family history of premature ASCVD contributes to a relevant proportion of ASCVD in the population. In the Health Family Tree Study, a positive or strongly positive family history of CAD was reported in 17% of families but accounted for 66% of CAD events in this population. Similarly, in an international cohort, the CAD risk attributable to family history of premature ASCVD was estimated between 11% and 14% (Williams et al. 2001). Although somewhat less prevalent than CAD, a family history of stroke also confers substantial population risk for stroke. In the Health Family Tree Study, a positive or strongly positive family history of stroke was reported in 12% of families and accounted for 84% of strokes at any age (Williams et al. 2001).

Family History of Premature Cardiovascular Disease and Cardiovascular Risk

Familial aggregation of CAD, CVD, and PAD is well-documented. On average, a family history of premature ASCVD is associated with an ~1.5- to two-fold increased risk of cardiovascular events (Table 9.1) (Lloyd-Jones et al. 2004a; Prushik et al. 2012a; Seshadri et al. 2010; Mvundura et al. 2009). Family history confers risk in the intermediate to long term (>10-year) more strongly than in the short term (<10-year) (Bachmann et al. 2012). A history of an event in one arterial bed confers risk for an event in that arterial bed but also increases the risk of an event in other arterial beds, though to a lesser extent (Lamina et al. 2014; Khaleghi et al. 2014a; Wannamethee et al. 1996a). Family history of ASCVD is associated with increased risk across the socioeconomic and race/ethnicity spectrum. In fact, it may be a stronger risk factor in individuals of African and Hispanic ancestry compared to those of European ancestry (Li et al. 2000; Chow et al. 2011a; Valerio et al. 2016). Conversely, despite some early reports, sex has not been shown to have a convincing influence on the cardiovascular risk conferred by family history – maternal and paternal diseases appear to carry a similar risk (Lloyd-Jones et al. 2004a; Weijmans et al. 2015). The impact of a family history of premature ASCVD depends on certain characteristics of the individual in whom risk is being assessed and their affected family members. Specifically, the age of the individual at the time of risk assessment, the age of the affected family member at the time of the ASCVD event, and the number and relatedness of affected family members are of particular importance.

The age of disease onset in family members and the age of the individual at the time of risk assessment are key determinants of the risk conferred by family history

Table 9.1 Cardiovascular family history and risk of cardiovascular disease

Sample	Study type	N	Family history definition	Outcome	Risk estimate[a]
Family history of ASCVD and CAD risk					
Danish National Register (Ranthe et al. 2015b)	Prospective cohort	4,445,255	MI in first-degree relative	Incident MI	IRR[a] 1.52 (95% CI 1.4–1.55)
Aberdeen Study of Cardiovascular Health in Women (Hasanaj et al. 2013b)	Case–control	945	Heart disease <60 years of age in either parent or any siblings	Prevalent CAD: Angina/MI EKG evidence of Ischemic heart disease	OR 1.67 (95% CI 1.21–2.31)
Framingham Offspring Cohort (Lloyd-Jones et al. 2004b)	Prospective cohort	2302	Parental ASCVD event <55 in father or < 65 in mother	ASCVD event: CAD death MI Coronary insufficiency Angina Ischemic stroke Intermittent claudication Cardiovascular death	Men: OR 2.0 (95% CI 1.2–3.1) Women: OR 1.7 (0.9–3.1)
INTERHEART study (Chow et al. 2011b)	Case–control	26,816	Parental MI <50 years of age	Prevalent MI	OR 2.36 (95% CI 1.89–2.95)
Eastern Finnish population-based sample (Jousilahti et al. 1996b)	Prospective cohort	15,620	Parental history of fatal or nonfatal MI or angina <60 years of age	Fatal and nonfatal MI	Men: RR 1.55 (1.31–1.83) Women: RR 1.80 (95% CI 1.37–2.37)
Family history of ASCVD and stroke risk					
Framingham offspring cohort	Prospective cohort	3443	Parental stroke/transient ischemic attack <65 years of age	Incident stroke/transient ischemic attack	HR 2.79 (95% CI 1.68–4.66)

British Regional Heart Study (Wannamethee et al. 1996b)	Prospective cohort	7735	Parental stroke death <70 Parental CAD death <70	Incident fatal and nonfatal stroke	Family history of stroke: 1.5 (95% CI 1.0–2.3) Family history of CAD: 1.4 (95% CI 1.0–1.9)
Japanese Collaborative Study (Eguchi et al. 2012)	Prospective cohort	53,691	Parental history of stroke	Incident fatal stroke	HR 1.16 (95% CI 1.04–1.29)
Family history of ASCVD and PAD risk					
Patients referred to the Mayo Clinic for lower extremity arterial evaluation and noninvasive laboratory and patients referred for stress echocardiographic screening for CAD (Khaleghi et al. 2014b)	Case–control	6686	PAD: ≥ 1 first-degree relative with revascularization for PAD <65 years of age CAD: ≥ 1 first-degree relative with MI or coronary revascularization <65 years of age	Prevalent PAD: ABI ≤0.9 at rest and/or after exercise History of lower extremity revascularization Poorly compressible leg arteries PAD ICD code	Family history of PAD: OR 1.97 (95% CI 1.60–2.46) Family history of CAD: OR 1.25 (1.12–1.40)
Framingham Offspring Cohort (Prushik et al. 2012b)	Prospective cohort	2970	Incident intermittent claudication	Parental intermittent claudication	HR 1.81 (95% CI 1.14–2.88)

ABI ankle–brachial pressure index, *CAD* coronary artery disease, *IRR* incidence rate ratio, *MI* myocardial infarction, *PAD* peripheral arterial disease
[a]All estimates are multivariable adjusted

of ASCVD, and a strong inverse relationship between age of onset and risk conferred is described (Marenberg et al. 1994; Lloyd-Jones et al. 2004a; Jousilahti et al. 1996a; Chow et al. 2011a; Sesso et al. 2001). The Framingham Offspring study, a prospective longitudinal population-based study of the offspring of participants in the original Framingham study, has been used extensively to study the familial aggregation of ASCVD given the unique availability of *verified* parental disease status rather than self-report. In this cohort, premature parental ASCVD was associated with an OR for ASCVD of 1.7–2.0 vs. 1.1–1.5 for non-premature parental ASCVD (Lloyd-Jones et al. 2004a). In an analysis of cross-sectional data from a population-based US sample in the HealthStyles study, individuals at high familial risk of stroke (≥ 1 first- or second-degree family member with early-onset stroke) had a fourfold higher prevalence of stroke compared to those at low to moderate familial risk (Mvundura et al. 2009). In fact, parental age has been linearly and negatively correlated with the age of ASCVD onset in offspring (Allport et al. 2016); in other words, a family history of premature ASCVD predisposes to premature ASCVD. Indeed, in the Framingham Offspring study, parental risk of premature stroke doubled the risk of stroke at any age but quadrupled the risk of premature stroke (Seshadri et al. 2010).

Conversely, a family history of premature ASCVD appears to be a relatively weak cardiovascular risk factor in older individuals (Philips et al. 2007; Rissanen 1979). In NHANES, a family history of premature CAD in a first-degree relative increased the odds of ASCVD by six-, three-, and twofold in participants aged 20–39, 40–59, and ≥ 60, respectively. In this study, the population risk attributable to family history of premature CAD was highest in the younger population (31% vs. 22% vs. 9% in 20–39, 40–50, and ≥ 60) (Moonesinghe et al. 2019). Some studies show an even more pronounced attenuation of cardiovascular risk with a family history of premature disease in older populations. In the Health Family Tree Study, family history or premature CAD was associated with a 2–four-fold (men, 95% CI 2.8–5.3; women, 1.0–3.8) relative increase in the risk of CAD among individuals aged 20–39, but by age 60, this risk was no longer significant (men, RR 1.2, 95% 0.8–1.6; women, 1.1, 95% CI 0.8–1.5) (Hunt et al. 1986). Similarly, in the Framingham Offspring Cohort, among individuals <60, ASCVD event rates were three times higher in those with a parental history of premature ASCVD compared vs. those without (8-year event rate, 65 vs. 22 per 1000, $p < 0.05$), but among individuals aged ≥60, ASCVD event rates were comparable in those with and without a parental history of ASCVD (8-year event rate, 192 vs. 98 per 1000, $p = 0.2$) (Lloyd-Jones et al. 2004a). In an international case–control study of ~27,000 individuals including 12,000 with a first MI, premature ASCVD was associated with an OR for MI in younger individuals (men <55 and women <65) vs. older individuals of 2 vs. 1.5, respectively ($p = 0.002$ for heterogeneity), (Chow et al. 2011a) but this heterogeneity disappeared after adjustment for cardiovascular risk factors, suggesting that family history of premature ASCVD might be a better predictor of cardiovascular risk in younger individuals due to a correlation and interaction with traditional risk factors in younger individuals (Philips et al. 2007).

Another important determinant of the risk conferred by a family history of ASCVD is the relatedness and number of affected family members. In fact, there

appears to be a dose–response relationship between the number and relatedness of individuals affected and risk conferred, with disease in first-degree relatives carrying greater risk than disease in second- and third-degree family members (Hunt et al. 1986; Khaleghi et al. 2014a; Ambroziak et al. 2020). In a study of >four million individuals and their relatives from the Danish national register with ascertainment of disease status based on a national patient register, compared to individuals with no family history of myocardial infarction (MI), the incidence of MI in those with 1, 2, and ≥ 3 first-degree relatives with a history of MI was 1.5-, 2.4-, and 3.6-fold higher, respectively, than the incidence of MI in those with no affected first-degree relatives. A similar but attenuated trend (incidence rate ratio 1.2-, 1.9-, and 2.2-fold higher, respectively) was observed for second-degree relatives (Ranthe et al. 2015a). Notably, the dose effect within each degree of relatedness may only apply when family members belong to different categories (Lloyd-Jones et al. 2004a; Jousilahti et al. 1996a). For example, in the Framingham Offspring study, the risk associated with a history of premature ASCVD in one parent was comparable to the risk of having a history in both parents (Lloyd-Jones et al. 2004a). In contrast, a risk differential is seen for disease in siblings vs. disease in parents with greater risk conferred by disease in siblings, (Khaleghi et al. 2014a; Nasir et al. 2004a) although this might be more applicable to CAD than to stroke (Yu et al. 2019).

Recognizing the significance of a more detailed family history inclusive of age, number, and relatedness of family members affected, there have been efforts to develop family history measures that capture these elements both within continuous and dichotomous variables (Ciampi et al. 2001; Silberberg et al. 1999) Continuous scores tend to discriminate risk better than categorical measures, but may not be superior to detailed categorical family history descriptions (Silberberg et al. 1999). Moreover, the value of continuous family history scores closely depends on family size, number of affected relatives in the pedigree, and completeness and accuracy of available disease status information, so these scores may not be appropriate for the real-world setting (Silberberg et al. 1999). In fact, the complexity of these scores both in their formulation and implementation has posed considerable barriers to widespread adoption.

In summary, a positive family history of premature ASCVD is highly prevalent in many populations and confers considerable cardiovascular risk at both the individual and population levels. A family history of ASCVD, depending on several parameters, may confer no risk at all or increase risk by up to 12- to 15-fold (Marenberg et al. 1994; Hunt et al. 1986), so restricting the categorization of family history to a simple binary form limits the amount of information it can convey. The risk conferred by a family history depends on a number of key factors, including the age of the individual at the time of risk assessment, as well as the age, event type, number, and relatedness of affected family members. To be reasonably informative for cardiovascular risk assessment, a family history should include, at a minimum, the age at disease onset and/or death, event type, and relatedness from, ideally, at least three–four generations and expressed as either categorical or continuous family history measure (Box 9.1).

Pathophysiology of Familial Cardiovascular Risk

Genetic Determinants of Familial Cardiovascular Risk

Box 9.1 Recommended components of an informative cardiovascular family history

- 3-4 generations
- Define affected individuals
- Define relatedness
- Define vital status (living or deceased)
- Age (or age of death)
- Age at cardiovascular event
- Presence of risk factors (including subclinical atherosclerosis)
- Presence of stigmata of monogenic disorders

In studies of high-risk families and twin studies, CAD is estimated to have a heritability of 40–60%, with the greatest heritable component in younger individuals that develop premature ASCVD (Marenberg et al. 1994; Zdravkovic et al. 2002; Wienke et al. 2005). Genetics plays a major role in familial cardiovascular risk. In the Swedish Twin study, the death of a twin from CAD aged <65 conferred a risk of death from CAD up to 15 times that of the general population in the living twin of a monozygotic pair (siblings share 100% of their genetic material), compared to only 4 times that of the general population in the living twin of a dizygotic pair (sibling share 50% of their genetic material), suggesting that greater genetic similarity confers a higher risk (Marenberg et al. 1994). Familial clustering of cardiovascular disease has both monogenic and polygenic genetic determinants, which may coexist with additive effects. By far the most common monogenic etiology of familial ASCVD, with an estimated prevalence of ~1:250, is FH – a heritable autosomal co-dominant disorder of elevated LDL-C and premature cardiovascular disease. A representative FH pedigree is shown in Fig. 9.1. FH is typically caused by mutations in the *LDLR* gene, but in a minority of cases may be associated with mutations in either *APOB, PCSK9,* or *LDLRAP1*. However, a causative genetic variant is only found in around 40–50% of those meeting clinical criteria for FH in the United States, suggesting the possibility of other unknown or not assessed variants or polygenic causes of dyslipidemia (Ahmad et al. 2012; Berberich and Hegele 2019). With effective lipid-lowering treatment, the life expectancy of individuals with FH is comparable to individuals in the general population; however, <10% of individuals are diagnosed and fewer are appropriately treated (Nordestgaard et al. 2013), such that FH accounts for 3–5% of premature CAD

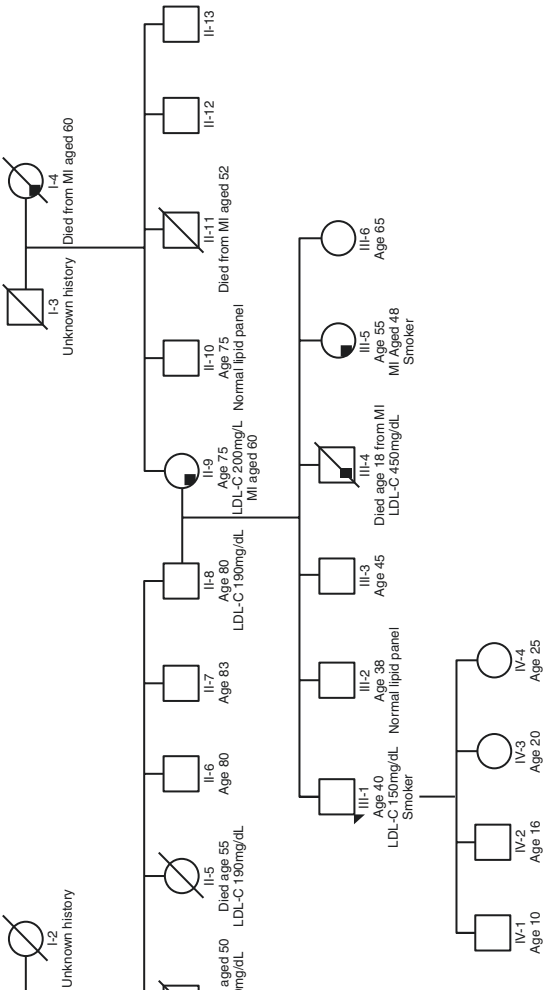

Fig. 9.1 Sample familial hypercholesterolemia pedigree. Squares indicate males, circles indicate females. A box or circle striked across a shape indicates that the individual is deceased. Key information about the individual is included below their symbol if available. The shaded box denotes the presence of MI/CAD. The proband is indicated by the arrow

cases (Nanchen et al. 2015; Genest et al. 1992). Given its prevalence, underdiagnosis, and treatability, FH is an important diagnosis to consider in individuals presenting with a family history of premature ASCVD, and screening these individuals for FH is widely recommended (Cardiovascular disease: risk assessment and reduction, including lipid modification 2020; Piepoli et al. 2016; Grundy et al. 2019). There are rarer monogenic causes of familial cardiovascular risk that should also be kept in mind when evaluating individuals with a family history of premature CAD (Table 9.2).

In most at-risk families, the genetic determinants of cardiovascular risk are polygenic, arising from thousands of small- to -moderate-effect variants found throughout the genome. These risk variants, weighted by their effect estimates, can be aggregated in polygenic risk scores (PRS) and used for cardiovascular risk prediction (Aragam and Natarajan 2020). In one study, individuals in the top 8% of the distribution (~ 1 in 12 individuals) of a 6.6-million variant PRS were at a ≥ threefold increased odds for CAD compared to the general population, which was comparable to the risk conferred by an FH-causing mutation (Khera et al. 2018). Within this high-risk group, family history of heart disease was more prevalent than in the general population (44 vs. 35%, $p < 0.001$) (Khera et al. 2018). Similarly, individuals in the highest quintile of an eight-variant PRS in another study had a significantly higher burden of family history of heart attack/angina compared to those in the lowest quintile (33.4 vs. 28.4%, $p < 0.0001$) (Iribarren et al. 2016). In another study, a standard deviation increase in a 1.7-million variant PRS was associated with a 21% increase in the odds of having a family history of heart disease (Inouye et al. 2018). Despite some overlap, the cardiovascular risk mediated by family history and PRS is partly independent. In one study, adjustment for family history had no effect on the association between an eight-variant PRS and incident CAD. In another study, the association between family history and MI was only modestly attenuated after adjusting for a nine-variant PRS (Chow et al. 2011a). Within the broader understanding that familial cardiovascular risk is only partly genetic, it seems reasonable that PRS do not fully explain the risk conferred by family history and vice versa. It should be noted, however, that some of the lack of overlap might arise from the incompleteness of our knowledge about the polygenic structure of ASCVD.

Clustering of Cardiovascular Risk Factors and Familial Cardiovascular Risk

An important way genetic and environmental pathways influence familial cardiovascular risk is through the clustering of cardiovascular risk factors in families (Li et al. 2000). In a population-based Atherosclerosis Risk in Communities Study (ARIC) sample of adults aged <65, a positive family history was associated with higher BMI, waist-to-hip ratio, LDL-C, Lp(a), TG, and lower HDL-C (Pereira et al.

Table 9.2 Selected Mendelian causes of premature cardiovascular disease

Key pathway affected	Condition	OMIM no.	Gene(s) affected	Global prevalence	Inheritance pattern	Key clinical cardiovascular features[a]
Lipoprotein metabolism	Autosomal recessive hypercholesterolemia	603,813	*LDLRAP1*	<1 in 10,000,000	AR	Similar to HoFH
	Cerebrotendinous xanthomatosis	*213,700*	*CYP27A1*	<5 in 100,000	AR	Tendon xanthomas CAD in childhood/adolescence Severely elevated plasma LDL-C and bile acid intermediates (also found in the urine)
	Familial hypercholesterolemia (FH – Heterozygous form, and HoFH, homozygous form)	143,890, 144,010, 603,776	*LDLR, APOB, PCSK9*	FH ~ 1 in 250–500 HoFH ~1 in 160,000–300,000	ACD	Severely elevated plasma LDL-C (HoFH > FH) Tendon xanthomas, premature corneal arcus (HoFH > FH) Onset CAD 50–60 (FH) and early adolescence (HoFH)
	Sitosterolemia I and II	210,250, 618,666	*ABCG5, ABCG8*	~ 1 in 2500	AR	Elevated plasma plant sterols Mild to severely elevated plasma cholesterol Tendon and tuberous xanthomas in childhood CAD onset <30
	Tangier disease	205,400	*ABCA1*	Very rare	AR	Very low HDL-C and low total and LDL-C Mild to moderately elevated serum TG Cholesterol accumulation in the reticuloendothelial system leading to orange tonsils, peripheral neuropathy, hypersplenism CAD onset age 50–60

(continued)

Table 9.2 (continued)

Key pathway affected	Condition	OMIM no.	Gene(s) affected	Global prevalence	Inheritance pattern	Key clinical cardiovascular features[a]
Connective tissue/ vascular	Williams–Beuren	194,050	7q11 deletion	~ 1: 7500?	AR	Generalized arterial stenosis including supravalvular aortic stenosis
	Familial thoracic aortic aneurysm and dissection	611,788	*ACTA2*	Very rare	AD	Arterial dissection Premature atherosclerosis (especially CAD and stroke)
	Pseudoxanthoma elasticum	264,800	*ABCC6*	1 in 50,000 (carriers 1–2 in 300)	AD, AR	Premature atherosclerosis (CAD, CVD, and PAD)
	Fibromuscular dysplasia	135,580	Unknown	Unknown	AD	Focal arterial narrowing – Particularly of the renal and cerebral vasculature
Insulin	Autosomal-dominant coronary artery disease 2	*603,507*	*LRP6*	Very rare	AD	Metabolic syndrome Premature CAD (<50 in men, <55 in women)
	Familial partial lipodystrophy 1 Familial partial lipodystrophy 2	608,600 151,660	Unknown *LMNA*	1 in 1,000,000	AD	Lipodystrophy Metabolic syndrome/insulin resistance Premature atherosclerosis
Other	Homocystinuria	236,200, 236,250	*CBS, MTHFR*	~ 1 in 350,000	AR	Premature atherosclerosis (especially CAD and stroke)
	Hutchison–Gilford progeria	176,670	*LMNA*	Very rare	AD	Premature atherosclerosis
	Werner syndrome	277,700	*RECQL2*	Very rare		Premature atherosclerosis

Table adapted from (Stitziel and MacRae 2014)

ACD autosomal co-dominant, *AD* autosomal dominant, *AR* autosomal recessive, *CAD* coronary artery disease, *CVD* cerebrovascular disease, *FH* heterozygous familial hypercholesterolemia, *HoFH* homozygous familial hypercholesterolemia, *PAD* peripheral arterial disease, *TG* triglyceride

[a] Key clinical features relevant to the cardiovascular presentation of these disorders that have been reported in the literature are presented. However, as a rule, clinical heterogeneity is well recognized for all of the disorders listed

2000). In one study, compared to men without a family history of premature CAD, those with a family history of premature CAD had higher systolic and diastolic blood pressures, total cholesterol levels, BMI, and a higher prevalence of diabetes (Jousilahti et al. 1996a). The contribution of cardiovascular risk factors to familial cardiovascular risk is further demonstrated by the attenuation of the association between parental history of ASCVD and cardiovascular risk after adjustment for cardiovascular risk factors (Lloyd-Jones et al. 2004a). Moreover, consistent with the higher risk conferred by a sibling vs. a parental history of ASCVD, (Nasir et al. 2004b) a sibling history of premature ASCVD is associated with a higher prevalence of hypertension and dyslipidemia compared to a parental history of premature ASCVD (Nasir et al. 2004b).

Importantly, a family history of ASCVD is also associated with a higher frequency of adverse lifestyle and behaviors such as smoking (Lloyd-Jones et al. 2004a; Seshadri et al. 2010; Pereira et al. 2000), physical inactivity, and poor diet (Kulshreshtha et al. 2015). In fact, shared habits not only contribute to familial aggregation of ASCVD, but lifestyle interventions can help modify the increased risk that accompanies a family history (Khera et al. 2016). The relationship between cardiovascular risk factors and family history is somewhat complex. The degree of risk conferred by family history is modified by the risk factor burden background, such that a family history of ASCVD is a stronger risk factor in those at intermediate predicted cardiovascular risk compared to those at the extremes of predicted risk (Lloyd-Jones et al. 2004a; Michos et al. 2005).

Traditional cardiovascular risk factors only partly mediate the cardiovascular risk conferred by a family history of premature ASCVD (Jousilahti et al. 1996a; Chow et al. 2011a; Mehta et al. 2020). The importance of broader socioeconomic factors requires further attention but appears to be modest. It is also possible that family history may influence cardiovascular risk via non-atherosclerotic pathways. For example, in one study designed to examine the relationship between family history of MI, coronary artery calcification (CAC), and incident CAD in the population-based Dallas Heart Study (DHS), family history of MI and coronary artery calcification were independently associated with CAD and shown to be additive in effect (Paixao et al. 2014).

In summary, the mechanisms that underlie familial cardiovascular risk are multifactorial, encompassing genetic and environmental factors that influence cardiovascular risk in part through their effects on cardiovascular risk factors such as hypertension, diabetes, dyslipidemia, smoking, physical inactivity, and poor diet. The identification of familial cardiovascular disease should first prompt consideration of screening for a Mendelian disorder with cardiovascular manifestations, particularly familial hypercholesterolemia (Fig. 9.2). If this screening is negative or not pursued, careful screening for cardiovascular risk factors and aggressive risk factor management should follow, particularly in younger individuals where this history carries the greatest risk and the impact of prevention might be greatest.

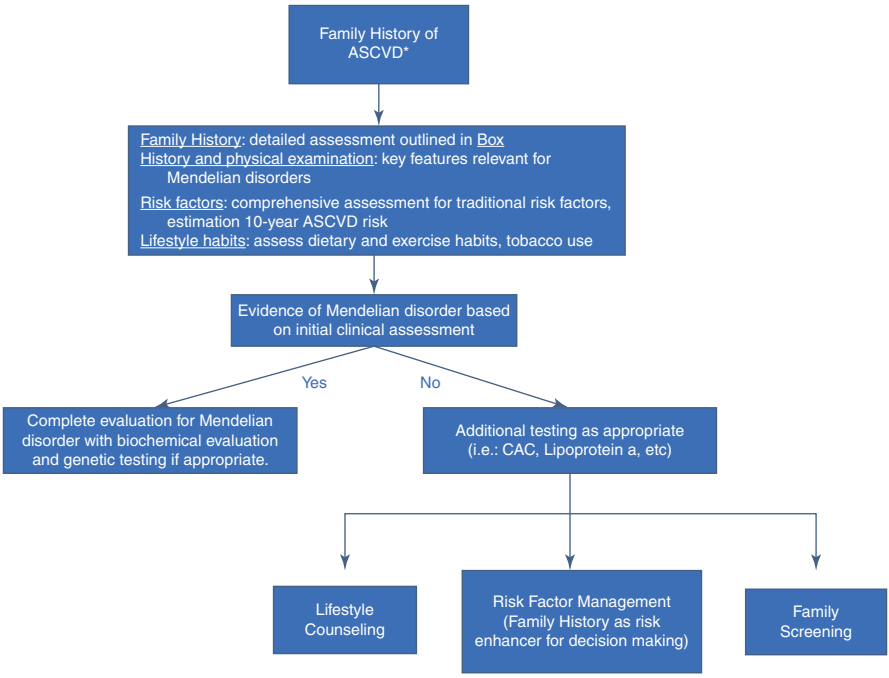

Fig. 9.2 Approach to the patient with a family history of premature ASCVD. * A history of ≥1 first-, second-, or third-degree relative with a premature ASCVD

Family History of Premature ASCVD in Clinical Practice

Accuracy of Family History of Premature Cardiovascular Disease

An important prerequisite for a diagnostic or screening tool to be implemented into clinical practice is an acceptable level of accuracy. The accuracy of family history reports has been examined by comparing proband reports to family member reports, medical records, or death certificates. Proband reported family history of premature ASCVD is highly specific (>90%) with variable sensitivity (60–80%) based on ascertainment method, age of the proband, and the definition of family history. Using family member report as the standard, the accuracy of proband report was examined in the NHLBI Family Heart Study using ~3000 middle-aged adults (Bensen et al. 1999). They found that the sensitivity of proband report of CAD in first-degree relatives was high (>80%) and specificity was very high (>95%). In this study, the sensitivity of the proband report varied based on proband characteristics

such as age – for example, the sensitivity of sibling disease reports was lower in older probands (Bensen et al. 1999). In the Framingham Offspring study where parental medical records were used as the standard, proband report was highly specific for parental disease status (≥ 95%), but was only moderately also affected the accuracy of reporting – probands with incorrect reports were on average 2–4 years older than their counterparts with correct reports. Broadening the definition of family history to include coronary disease at any age improved the accuracy of the proband's report (Murabito et al. 2004). In a study with a population-based cohort that used a death certificate as the standard, proband report of parental cardiovascular mortality was associated with a sensitivity and specificity of 89% and 86%, respectively. In this study, sensitivity trended toward being lower in older offspring (Watt et al. 2000; Silberberg et al. 1998). Of note, these findings are consistent in cardiovascular disease cohorts (Kee et al. 1993; Øygarden et al. 2016).

Family History of Premature Cardiovascular Disease and Risk Prediction

The clinical contribution of family history of premature ASCVD can be examined by assessing whether it improves the prediction of cardiovascular events when combined with traditional cardiovascular risk factors. Family history of CAD has consistently been shown to provide a significant albeit modest improvement in risk prediction when added to models based on traditional risk factors (Hasanaj et al. 2013a). In a sample of middle-aged population-based British individuals at intermediate cardiovascular risk, adding family history of CAD to the Framingham Risk Score led to marginal improvement in net reclassification (~2% reclassification) (Sivapalaratnam et al. 2010). In the population-based Multiethnic Study of Atherosclerosis (MESA) US cohort, the Reynolds Risk Score, a derivative of the Framingham Risk Score that includes family history, only modestly improved risk prediction compared to the Framingham Risk Score (DeFilippis et al. 2015). The value of family history of premature ASCVD is of particular importance in individuals estimated to be at intermediate cardiovascular risk based on traditional cardiovascular factors as guidelines recommend its use to stratify risk within this group. Using 1330 MESA participants at intermediate risk, adding family history to a base model that included FRS and race/ethnicity led to modest discriminatory improvement (0.675 vs. 0.623, $p < 0.01$) without improving reclassification ($p = 0.16$) (Yeboah et al. 2012). In the DHS, the addition of family history of premature MI in a first-degree relative significantly albeit modestly improved the c-statistic (0.86 vs. 0.87, $p = 0.04$) and led to significantly improved net reclassification (0.55, 95% CI 0.27–0.83, $p < 0.001$), a clinically more useful metric than the c-statistic (Paixao et al. 2014).

Clinical Applications of Family History of Premature Cardiovascular Disease

The 2018 AHA/ACC guidelines on the management of blood cholesterol recommended using the pooled cohort equation (PCE) to estimate the 10-year risk of fatal and nonfatal MI and stroke in adults aged 40–75. Family history of premature ASCVD was not included in the PCE but was listed as one of 12 risk-enhancing factors (Table 9.3) to be used in a clinician–patient risk discussion regarding statin therapy in individuals at borderline (5–7.4%; class IIb) and intermediate (7.5–19.9%; class I) estimated 10-year cardiovascular risk. The presence of risk enhancers, including family history of premature ASCVD, in the context of shared decision-making in these groups, favors initiation of statin therapy in these recommendations (Grundy et al. 2019). The presence of a family history of premature ASCVD is also provided as an indication for statin therapy in adults aged >20 if associated with moderate primary hypercholesterolemia (LDL-C 160–189 mg/dL) refractory to

Table 9.3 Risk-enhancing/risk-modifying factors listed in ACC/AHA and ESC guidelines

Risk-enhancing factors – AHA/ACC guidelines	Risk modifiers – ESC guidelines
Family history of premature ASCVD (males, age < 55; females, age < 65)	Social deprivation
Primary hypercholesterolemia (LDL-C, 160–180 mg/dL, non-HDL-C 190–2019 mg/dL)	Obesity and central obesity
Metabolic syndrome [≥ 3 of increased waist circumference, elevated TG (>150 mg/dL), elevated blood pressure, elevated blood glucose, low HDL-C (<40 mg/dL in men, <50 mg/dL in women)]	Physical inactivity
Chronic kidney disease (eGFR 15–59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation)	Psychosocial stress including vital exhaustion
Chronic inflammatory conditions; e.g., psoriasis, RA, or HIV/AIDs	Family history of premature ASCVD (males, age < 55; females, age < 60)
History of premature menopause (before age 40) and history of pregnancy-associated conditions that increase lifetime ASCVD risk; e.g., pre-eclampsia	Chronic immune-mediated inflammatory disorder
High-risk races/ethnicities (e.g., south Asian ancestry)	Major psychiatric disorders
Biomarkers:	Treatment for HIV/AIDS
Persistently elevated (≥3 separate measurements) primary hypertriglyceridemia (≥ 175 mg/dL)	Atrial fibrillation
Elevated high-sensitivity c-reactive protein (≥ 2.0 mg/L)	Left ventricular hypertrophy
Elevated Lp(a) (≥ 50 mg/dL or ≥ 125 nmol/L) – Relative indication for measurement is a family history of premature ASCVD	Chronic kidney disease
Elevated apoB (≥ 130 mg/dL)	Obstructive sleep apnea syndrome
ABI <0.9	Nonalcoholic fatty liver disease
	Arterial (carotid and/or femoral) plaque on arterial ultrasonography
	CT coronary calcium score

ACC American College of Cardiology, *AHA* American Heart Association, *AID* acquired immunodeficiency syndrome, *ABI* ankle–brachial pressure index, *ESC* European Society of Cardiology, *HIV* human immunodeficiency virus, *RA* rheumatoid arthritis

lifestyle measures. Finally, in these guidelines, a positive family history is used to identify children to screen for FH from as early as the age of 2, and statin initiation is recommended in children aged ≥10 with an LDL-C > 190 mg/dL or family history of premature ASCVD consistent with FH and LDL-C > 160 mg/dL, despite 3–6 months of lifestyle therapy (class IIa).

The 2016 European Society of Cardiology (ESC) Guidelines on Cardiovascular Disease Prevention gave its strongest recommendation for systematic cardiovascular risk assessment to individuals at increased cardiovascular risk that includes those with a family history of premature ASCVD (Piepoli et al. 2016). Here, calculation of the 10-year risk of a fatal ASCVD event with the Systematic Coronary Risk Estimation (SCORE) system was recommended and family history of premature ASCVD in first-degree relatives listed as one of several risk modifiers (Table 9.3) to be used to adjust risk estimates at decisional thresholds (Piepoli et al. 2016). The ESC guidelines also recommended that all individuals with a family history of premature ASCVD in a first-degree relative below the age of 50 be screened for FH (Piepoli et al. 2016; Mach et al. 2020).

As it has been proposed as a risk enhancer, it is useful to consider how family history of premature ASCVD compares to other risk enhancers and nontraditional cardiovascular risk factors in improving cardiovascular risk prediction in the intermediate-risk group. In the Multiethnic Study of Atherosclerosis (MESA) study, adding family history of ASCVD to a base model that included only traditional cardiovascular risk factors improved risk prediction far more than adding all of the other risk enhancers examined (ankle–brachial index, high-sensitivity C-reactive protein, carotid intimamedia thickness) except CAC. CAC improved the discrimination and net reclassification of the base model considerably more than family history (Yeboah et al. 2012). As mentioned, several studies have demonstrated an increased prevalence of CAC in those with a family history of premature ASCVD (Philips et al. 2007; Nasir et al. 2004b), and thus CAC scanning may be considered in select lower-risk individuals (<5% 10-year risk of ASCVD) with such histories (Hecht et al. 2017). In individuals with both a premature family history of ASCVD and CAC, the increased risks from these two conditions are additive (Paixao et al. 2014). Lp(a) has been shown to be a strong independent predictor of cardiovascular risk and is increasingly used in cardiovascular risk prediction. The 2018 ACC/AHA and the 2019 ESC Cholesterol Guidelines advocate for measuring Lp(a) in select patients with a family history of premature cardiovascular disease. These individuals more commonly have elevated Lp(a) levels, and the predictive effects for cardiovascular events of Lp(a) are also additive to those of family history of premature ASCVD (Mehta et al. 2020).

The guidelines described predominantly focus on cholesterol management. As mentioned, individuals with a family history of premature ASCVD also have a higher prevalence of several traditional risk factors, and a more vigilant and comprehensive assessment for all traditional risk factors is warranted when a family history is present (Fig. 9.2). Given that adverse lifestyle habits can accompany a family history of premature ASCVD, individuals with such histories should be counseled on healthy dietary habits, the importance of habitual exercise, and the imperative for

smoking cessation if they are active tobacco users. In one study, healthy lifestyle habits were associated with a nearly 50% lower risk of coronary events in those at high genetic risk for CAD (Khera et al. 2016). Similarly, the increased risk of MI in carriers of pathogenic variants of the 9p21 gene was significantly attenuated in those with a healthy dietary pattern (Do et al. 2011). Furthermore, the presence of a family history of premature ASCVD should also lead to at least a basic clinical assessment for a monogenic etiology (Stitziel and MacRae 2014). The evaluation of an individual with a family history of premature cardiovascular disease should be systematic, encompassing appropriate assessment for Mendelian etiologies and broad risk stratification and management (Fig. 9.2). Further, once a family history is identified, including any biological or genetic correlates, additional family members should also undergo comprehensive screening, including children and siblings.

Current Utilization of Family History of Premature Cardiovascular Disease

Despite its widespread adoption in the guidelines, family history of ASCVD remains grossly underutilized and incompletely recorded in clinical practice, raising questions about its clinical utility (Dhiman et al. 2014; Orlando et al. 2016; De Sutter et al. 2003). An assessment of the clinical utility of including family history of premature ASCVD in cardiovascular risk assessment should take into account the availability of effective interventions based on the assessed risk, health risks and benefits of familial risk assessment and associated interventions, and the economic assessment of associated interventions if available (Yoon et al. 2003). There are a number of low-risk, highly efficacious pharmacological and nonpharmacological interventions available for primary prevention in individuals deemed to be at high cardiovascular risk based on the presence of a positive family history of premature CAD. In a post-hoc analysis of the St. Francis Heart Study, a trial that randomized adults 50–70 years of age to atorvastatin 20 mg /day or placebo, individuals with a positive family history of premature CAD and positive CAC experienced a 45% relative reduction in cardiovascular events but no effect was observed in those with positive CAC with no family history of premature CAD (Mulders et al. 2012).

Ultimately, the effectiveness of preventative measures depends on uptake (Orlando et al. 2016), which, in turn, depends on an understanding and acceptance of assessed risk by affected individuals and their providers, and a willingness to follow relevant recommendations. Although somewhat sparse, the available data suggests that individuals with a family history of premature CVD have a higher perceived risk of personal ASCVD, (Imes and Lewis 2014; Petr et al. 2014) but this does not consistently lead to a change in preventive health behaviors (Imes and Lewis 2014). Interestingly, women may not perceive the implications of a family history of premature ASCVD to the same degree as men (Patel et al. 2007). The importance of the provider in translating risk assessment to behavioral change must be emphasized. In a study designed to facilitate the uptake of risk-stratified

guidelines for hereditary cancers and thrombophilias in the primary care setting, only a third of patients that met the criteria for screening had relevant orders entered by their physician. When these orders were entered, only half of the patients followed through with the order (Orlando et al. 2016). In a different study designed to determine the impact of automated family history assessment and tailored messages for six chronic diseases, including CAD, successful delivery of the intervention led to favorable dietary modifications and increased exercise but reduced cholesterol screening (Ruffin et al. 2011).

These findings suggest that the failure to adopt preventive behaviors is in part attributable to the failure of providers to collect and act on a positive family history (De Sutter et al. 2003). For providers, barriers to implementing family history-based patient care that have been recognized include time restrictions, lack of a framework for collecting family history, and difficulty interpreting family history data (Orlando et al. 2016). As such, innovative family history collection tools that address these barriers have been sought (Table 9.4) (Ginsburg et al. 2019).

Table 9.4 Selected US-based patient-facing web-based tools available for collecting cardiovascular family history

Tool	Organization	Disease categories	Availability to patients	Decision support provided to	EHR integration	Reference
AncestryHealth	Ancestry	Several	Public – free[a]	Patient	No	–
Health Heritage	Northshore University Health system	Several	Patient portal	Patient and clinicians	Yes	Cohn et al. (2010)
MyLegacy	Cleveland Clinic	Several	Patient portal	Patient and clinician	Yes	–
Family Healthware	Sanitas Inc.	Several	Public – fee-based	Patient	No	Rubinstein et al. (2011)
Family HealthLink	Ohio State University Medical Center	Several	Public – free	Patient	No	Sweet et al. (2015)
My Family Health Portrait	CDC	Several	Public – free	Patient	No	Facio et al. (2010)
MeTree	Duke University Medical Center	Several	Research only	Patient and clinician	Yes	Wu et al. (2019)
Family History Questionnaire	Progeny Software	Several	Patient Portal	Clinician	Yes	–
VICKY	Boston Medical Center	Several	Research only	None	Yes	Wang et al. (2015)

Adapted from (Welch et al. 2018)
CDC Centers for Disease Control and Prevention, *EHR* electronic health record, *VICKY* Virtual Counselor for Knowing Your Family History
[a]Currently closed to new users

Ethical, Legal, and Social Implications of Collecting Family History of Premature Cardiovascular Disease

The key legal issues surrounding familial cardiovascular risk assessment involve informed consent, data ownership, obligation to disclose, and reporting requirement. In the United States, of the laws at the federal and state level that govern these issues, (Genetic Discrimination 2020) the Health Insurance Portability and Accountability Act (HIPAA) privacy rule and the Genetic information Nondiscrimination Act (GINA) are of particular importance. Under the HIPAA privacy rule, health-care providers are permitted to disclose protected health information about an individual to another provider, when this information is requested for the treatment of the individual's family member (Frequently Asked Questions 2020). This disclosure is permitted without the individual's written authorization or other agreement with a few exceptions. Physicians may decline to disclose protected health information especially if they agree to a patient's request not to do so, although the HIPAA privacy act does not oblige physicians to comply with such requests. GINA protects individuals from genetic discrimination in health insurance and employment (Genetic Discrimination 2020; Genetic Information Nondiscrimination Act 2020). Under GINA, family health history is included in the definition of "genetic information." GINA prohibits health insurers or employers to require or use genetic information to make decisions about eligibility, pricing, or coverage for health-care insurance, employment, and pay. However, one important criticism of GINA is its limited scope – it does not protect against the use of genetic information by institutions such as life, disability, and long-term care insurance companies, schools, and mortgage lenders, leaving loopholes for exploitation. It is unclear what impact the provisions and limitations of these laws have in clinical practice. These issues and the potential of family history of premature ASCVD to lead to stigmatization need to be further explored.

In summary, patient reports of family history of cardiovascular disease are accurate and improve cardiovascular risk prediction when added to traditional cardiovascular risk factors including CAC. A family history of premature ASCVD is of particular importance in younger individuals where it carries the greatest risk and traditional cardiovascular risk factors are less common and less useful for risk discrimination. Wherever possible, family history collection should begin outside the clinical encounter using the growing number of resources available to help patients collect family histories at home, where family members can participate in this process. Given its relatively low cost and broad availability, the inclusion of family history of ASCVD in cardiovascular risk assessment is widely supported by major guidelines that recommend its use in screening and treatment decisions. Individuals with a positive family history of ASCVD should be screened for FH and should undergo thorough cardiovascular risk factor screening with aggressive risk management through lifestyle and pharmacological measures. In some circumstances, additional testing such as CAC scanning or Lp(a) measurement.

Practical Considerations in Obtaining a Family History

An important practical consideration is *how* to collect a family history of ASCVD in a standardized and clinically useful format within the constraints of modern practice. Family history collection has two main purposes: to identify monogenic causes of premature cardiovascular disease and, more importantly, inform cardiovascular risk assessment. Regardless of the method used, a complete cardiovascular family history should include certain information to be useful (Box). Constructing a three–four generation pedigree remains the gold standard for family history collection. This should be pursued when feasible, over several clinic visits if necessary. Admittedly, however, pedigree construction may take ≥20 minutes**,** not accounting for the time required for interpretation, and so is generally impractical. One alternative to drawing pedigrees is to record information using the family history module found in many electronic health record (EHR) systems that allow entry of both structured and free-text family information. An example of the fields available in a family history domain is shown in Fig. 9.3. Some EHR vendors provide the option of constructing pedigrees using the information recorded in the family history module. One issue with EHR family history modules is that their structured fields do not allow for detailed information important for cardiovascular risk assessment such as risk factor profile, age, and cause of death, and much of this is left for free-text entry. Moreover, few EHRs are currently able to translate this information into risk-based individualized recommendations.

As such, perhaps the most important development in family history implementation has been the move to empower patients to do this outside the clinical setting. Leveraging the availability of EHRs and widespread internet availability and web literacy, a number of web-based patient-facing family health history tools have been developed (Ginsburg et al. 2019; Welch et al. 2018). Many of these have been developed exclusively for cancer, but a handful gather information on multiple chronic diseases, including cardiovascular diseases (Table 9.4). Validation of many of these tools is ongoing, but early evidence demonstrates acceptability to both patients and

Fig. 9.3 EPIC family history module. Bro brother, Fa father, MGFa maternal grandfather, MGMo maternal grandmother, Mo mother, Sis sister, PGFa paternal grandfather, PGMo paternal grandmother

clinicians and comparable accuracy to family history ascertainment with a genetic counselor (Ginsburg et al. 2019). In addition, many provide risk management recommendations to clinicians, patients, or both and improve risk stratification compared to paper-based and ad hoc family history collection. Currently, none of the freely available tools are interoperable with the EHR, which is a major limitation, although all allow easy data sharing. As we look to the future and to improve the collection of meaningful family histories in routine practice, it is clear that data collection will increasingly occur outside the clinical setting. With this shift, the clinician's role will become teaching patients what information needs to be recorded in the family history, updating and interpreting the history in the EHR. For this to occur, EHR integration with web-facing family history tools will be crucial (de Hoog and Portegijs 2014; Feero et al. 2008).

Conclusion

A family history of premature ASCVD captures valuable information about genetic and environmental exposure like no other tool available for cardiovascular risk assessment. This information is readily obtained, inexpensive, and widely acceptable to patients. Moreover, family histories can be used to simultaneously assess predisposition to multiple diseases. For these reasons among others, despite genomic advances, family history collection is likely to remain an essential part of cardiovascular risk assessment. It should be carried out systematically and used to inform cardiovascular risk management from as early as childhood. Clinicians should be aware of how to obtain a complete and informative family history and of web-facing tools that patients can use to start this process before the clinical encounter. Guidelines have generally applied family history as a risk-enhancing factor when the decision for preventive therapies is uncertain. The presence of a family history of premature ASCVD should also prompt assessment for Mendelian disorders such as FH, more rigorous surveillance for traditional risk factors and adverse lifestyle habits, and more aggressive intervention of these modifiable factors. Underutilization of family history in clinical practice undermines the individual and public health potential of this tool – addressing this problem should be a priority for all clinicians.

References

Ahmad Z, Adams-Huet B, Chen C, Garg A. Low prevalence of mutations in known loci for autosomal dominant hypercholesterolemia in a multiethnic patient cohort. Circ Cardiovasc Genet. 2012;5:666.

Allport SA, Kikah N, Abu Saif N, Ekokobe F, Atem FD. Parental age of onset of cardiovascular disease as a predictor for offspring age of onset of cardiovascular disease. PLoS One. 2016;11:e0163334.

Ambroziak M, Niewczas-Wieprzowska K, Maicka A, Budaj A. Younger age of patients with myocardial infarction is associated with a higher number of relatives with a history of premature atherosclerosis. BMC Cardiovasc Disord. 2020;20:410.

Aragam KG, Natarajan P. Polygenic scores to assess atherosclerotic cardiovascular disease risk. Circ Res. 2020;126:1159–77.

Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Circulation. 2019;140:e596–646.

Bachmann JM, Willis BL, Ayers CR, Khera A, Berry JD. Association between family history and coronary heart disease death across long-term follow-up in men: the cooper center longitudinal study. Circulation. 2012;125:3092.

Bensen JT, Liese AD, Rushing JT, Province M, Folsom AR, Rich SS, et al. Accuracy of proband reported family history: the NHLBI Family Heart Study (FHS). Genet Epidemiol. 1999;17:141.

Berberich AJ, Hegele RA. The complex molecular genetics of familial hypercholesterolaemia. Nat Rev Cardiol. 2019;16:9.

Boas EP, Parets AD, Adlersberg D. Hereditary disturbance of cholesterol metabolism: a factor in the genesis of atherosclerosis. Am Heart J. 1948;35:611–22.

Cardiovascular disease: risk assessment and reduction, including lipid modification [Internet]. [cited 2020 Nov 18]. Available from: https://www.nice.org.uk/guidance/cg181/chapter/1-Recommendations#identifying-and-assessing-cardiovascular-disease-cvd-risk-2

Chow CK, Islam S, Bautista L, Rumboldt Z, Yusufali A, Xie C, et al. Parental history and myocardial infarction risk across the world: the INTERHEART study. J Am Coll Cardiol. 2011a;57:619.

Chow CK, Islam S, Bautista L, Rumboldt Z, Yusufali A, Xie C, et al. Parental history and myocardial infarction risk across the world: the INTERHEART study. J Am Coll Cardiol. 2011b;57:619.

Ciampi A, Courteau J, Niyonsenga T, Xhignesse M, Lussier-Cacan S, Roy M. Family history and the risk of coronary heart disease: comparing predictive models. Eur J Epidemiol. 2001;17:609–20.

Cohn WF, Ropka ME, Pelletier SL, Barrett JR, Kinzie MB, Harrison MB, et al. Health Heritage©, a web-based tool for the collection and assessment of family health history: initial user experience and analytic validity. Public Health Genomics. 2010;13:477.

de Hoog CLMM, Portegijs PJM, Stoffers HEJH. Family history tools for primary care are not ready yet to be implemented. A systematic review. Eur J Gen Pract. 2014;20:125–33.

De Sutter J, De Bacquer D, Kotseva K, Sans S, Pyörälä K, Wood D, et al. Screening of family members of patients with premature coronary heart disease: results from the EUROASPIRE II family survey. Eur Heart J. 2003;24:249.

DeFilippis AP, Young R, Carrubba CJ, McEvoy JW, Budoff MJ, Blumenthal RS, et al. An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. Ann Intern Med. 2015;162:266.

Dhiman P, Kai J, Horsfall L, Walters K, Qureshi N. Availability and quality of coronary heart disease family history in primary care medical records: implications for cardiovascular risk assessment. PLoS One. 2014;9:e81998.

Do R, Xie C, Zhang X, Männistö S, Harald K, Islam S, et al. The effect of chromosome 9p21 variants on cardiovascular disease may be modified by dietary intake: evidence from a case/control and a prospective study. PLoS Med. 2011;8:e1001106.

Eguchi E, Iso H, Wada Y, Kikuchi S, Watanabe Y, Tamakoshi A, et al. Parental history and lifestyle behaviors in relation to mortality from stroke among japanese men and women: the japan collaborative cohort study. J Epidemiol. 2012;22:331.

Facio FM, Feero WG, Linn A, Oden N, Manickam K, Biesecker LG. Validation of My Family Health portrait for six common heritable conditions. Genet Med. 2010;12:370.

Feero WG, Bigley MB, Brinner KM. New standards and enhanced utility for family health history information in the electronic health record: an update from the American Health Information Community's Family Health History Multi-Stakeholder Workgroup. J Am Med Informatics Assoc. 2008;15:723.

Frequently Asked Questions [Internet]. [cited 2020 Nov 21]. Available from: https://www.hhs.gov/hipaa/for-professionals/faq/512/under-hipaa-may-a-health-care-provider-disclose-information-requested-for-treatment/index.html

Genest JJ, Martin-Munley SS, McNamara JR, Ordovas JM, Jenner J, Myers RH, et al. Familial lipoprotein disorders in patients with premature coronary artery disease. Circulation. 1992;85:2025–33.

Genetic Discrimination [Internet]. [cited 2020 Dec 6]. Available from: https://www.genome.gov/about-genomics/policy-issues/Genetic-Discrimination#otherlaws

Genetic Information Nondiscrimination Act [Internet]. [cited 2020 Dec 6]. Available from: http://www.ginahelp.org/GINAhelp.pdf

Ginsburg GS, Wu RR, Orlando LA. Family health history: underused for actionable risk assessment. Lancet. 2019;394:596.

Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol. J Am Coll Cardiol. 2019;139:e1046.

Hasanaj Q, Wilson BJ, Little J, Montazeri Z, Carroll JC. Family history: impact on coronary heart disease risk assessment beyond guideline-defined factors. Public Health Genomics. 2013a;16:208.

Hasanaj Q, Wilson BJ, Little J, Montazeri Z, Carroll JC. Family history: impact on coronary heart disease risk assessment beyond guideline-defined factors. Public Health Genomics. 2013b;16:208.

Hecht H, Blaha MJ, Berman DS, Nasir K, Budoff M, Leipsic J, et al. Clinical indications for coronary artery calcium scoring in asymptomatic patients: expert consensus statement from the Society of Cardiovascular Computed Tomography. J Cardiovasc Comput Tomogr. 2017;11:157.

Hunt SC, Williams RR, Barlow GK. A comparison of positive family history definitions for defining risk of future disease. J Chronic Dis. 1986;39:809.

Imes CC, Lewis FM. Family history of cardiovascular disease, perceived cardiovascular disease risk, and health-related behavior: a review of the literature. J Cardiovasc Nurs. 2014;29:108.

Inouye M, Abraham G, Nelson CP, Wood AM, Sweeting MJ, Dudbridge F, et al. Genomic risk prediction of coronary artery disease in 480,000 adults. J Am Coll Cardiol. 2018;72:1883–93.

Iribarren C, Lu M, Jorgenson E, Martínez M, Lluis-Ganella C, Subirana I, et al. Clinical utility of multimarker genetic risk scores for prediction of incident coronary heart disease. Circ Cardiovasc Genet. 2016;9:531–40.

Jousilahti P, Puska P, Vartiainen E, Pekkanen J, Tuomilehto J. Parental history of premature coronary heart disease: an independent risk factor of myocardial infarction. J Clin Epidemiol. 1996a;49:497.

Jousilahti P, Puska P, Vartiainen E, Pekkanen J, Tuomilehto J. Parental history of premature coronary heart disease: an independent risk factor of myocardial infarction. J Clin Epidemiol. 1996b;49:497.

Kee F, Tiret L, Robo JY, Nicaud V, McCrum E, Evans A, et al. Reliability of reported family history of myocardial infarction. BMJ England. 1993;307:1528–30.

Khaleghi M, Isseh IN, Bailey KR, Kullo IJ. Family history as a risk factor for peripheral arterial disease. Am J Cardiol. 2014a;114:928.

Khaleghi M, Isseh IN, Bailey KR, Kullo IJ. Family history as a risk factor for peripheral arterial disease. Am J Cardiol. 2014b;114:928.

Khera AV, Emdin CA, Drake I, Natarajan P, Bick AG, Cook NR, et al. Genetic risk, adherence to a healthy lifestyle, and coronary disease. N Engl J Med. 2016;375:2349–58.

Khera AV, Chaffin M, Aragam KG, Haas ME, Roselli C, Choi SH, et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. Nat Genet. 2018;50:1219.

Kulshreshtha A, Vaccarino V, Goyal A, McClellan W, Nahab F, Howard VJ, et al. Family history of stroke and cardiovascular health in a national cohort. J Stroke Cerebrovasc Dis. 2015;24:447.

Lamina C, Linsenmeyer J, Weissensteiner H, Kollerits B, Meisinger C, Rantner B, et al. Correlation between a positive family risk score and peripheral artery disease in one case-control and two population-based studies. Atherosclerosis. 2014;237:243.

Li R, Bensen JT, Hutchinson RG, Province MA, Hertz-Picciotto I, Sprafka JM, et al. Family risk score of coronary heart disease (CHD) as a predictor of CHD: the atherosclerosis risk in communities (ARIC) study and the NHLBI family heart study. Genet Epidemiol. 2000;18:236.

Lloyd-Jones DM, Nam BH, D'Agostino RB, Levy D, Murabito JM, Wang TJ, et al. Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: a prospective study of parents and offspring. J Am Med Assoc. 2004a;291:2204.

Lloyd-Jones DM, Nam BH, D'Agostino RB, Levy D, Murabito JM, Wang TJ, et al. Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: a prospective study of parents and offspring. J Am Med Assoc. 2004b;291:2204.

Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41:111.

Marenberg ME, Risch N, Berkman LF, Floderus B, de Faire U. Genetic susceptibility to death from coronary heart disease in a study of twins. N Engl J Med. 1994;330:1041.

Mehta A, Virani SS, Ayers CR, Sun W, Hoogeveen RC, Rohatgi A, et al. Lipoprotein(a) and family history predict cardiovascular disease risk. J Am Coll Cardiol. 2020;76:781–93.

Michos ED, Nasir K, Rumberger JA, Vasamreddy C, Braunstein JB, Budoff MJ, et al. Relation of family history of premature coronary heart disease and metabolic risk factors to risk of coronary arterial calcium in asymptomatic subjects. Am J Cardiol. 2005;95:655.

Moonesinghe R, Yang Q, Zhang Z, Khoury MJ. Prevalence and cardiovascular health impact of family history of premature heart disease in the United States: Analysis of the National Health and Nutrition Examination Survey, 2007–2014. J Am Heart Assoc. 2019;8:e012364.

Mulders TA, Sivapalaratnam S, Stroes ESG, Kastelein JJP, Guerci AD, Pinto-Sietsma SJ. Asymptomatic individuals with a positive family history for premature coronary artery disease and elevated coronary calcium scores benefit from statin treatment: a post hoc analysis from the St. Francis heart study. JACC Cardiovasc Imaging. 2012;5:252.

Murabito JM, Nam BH, D'Agostino RB, Lloyd-Jones DM, O'Donnell CJ, Wilson PWF. Accuracy of offspring reports of parental cardiovascular disease history: the Framingham Offspring Study. Ann Intern Med. 2004;140:434.

Mvundura M, Mcgruder H, Khoury MJ, Valdez R, Yoon PW. Family history as a risk factor for early-onset stroke/transient ischemic attack among adults in the United States. Public Health Genomics. 2009;13:13.

Nanchen D, Gencer B, Auer R, Räber L, Stefanini GG, Klingenberg R, et al. Prevalence and management of familial hypercholesterolaemia in patients with acute coronary syndromes. Eur Heart J. 2015;36:2438–45.

Nasir K, Michos ED, Rumberger JA, Braunstein JB, Post WS, Budoff MJ, et al. Coronary artery calcification and family history of premature coronary heart disease: sibling history is more strongly associated than parental history. Circulation. 2004a;110:2150.

Nasir K, Michos ED, Rumberger JA, Braunstein JB, Post WS, Budoff MJ, et al. Coronary artery calcification and family history of premature coronary heart disease. Circulation. 2004b;110:2150–6.

Nordestgaard BGBG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J. 2013;34:3478–90.

Orlando LA, Wu RR, Myers RA, Buchanan AH, Henrich VC, Hauser ER, et al. Clinical utility of a Web-enabled risk-assessment and clinical decision support program. Genet Med. 2016;18:1020.

Øygarden H, Fromm A, Sand KM, Eide GE, Thomassen L, Naess H, et al. Can the cardiovascular family history reported by our patients be trusted? The Norwegian Stroke in the Young Study. Eur J Neurol. 2016;23:154.

Paixao ARM, Berry JD, Neeland IJ, Ayers CR, Rohatgi A, De Lemos JA, et al. Coronary artery calcification and family history of myocardial infarction in the dallas heart study. JACC Cardiovasc Imaging. 2014;7:679.

Patel MJ, de Lemos JA, Philips B, Murphy SA, Vaeth PC, McGuire DK, et al. Implications of family history of myocardial infarction in young women. Am Heart J. 2007;154:454.

Pereira MA, Schreiner PJ, Pankow JS, Williams RR, Higgins M, Province MA, et al. The family risk score for coronary heart disease: associations with lipids, lipoproteins, and body habitus in a middle-aged bi-racial cohort: the ARIC study. Ann Epidemiol. 2000;10:239.

Petr EJ, Ayers CR, Pandey A, De Lemos JA, Powell-Wiley TM, Khera A, et al. Perceived lifetime risk for cardiovascular disease (from the Dallas Heart Study). Am J Cardiol. 2014;114:53.

Philips B, de Lemos JA, Patel MJ, DK MG, Khera A. Relation of family history of myocardial infarction and the presence of coronary arterial calcium in various age and risk factor groups. Am J Cardiol. 2007;99:825.

Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. European guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2016;2016:2315–81.

Prushik SG, Farber A, Gona P, Shrader P, Pencina MJ, Dagostino RB, et al. Parental intermittent claudication as risk factor for claudication in adults. Am J Cardiol. 2012a;109:736.

Prushik SG, Farber A, Gona P, Shrader P, Pencina MJ, D'Agostino RB, et al. Parental intermittent claudication as risk factor for claudication in adults. Am J Cardiol. 2012b;109:736.

Ranthe MF, Petersen JA, Bundgaard H, Wohlfahrt J, Melbye M, Boyd HA. A detailed family history of myocardial infarction and risk of myocardial infarction – a nationwide cohort study. PLoS One. 2015a;10:e0125896.

Ranthe MF, Petersen JA, Bundgaard H, Wohlfahrt J, Melbye M, Boyd HA. A detailed family history of myocardial infarction and risk of myocardial infarction – a Nationwide Cohort Study. PLoS One. 2015b;10:e0125896.

Rissanen AM. Familial occurrence of coronary heart disease: effect of age at diagnosis. Am J Cardiol. 1979;44:60–6.

Rubinstein WS, Acheson LS, O'Neill SM, Ruffin MT, Wang C, Beaumont JL, et al. Clinical utility of family history for cancer screening and referral in primary care: a report from the Family Healthware Impact Trial. Genet Med. 2011;13:956.

Ruffin MT, Nease DE, Sen A, Pace WD, Wang C, Acheson LS, et al. Effect of preventive messages tailored to family history on health behaviors: the family healthware impact trial. Ann Fam Med. 2011;9:3–11.

Seshadri S, Beiser A, Pikula A, Himali JJ, Kelly-Hayes M, Debette S, et al. Parental occurrence of stroke and risk of stroke in their children: the Framingham study. Circulation. 2010;121:1304.

Sesso HD, Lee IM, Gaziano JM, Rexrode KM, Glynn RJ, Buring JE. Maternal and paternal history of myocardial infarction and risk of cardiovascular disease in men and women. Circulation. 2001;104:393.

Silberberg JS, Wlodarczyk J, Fryer J, Ray CD, Hensley MJ. Correction for biases in a population-based study of family history and coronary heart disease: the Newcastle family history study I. Am J Epidemiol. 1998;147:1123.

Silberberg J, Fryer J, Wlodarczyk J, Robertson R, Dear K. Comparison of family history measures used to identify high risk of coronary heart disease. Genet Epidemiol. 1999;16:344–55.

Sivapalaratnam S, Boekholdt SM, Trip MD, Sandhu MS, Luben R, Kastelein JJP, et al. Family history of premature coronary heart disease and risk prediction in the EPIC-Norfolk prospective population study. Heart. 2010;96:1985.

Stitziel NO, MacRae CA. A clinical approach to inherited premature coronary artery disease. Circ Cardiovasc Genet. 2014;7:554.

Sweet K, Sturm AC, Rettig A, McElroy J, Agnese D. Clinically relevant lessons from Family HealthLink: a cancer and coronary heart disease familial risk assessment tool. Genet Med. 2015;17:493.

Valerio L, Peters RJ, Zwinderman AH, Pinto-Sietsma SJ. Association of family history with cardiovascular disease in hypertensive individuals in a multiethnic population. J Am Heart Assoc. 2016;5:e004260.

Wang C, Bickmore T, Bowen DJ, Norkunas T, Campion MA, Cabral H, et al. Acceptability and feasibility of a virtual counselor (VICKY) to collect family health histories. Genet Med. 2015;17:822.

Wannamethee SG, Shaper AG, Ebrahim S. History of parental death from stroke or heart trouble and the risk of stroke in middle-aged men. Stroke. 1996a;27:1498.

Wannamethee SG, Shaper AG, Ebrahim S. History of parental death from stroke or heart trouble and the risk of stroke in middle-aged men. Stroke. 1996b;27:1492.

Watt G, McConnachie A, Upton M, Emslie C, Hunt K. How accurately do adult sons and daughters report and perceive parental deaths from coronary disease? J Epidemiol Community Health. 2000;54:859.

Weijmans M, Van Der Graaf Y, Reitsma JB, Visseren FLJ. Paternal or maternal history of cardiovascular disease and the risk of cardiovascular disease in offspring. A systematic review and meta-analysis. Int J Cardiol. 2015;179:409.

Welch BM, Wiley K, Pflieger L, Achiangia R, Baker K, Hughes-Halbert C, et al. Review and comparison of electronic patient-facing family health history tools. J Genet Couns. 2018;27:381.

Wienke A, Herskind AM, Christensen K, Skytthe A, Yashin AI. The heritability of CHD mortality in Danish twins after controlling for smoking and BMI. Twin Res Hum Genet. 2005;8:53–9.

Williams RR, Hunt SC, Heiss G, Province MA, Bensen JT, Higgins M, et al. Usefulness of cardiovascular family history data for population-based preventive medicine and medical research (The Health Family Tree Study and the NHLBI Family Heart Study). Am J Cardiol. 2001;87:129.

Wu RR, Myers RA, Sperber N, Voils CI, Neuner J, McCarty CA, et al. Implementation, adoption, and utility of family health history risk assessment in diverse care settings: evaluating implementation processes and impact with an implementation framework. Genet Med. 2019;21:331.

Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, et al. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. JAMA. 2012;308:788.

Yoon PW, Scheuner MT, Khoury MJ. Research priorities for evaluating family history in the prevention of common chronic diseases. Am J Prev Med. 2003;24:128.

Yu S, Su Z, Miao J, Yu Y, Zhang S, Wu J, et al. Different types of family history of stroke and stroke risk: results based on 655,552 individuals. J Stroke Cerebrovasc Dis. 2019;28:587.

Zdravkovic S, Wienke A, Pedersen NL, Marenberg ME, Yashin AI, De Faire U. Heritability of death from coronary heart disease: a 36-year follow-up of 20 966 Swedish twins. J Intern Med. 2002;252:247–54.

Chapter 10
Primary Prevention and Cardiovascular Risk Assessment in Women

Lori-Ann Peterson, Priya M. Freaney, and Martha Gulati

The leading cause of death in women in the United States is cardiovascular disease (CVD), accounting for 418,665 deaths in women in 2016 (Virani et al. 2020). Over 60 million women are living with some form of CVD, with a lifetime risk for a 40-year-old woman of 1 in 2 for developing any CVD, 1 in 3 for developing coronary heart disease (CHD), 1 in 5 for developing heart failure, and 1 in 5 for having a stroke (Virani et al. 2020). Since 2001, there had been a continuous decline in mortality from heart disease in women until 2010, following which mortality for CVD has risen in both sexes (Virani et al. 2020). Notably, for younger women (under the age of 55 years), there has been no significant improvement in cardiovascular mortality over the past two decades (Wilmot et al. 2015). Furthermore, this age group has the highest mortality rates after being diagnosed with CVD (Arora et al. 2019).

Both sex and gender impact CVD and outcomes, and it is important to understand the differences between them. Sex is determined at birth and is biologic, based on chromosome. Gender is based on sociocultural definitions and is nonbinary. Both affect CVD in women and men, given the differences in the impact of traditional risk factors, sex-specific CVD risk factors, differences in treatment and management strategies for both primary and secondary prevention of CVD, response to medications, social determinants of health, in addition to pathophysiological differences in CVD.

Primary prevention of CVD in women is strongly influenced by awareness of CVD as a leading cause of morbidity and mortality. Even though cardiovascular mortality rates were higher in women than in men in the United States, it was not

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until 1991 that the National Institute of Health (NIH) established a policy that all NIH-funded trials must include both women and men when studying conditions that affect both sexes. Only recently, in 2016, the NIH made it mandatory to include both sexes in cell and animal studies (Clayton and Collins 2014). While awareness of CVD as the leading cause of death in women has improved over time, it remains suboptimal, particularly in racial and ethnic minorities (Mosca et al. 2013). A nationally representative survey done by the Women's Health Alliance showed that even though 74% of women had one or more CVD risk factors, only 16% of women were informed that they were at risk for heart disease (Merz et al. 2016). Physician awareness, education, and assessment of women's CVD risk are also far from expected. This same survey showed that primary care physicians prioritized weight and breast health over concerns for CVD. Additionally, only 22% of primary care physicians and 42% of cardiologists felt well-equipped to assess CVD in women, and very few implemented the guidelines for CVD risk assessment in their practice in their women patients (16% of primary care physicians, 22% of cardiologists; $p = NS$) (Bairey Merz et al. 2017). A 2019 survey from the American Heart Association that has been performed every decade demonstrated a decline in awareness of heart disease as the leading cause of death in all races and age groups, aside from women over the age of 65 years (Cushman et al. 2021).

Sex, Gender, and Genetic Differences in CVD

Sex is defined as "the classification of living things, generally as male or female according to their reproductive organs and functions assigned by the chromosomal complement." (Exploring the biological contributions 2001) Sex differences in CVD result from the biological differences in the structure and function of the cardiovascular systems of men and women, in contrast to gender differences that stem from a person's self-representation, resulting in psychosocial roles and behaviors imposed by society. Certainly, gender impacts outcomes differences seen in CVD, but these are very different from sex differences that arise from the genetic differences between men and women. Sex differences are a result of the chromosomal differences between those who are biologically men (XY) and those who are biologically women (XX), regardless of gender.

Whether there is a specific genetic marker that can predict CVD in women remains unknown. In the Women's Health Genome Study, 19,313 Caucasian women were followed prospectively for a median of 12.3 years to assess whether a genetic risk score could improve the predictive cardiac risk assessment of women beyond the assessment made with traditional risk factors (Paynter et al. 2010). There was no significant improvement of CVD risk prediction in women using the genetic risk score. To date, there is no known genetic marker that can be used to improve risk assessment in women, beyond traditional methods.

Cardiovascular Risk Factors in Women

Traditional CVD Risk Factors and Their Impact on Women

Age

Age is a powerful predictor of CVD, and more specifically, CHD. The prevalence of CVD across the life span increases in both women and men; however, CHD events are delayed at least 10 years in women compared to men (Virani et al. 2020). The prevalence of CHD increases to 1 in 3 women after the age of 65, in contrast to 1 in 8 in women aged 45–64 years. The atherosclerotic CVD (ASCVD) risk score increases with increasing age (Virani et al. 2020; Grundy et al. 2019). Rates of CHD mortality have significantly improved over the last three decades in young and middle-aged men (25–54 years), while the same progress has not been realized in women – with CHD mortality rates in this same age group of women stagnating over the last three decades. In contrast, in both older age men and women (65+ years), CHD mortality rates have declined over time (Wilmot et al. 2015).

Family History

Family history of premature CHD impacts an individual's future ASCVD risk. A history of premature CHD in a first-degree relative doubles the risk for a future cardiovascular event. The ASCVD risk estimator defines a family history of premature CHD as any CHD in a female first-degree relative before the age of 65 years or any male first-degree relative before the age of 55 years (Grundy et al. 2019). Premature CHD in a first-degree female relative is a more potent risk factor compared to a male relative (Scheuner et al. 2008). Additionally, women classified as low risk for CHD (using the Framingham Risk Score) but with a female sibling with premature CHD are more likely to have evidence of subclinical CHD by coronary artery calcium than those with a male sibling with premature CHD, demonstrated in a study of 102 asymptomatic women (Michos et al. 2005). The 2018 ACC/AHA guidelines on the treatment of blood cholesterol to reduce ASCVD risk in adults recommend the consideration of any family history of premature CVD when assessing risk in asymptomatic adults (Grundy et al. 2019).

Hypertension

Hypertension diagnosis thresholds have been redefined and lowered from 140/90 mmHg to 130/80 mmHg, and as a result, the prevalence of high blood pressure and hypertension has increased (Whelton et al. 2018). Women have a lower

overall prevalence of hypertension compared to men. Based on the National Health and Nutrition Examination Survey (NHANES) 2017–2018, the overall prevalence of hypertension is higher among men (51.0%) compared with women (39.7%), with the lower overall rate in women largely driven by low rates of hypertension in premenopausal women. After the age of 60, hypertension rates are not significantly different between women and men (73.9% vs. 75.2%, respectively) (Ostchega et al. 2020). Women are more likely to be aware of their diagnosis of hypertension and are more likely to have their hypertension controlled when compared with men (53% vs. 46%) (Fryar et al. 2017). Oral contraception raises blood pressure on average 7–8 mmHg, yielding a two- to threefold rise in hypertension in women (Shufelt and Bairey Merz 2009).

Hypertension has a greater impact on CVD in women over the age of 60 when compared with men. Hypertension is associated with an increased risk of the development of congestive heart failure in both sexes, but the risk appears to be greater in women (Drazner 2011). Women are more likely to have a history of hypertension when presenting with a stroke compared with men (Bushnell et al. 2014). The lifetime risk of a stroke is greater in women compared with men, related to a greater life expectancy in women, since the risk of a stroke increases with age. In one study of both conventional and ambulatory blood pressure assessments that included 4960 men and 4397 women, women were found to have a larger increase in the risk of cardiovascular events with increases in blood pressure when compared with men (Boggia et al. 2011).

Although it is well established that blood pressure increases with age, the increase noted is not simply a result of menopause in women. Recent work has demonstrated significant sex differences in blood pressure trajectories with age, with evidence that in women systolic blood pressure increases more rapidly and begins early in life (Ji et al. 2020). Such biological differences may assist in explaining the sex-specific pathophysiological effects of hypertension that are seen in women.

Diabetes

Although the prevalence of diabetes is similar in women and men (32.4% vs. 32.7%, respectively), the presence of diabetes confers a greater risk for CHD in women compared with men, increasing a woman's risk of CHD by three- to sevenfold with only a two- to threefold increase in diabetic men. In addition, the risk of fatal CHD in a diabetic woman is 3.5 times higher than in a nondiabetic woman, and higher than seen in diabetic men (relative risk of fatal CHD is twice that of a nondiabetic man) (Regensteiner et al. 2015). Similarly, type 1 diabetes poses a greater risk for cardiovascular events in women when compared with men. Women with type 1 diabetes have double the risk of fatal and nonfatal cardiovascular events when

compared with men with type 1 diabetes, in addition to a 40% greater risk of all-cause mortality (Huxley et al. 2015). In a very large meta-analysis that included 47 cohort studies, it was demonstrated that diabetes was associated with a greater risk of heart failure in women when compared with men with diabetes, and the sex difference was greatest in those with type 1 diabetes (Ohkuma et al. 2019).

The American Diabetes Association (ADA) suggests screening for diabetes in women and men over the age of 45 years, and then every 3 years if the results are normal (Professional Practice Committee 2020). Nonetheless, in women with a history of gestational diabetes, diabetes screening should occur 6–12 weeks postpartum, and then should continue every 3 years, if the test results are normal. Additionally, the ADA recommends screening women with polycystic ovarian syndrome if they are overweight or obese due to the association of polycystic ovarian syndrome with insulin resistance and diabetes (Professional Practice Committee 2020).

Dyslipidemia

The NHANES 2015–2018 data shows that although dyslipidemia is common in women, it is decreasing over time (Carroll and Fryar 2020). Elevated total cholesterol (greater than 240 mg/dL) is present in 12.1% of adult women and 10.5% of men. The only age group where women have a lower total cholesterol than men is those under the age of 40 years. Elevated total cholesterol is affected by women having higher high-density lipoprotein cholesterol (HDL-C) levels compared with men, but this may also reflect undertreatment of dyslipidemia in women. Despite women being eligible for statin therapy, it has been shown that women are less likely to be treated with any statin, and once started on a statin, are less likely to be treated with the recommended intensity of statin based on risk (Nanna et al. 2019).

HDL-C levels remain higher in women throughout their lives, (Carroll et al. 2015-2016) and on average HDL-C levels in women are ~10 mg/dL higher than in men. HDL-C is inversely associated with ASCVD events, (Mora et al. 2011) but HDL-C as a target of therapy has never improved outcomes, and thus far, is not the target of ASCVD risk assessment.

Low-density lipoprotein cholesterol (LDL-C) remains the primary target of ASCVD risk assessment (Grundy et al. 2019). Nuclear magnetic resonance (NMR) spectroscopy lipoprofiles, apolipoproteins, and particle size and density have not demonstrated superiority over a standard fasting lipid profile for cardiovascular risk assessment in asymptomatic women (Mora et al. 2009).

Adverse lipid profile changes occur during menopause in women, including increased total cholesterol, LDL-C and triglyceride levels, and decreased HDL-C levels, although it remains unclear how much of these changes in lipids are due to aging alone, as opposed to being due to menopause-related hormonal changes (Polotsky and Polotsky 2010a).

Cigarette Smoking

Cigarette smoking remains the leading cause of preventable cardiovascular deaths. Although public health measures have effectively reduced the prevalence of cigarette smoking in the United States, in 2018, 16% of men and 12% of women reported regular tobacco use, and the prevalence of newer tobacco products such as e-cigarettes has increased (Creamer et al. 2019). Although women smoke less than men, the effects of cigarettes may be more detrimental in women than men (Palmer et al. 2019). Female smokers die 14.5 years earlier than female nonsmokers, and male smokers die 13.2 years earlier than male nonsmokers (US UDoHaHS, Department of Health and Human Services PHS, Centers for Disease Control and Prevention NCfC, Disease Prevention and Health Promotion OoSa, Health 2004). Women aged 18–49 years who smoke cigarettes have a 13 times greater risk for myocardial infarction (MI) than nonsmoking women. Oral contraception use combined with cigarette use produces pro-thrombotic effects that promote a higher risk for MI than cigarette smoking alone. The risk for MI in a woman smoking 25 or more cigarettes a day increases by 12-fold, while the risk of smoking 25 or more cigarettes a day *and* taking oral contraception increases a woman's risk for MI by 32-fold (Rosenberg et al. 2001). Third-generation hormonal contraceptives appear to pose less risk than prior generation formulations (Shufelt and Bairey Merz 2009). The current recommendations from the American College of Obstetricians and Gynecologists (ACOG) caution against prescribing oral contraceptives to women over the age of 35 who smoke cigarettes (Shufelt and Bairey Merz 2009).

Smoking cessation significantly reduces CVD risk in women. The risk of mortality of any cause in former smokers decreases to nearly that of never smokers after smoking cessation has been achieved for 15 years (Pirie et al. 2013). Smoking cessation works differently in women compared with men as a result of biological differences between the sexes. There are more nicotine receptors in the male brain, and as a result, nicotine replacement appears to be more effective in men when compared with women. Varenicline, on the other hand, has been shown to be more effective as a smoking cessation aid in women (McKee et al. 2016).

Physical Activity/Physical Fitness

The association of physical activity and cardiovascular health is well-defined, but physical inactivity is far too common and particularly prevalent in women of all ages when compared with men. Women are more likely to report not meeting the physical activity guidelines compared with men (47% vs. 38%), and this difference worsens with age (Control CfD 2017). Nonetheless, there is a gender bias in physical activity measurement instruments, which do not collect domestic activities such as cooking, cleaning, and childcare, and may account for these observed

differences. Based on the 2017 National Health Interview Survey, adult women reported performing less leisure-time physical activity than men in all age categories (Control CfD 2017). Physical inactivity is associated with higher blood pressure, elevated cholesterol, poorer glucose metabolism, poorer mental health, and obesity. Physical inactivity, quantified by prolonged sitting time, has been shown to be an independent risk factor for CVD in women beyond leisure-time physical activity (Chomistek et al. 2013).

Exercise capacity, also known as physical fitness, strongly and independently predicts all-cause mortality in asymptomatic women and can be quantified. In the Women Take Heart Project, asymptomatic women who did not achieve 5 metabolic equivalents (METs) on the Bruce protocol had a threefold increased risk of death compared with women who achieved >8 METs (Gulati et al. 2003). Furthermore, the risk of death among asymptomatic and symptomatic women whose exercise capacity was less than 85% of the predicted value for age was at least twice that of women whose exercise capacity was at least 85% of their age-predicted value (Gulati et al. 2005). Age-predicted fitness can be estimated using the validated nomogram (Fig. 10.1).

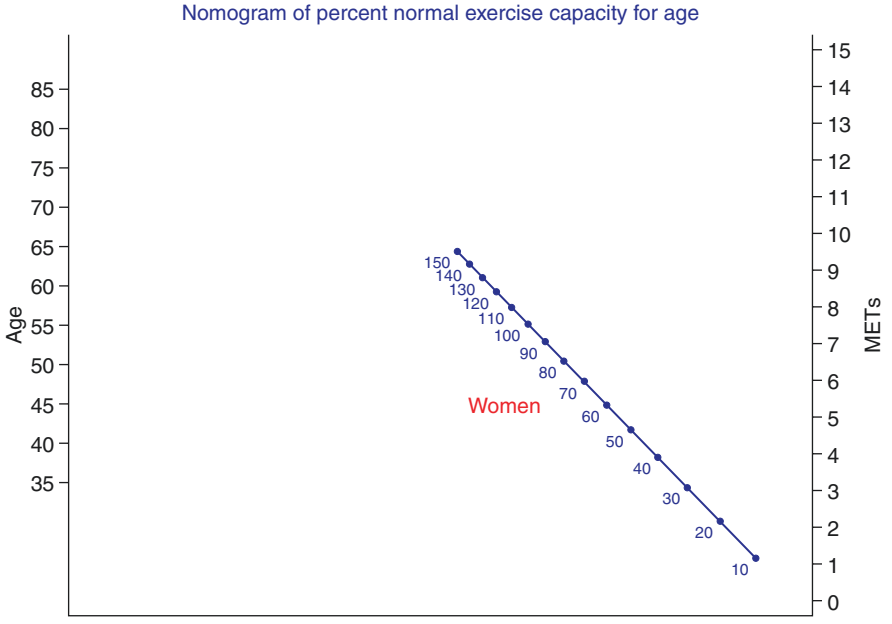

Fig. 10.1 Nomogram of the percentage or predicted exercise capacity for age in asymptomatic women. A line drawn from the patient's age on the left-hand scale to the MET value on the right-hand scale will cross the percentage line corresponding to the patient's percentage of predicted exercise capacity for age. METS metabolic equivalents. (From Gulati et al. 2005)

Metabolic Syndrome

There is no difference in the prevalence of metabolic syndrome in women and men based on the NHANES data from 2011 to 2016 (35.1% of women vs 34.3% of men, $p = 0.47$) (Hirode and Wong 2020). Women with metabolic syndrome have a greater risk of developing CHD, with a relative risk of 2.63, compared to a relative risk of 1.98 in men with metabolic syndrome, when compared to their same gender counterparts without metabolic syndrome (Gami et al. 2007).

Obesity

Obesity is defined as a body mass index (BMI) of >30 kg/m^2 and, based on the 2017–2018 NHANES data, affects 41.8% of women, similar to what is seen in men (Hales et al. 2020). The obesity epidemic is tied closely to the rise in diabetes because the two are inextricably linked. In the Nurses' Health Study, obesity was the most powerful predictor of diabetes in women, and those with a BMI ≥35 kg/m^2 had an almost 40-fold greater relative risk for diabetes when compared with women with a BMI under 23 kg/m^2. The pattern of obesity appears to affect CVD risk – for example, an elevated waist circumference above 35 inches, indicative of visceral obesity, is associated with elevated CVD risk, whereas elevated with BMI alone is not (Olson et al. 2006).

Although obesity has also been associated with increased mortality from CVD and shortened life expectancy from CVD, (Flegal et al. 2007) obesity itself does not appear to be an independent risk factor for CVD given that obesity is strongly associated with many of the traditional CHD risk factors (Flegal et al. 2013). The effect of obesity may be countered by physical fitness. Women who are obese and fit have been shown to not be at an elevated risk of CVD; in contrast, lean women who are not physically fit appear to have an elevated risk of CVD (Wessel et al. 2004).

High-Sensitivity C-Reactive Protein

High-sensitivity C-reactive protein (hsCRP) is a marker of inflammation, with a noted elevation in hsCRP in premenopausal women, possibly due to the effect of estrogen on hsCRP (Lakoski et al. 2006). hsCRP has not been shown to be a causal risk factor for CVD, but it may improve risk detection in women (Cook et al. 2006). The Women's Health Study demonstrated that CVD risk prediction in women improved in a model that included hsCRP (Cook et al. 2006). For women with metabolic syndrome, hsCRP may add prognostic information regarding cardiac risk. In one study, women with metabolic syndrome and hsCRP levels greater than 3.0 mg/L had almost twice the risk of future cardiovascular events than women with metabolic syndrome and an hsCRP less than 3.0 mg/L (5 s1) (Ridker et. al 2003). Measuring hsCRP is not recommended in routine risk assessment of women, but rather as an option in those persons in the intermediate-risk range based on the

ASCVD Risk Score (Pearson et al. 2003). An elevated hsCRP (>2.0 mg/L) is considered an ASCVD risk-enhancing factor (Grundy et al. 2019).

Sleep Apnea

Obstructive sleep apnea is more prevalent in men compared with women, with a male-to-female ratio of about 2:1, but remains common in women and is particularly associated with obesity (Franklin and Lindberg 2015). Sleep apnea is often underrecognized in terms of its impact on CVD. Sleep apnea is believed to induce severe intermittent hypoxemia and CO_2 retention during sleep, with oxygen saturation sometimes dropping to ≤60%, disrupting the normal autonomic and hemodynamic responses to sleep. Untreated obstructive sleep apnea is associated with an increased risk of hypertension, coronary artery disease, stroke, and atrial fibrillation in women (Campos-Rodriguez et al. 2012). Untreated sleep apnea in women is associated with at least a threefold greater risk of dying from CVD. However, this risk is reduced to the same as a woman without sleep apnea once the sleep apnea is treated (Campos-Rodriguez et al. 2012).

Sex-Specific Risk Factors

Age of Menarche

The age at onset of menarche is associated with the development of ASCVD. Both early (occurring at or before the age of 12 years) and late menarche (>15 years) are associated with an increased risk of MI, stroke, and heart failure hospitalizations. In the WISE (Women's Ischemia Syndrome Evaluation) study, a history of menarche at age ≤ 10 years or ≥ 15 years was associated with an increased risk of cardiovascular events, with a hazard ratio of 4.53 (95% CI 2.13–9.63) and 2.58 (95% CI, 1.28–5.21), respectively, when compared with women with menarche at age 12 years (Lee et al. 2019).

Pregnancy-Associated Conditions

Eclampsia, Preeclampsia, and Gestational Hypertension

Pregnancy-induced hypertension, which includes gestational hypertension, preeclampsia, and eclampsia, is associated with an increased risk of hypertension, chronic kidney disease, diabetes, and CVD (including heart failure, stroke, and myocardial infarction) (Savitz et al. 2014; Mannisto et al. 2013; Brown et al. 2006). The UK Biobank cohort, a prospective study of over 220,000 women followed for a median of 7 years, demonstrated that women with hypertension during pregnancy

were not just at greater risk of chronic hypertension, but also had a greater risk of developing coronary artery disease, heart failure, aortic stenosis, and mitral regurgitation (Honigberg et al. 2019). From a causal standpoint, 64% of those with coronary artery disease and 49% of those with heart failure were driven by chronic hypertension, meaning that treating hypertension in this group is of critical importance. In women with a history of preeclampsia, there is a twofold increased risk for subsequent ischemic heart disease, stroke, or venous thromboembolic events over the 5–10 years that follow the pregnancy (Bellamy et al. 2007). In those with prior preeclampsia, the median age of a stroke is ≤50 years, suggesting an acceleration of ASCVD, despite most women being premenopausal and lower risk using traditional risk scores (Ben-Ami et al. 2010). Despite this association with elevated ASCVD events, it is unclear whether future cardiac events are a result of the hypertension during pregnancy or a consequence of pre-pregnancy risk factors (Romundstad et al. 2010). Hypertension during pregnancy has been recognized as a risk-enhancing factor by the 2018 guidelines on the management of blood cholesterol (Grundy et al. 2019). Hypertensive disorders of pregnancy are noted in the 2014 guidelines for stroke prevention in women to be associated with an increased risk of stroke during pregnancy and also after the associated pregnancy, both immediately and years after (Bushnell et al. 2014).

Gestational Diabetes

Gestational diabetes is associated with an increased risk of future diabetes and CVD. A nationwide study from France followed all women who gave birth from 2007 to 2008; those with gestational diabetes had a greater risk of myocardial infarction, angina, and hypertension over the 7 years that followed (Goueslard et al. 2016). Another analysis of over five million women from a pooled analysis of nine studies demonstrated that women with gestational diabetes had a twofold greater risk of cardiovascular events in the first 10 years postpartum, compared with women without gestational diabetes, independent of those who developed type II diabetes (Kramer et al. 2019).

Preterm Delivery

Preterm delivery is defined as birth prior to 37 weeks' gestation and complicates about 11% of deliveries. The underlying causes and mechanisms are not entirely clear, but there is a strong association with preterm delivery and maternal risk of CHD and stroke, with an even greater risk in preterm deliveries before 32 weeks' gestation (Wu et al. 2018).

Small-for-Gestational-Age Infant

Small-for-gestational-age (SGA) births are defined as newborns below the tenth percentile for the gestational age and are estimated to occur in 15 of every 1000 births in the United States (Ewing et al. 2017). SGA can be a result of maternal factors, including height, weight, race, and ethnicity, but also a result of environmental factors. Delivery of an SGA infant has been shown to be associated with an increased maternal risk of ASCVD. The National Health and Nutrition Examination Survey has demonstrated an increased risk of ischemic heart disease in women with an SGA delivery, independent of risk factors for ischemic heart disease (Bukowski et al. 2012). Risk of maternal CVD after delivering an SGA infant has been shown to be dose dependent, according to both the severity of SGA and the number of SGA infants (Ngo et al. 2015).

Miscarriages/Stillbirths

There is some association between miscarriages and stillbirths and an increased risk of CVD. The risk seems more associated with the risk of CHD rather than stroke, as demonstrated by the Women's Health Initiative, where the postmenopausal women who reported one or more miscarriages or stillbirths had a greater risk of CHD (Parker et al. 2014). This relationship appears to persist even after controlling for the increase in ASCVD risk factors (Hall et al. 2019). The risk of CHD appears to be greatest in those women with multiple miscarriages or stillbirths (Asgharvahedi et al. 2019). As part of a complete ASCVD risk assessment, a complete pregnancy history, including miscarriages and stillbirths, should be documented.

Assisted Reproductive Therapies

Hormonal therapies used for infertility have increased and are estimated to be used in approximately 1% of all births. To date, the available data does not suggest an increased risk of ASCVD in women who undergo assisted reproductive therapy (ART). The largest data available comes from Canada from the General Reproductive Assistance and Vascular Illness (GRAVID) study, which is a population-based study used to assess long-term risk of CVD following fertility therapy. In those women who gave birth and received fertility therapy, their risk of CVD or death in the next decade was approximately half that compared with women who gave birth without ART (HR 0.55, $p < 0.0001$) (Udell et al. 2013). Nonetheless, in women who require reproductive therapies, there has been a noted increase in pregnancy-induced hypertension (Thomopoulos et al. 2013). The use of fertility therapy in pregnancy is not

considered an independent risk factor for ASCVD. However, for women who fail to get pregnant with fertility therapy, there appears to be an early signal toward an increased risk for future ASCVD events (Udell et al. 2017). Failed fertility therapy may be an indicator for future ASCVD risk and may itself pose as a unique cardiometabolic stress test. This hypothesis warrants further investigation.

Polycystic Ovary Syndrome

Polycystic ovarian syndrome (PCOS) is unique to women and affects about 18% of reproductive-age women (Teede et al. 2010). The diagnosis of PCOS requires two or more of the following to be present: (Virani et al. 2020) menstrual irregularities, (Wilmot et al. 2015) hyperandrogenism, and (Arora et al. 2019) polycystic ovaries. Although the symptoms of PCOS are seen in premenopausal women, the association with CVD risk factors persists into the postmenopausal years. PCOS has been shown to be associated with an increase in the development of many CVD risk factors, including features of metabolic syndrome, insulin resistance, and diabetes, when compared with women without PCOS (Moran et al. 2010). Nonetheless, it remains unclear if PCOS is an independent risk factor for premature CVD in women. In the NHLBI-sponsored WISE study of postmenopausal women with PCOS and suspected myocardial ischemia, there was no greater risk of CVD or mortality over 10 years of follow-up when compared with women without PCOS (Shaw et al. 2008). Similarly, a case–control study of age-matched women with and without PCOS was followed for 21 years, and despite an increase in hypertension and higher triglycerides in women with PCOS, there was no increase in cardiovascular events (Schmidt et al. 2011). In contrast, a large Danish fertility registry showed that women with PCOS were at a 19% greater risk of developing CVD when under the age of 50, but after the age of 50 years there was no difference in the risk of CVD in those with or without PCOS (Oliver-Williams et al. 2020).

Functional Hypothalamic Amenorrhea

Functional hypothalamic amenorrhea (FHA) is a cause of premenopausal ovarian dysfunction and occurs when gonadotropin-releasing hormone increases, thereby increasing luteinizing hormone and reducing estrogen, ultimately causing amenorrhea. Psychological stressors or metabolic insults such as caloric restriction or excessive exercise can induce FHA. FHA may be associated with an increased risk of CVD. In a large cohort study, women with menstrual irregularities had a 50% increased risk of nonfatal and fatal coronary heart disease compared to women with regular menstrual cycling. The association of FHA with premature coronary atherosclerosis has been demonstrated in women who underwent coronary angiography, but the use of oral contraceptive therapy may offer some protection (Merz et al. 2006). Further work to delineate this risk needs to be done.

Premature Menopause and Premature Ovarian Insufficiency

The concept that circulating estrogen is cardioprotective has been the explanation for the delayed onset of CVD in women when compared with men. Premature menopause has been shown to be associated with an increased risk of CVD. A meta-analysis demonstrated that women who experienced menopause at an age younger than 45 years were more likely to have an incident of coronary heart disease event (RR 1.50 [1.28–1.76]) compared with women undergoing menopause at age ≥ 45 years (Muka et al. 2016). The UK Biobank data demonstrated an inverse relationship between age of menopause and risk of CHD and stroke (Peters and Woodward 2018).

Premature ovarian insufficiency (POI) differs from premature menopause, but is also associated with an increased risk of CVD (Christ et al. 2017; Daan et al. 2016). POI is defined as ovarian failure before the age of 40 years, resulting in a prolonged exposure of estrogen insufficiency in women. A meta-analysis from 10 observational studies, including more than 190,000 women, demonstrated that POI was modestly associated with an increased incidence of CHD (HR 1.69; $p = 0.0001$) but not with stroke (Roeters van Lennep et al. 2016).

The ACC/AHA guidelines recognized premature menopause (before age 40 years) as a risk-enhancing factor (Grundy et al. 2019). Noting the age of menopause or a history of premature ovarian insufficiency should be part of a woman's ASCVD risk assessment.

Reproductive Hormones

Oral Contraceptive Therapy

The use of combination estrogen–progestin oral contraceptives is associated with a low risk of CVD in most women who are healthy and free of CVD and cardiovascular risk factors. On the other hand, women who smoke over the age of 35, have uncontrolled hypertension, a history of thromboembolic disease, or a history of ischemic heart disease have an unacceptable elevated risk of CVD if using oral contraceptives, and these women must be counseled regarding their risk and consider other forms of contraceptive therapies (Shufelt and Bairey Merz 2009; Bushnell et al. 2014; Curtis et al. 2016).

Postmenopausal Hormone Therapy

The majority of women develop CVD when they are postmenopausal, and often concomitantly have an increase in CVD risk factors, including older age (Polotsky and Polotsky 2010b). The hypothesis that postmenopausal hormone therapy could reduce CVD risk was supported by observational data but not by randomized

controlled trials. The Heart and Estrogen/Progestin Replacement Study (HERS) I, HERS II, Women's Health Initiative (WHI), and Raloxifene Use for The Heart (RUTH) did not find that hormone therapy or selective estrogen receptor modulators (SERMs) prevent either primary or secondary CVD events. Hormone replacement therapy and SERMS should not be used for the primary or secondary prevention of CVD.

Sex-Predominant CVD Risk Factors

Autoimmune Disorders

Systemic inflammation is the basis of cardiovascular disease and also of autoimmune disorders. Women have greater levels of inflammation when compared with men and also have a greater prevalence of autoimmune diseases. Such disorders include rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), and both are associated with accelerated atherosclerosis, ischemic heart disease, and CVD mortality (Mason and Libby 2015; del Rincon et al. 2015; Faccini et al. 2016; Prasad et al. 2015). Individuals with RA have a two- to threefold higher risk of MI and a 50% higher risk of stroke (del Rincon et al. 2015). Cardiovascular events often occur in younger women with SLE, with a risk for acute MI 9- to 50-fold greater than the general population (Sinicato et al. 2013). Traditional risk factors such as smoking, family history of premature CHD, hypertension, and elevated cholesterol do not completely account for the increased risk of CHD in patients with SLE. Autoimmune disorders (diseases of chronic inflammation) are included as ASCVD risk enhancers in the 2018 ACC/AHA cholesterol guidelines (Grundy et al. 2019).

Breast Arterial Calcification

Breast arterial calcification can be identified on traditional mammography. Given its routine use in screening breast cancer in women, it is being evaluated as a potential ASCVD risk stratification tool and surrogate marker of ASCVD. This information comes with no additional radiation or costs, and is done routinely in women over the age of 40 years, with approximately 65% of women undergoing mammography in this age group (National Center for Health Statistics (US) 2017). Mammography detects patterns of calcifications in breast tissue, with the goal to identify precancerous or malignant cells, but similar calcifications can deposit along the arteries in the breast in a linear fashion. Multiple observational studies have demonstrated an association between breast arterial calcification and ASCVD, (Maas et al. 2007; Yoon et al. 2019; Newallo et al. 2015; Margolies et al. 2016) although one study has demonstrated no association between such calcifications and ASCVD (Moradi et al. 2014). To date, there are no prospective studies to validate these findings and

provide a clinical application. There are some technological challenges for reproducible assessment, some of which may be operator dependent. Nonetheless, there is a need to push for mammography reports to include breast arterial calcification, which can then be incorporated into the risk-stratification assessment for ASCVD.

Breast Cancer Therapy

Although breast cancer can occur in men, it occurs with a much greater incidence in women. Recent advances in breast cancer treatment have led to improved survival for women but an elevated risk for CVD (Bradshaw et al. 2016). Breast cancer and CVD share a number of common risk factors, and in addition, the therapies used to treat breast cancer have the potential for direct cardiovascular injury that can accelerate both atherosclerosis and heart failure (Gulati and Mulvagh 2018). Commonly used chemotherapeutic agents, such as anthracyclines and trastuzumab, increase the risk of heart failure. In a large retrospective analysis of Medicare data of more than 45,000 older women who had early-stage breast cancer, the risk of developing heart failure was increased in women who received either trastuzumab (32.1/100 patients) or anthracycline plus trastuzumab (41.9/100 patients) compared with no adjuvant therapy (18.1/100 patients, $p < 0.001$). The addition of trastuzumab to anthracycline therapy added 12.1, 17.9, and 21.7 heart failure/cardiomyopathy events per 100 patients over 1, 2, and 3 years of follow-up, respectively (Chen et al. 2012). Radiation therapy for breast cancer is associated with an increased risk of atherosclerosis and the development of ischemic heart disease. The risk is directly proportional to the mean radiation dose, with an increase in CVD events of 7.4% for every Gray (Gy) of radiation (95% CI, 2.9–14.5; $p < 0.001$). The risk of IHD begins within a few years after exposure and appears to continue for at least 20 years following the radiation exposure. The risk is greater in those with more CVD risk factors present at the time of radiation initiation (Darby et al. 2013).

Providing ASCVD risk assessment at the time of the breast cancer diagnosis and treatment is vital and should be a combined effort of oncologists and cardiologists to emphasize to women that a history of breast cancer is considered an ASCVD risk-enhancing factor (Grundy et al. 2019). Further, a long-term post-treatment surveillance strategy for CVD needs to be implemented in women with a history of breast cancer therapies.

Cardiovascular Disease Risk Assessment

ASCVD risk assessment helps identify those at the highest risk of developing ASCVD. This allows the appropriate intensity of screening and allocation of preventive therapies, including therapeutic lifestyle changes to reduce ASCVD risk. Although there are a number of risk assessment tools available, the tool chosen should be validated on the population to which it is being applied to. The risk

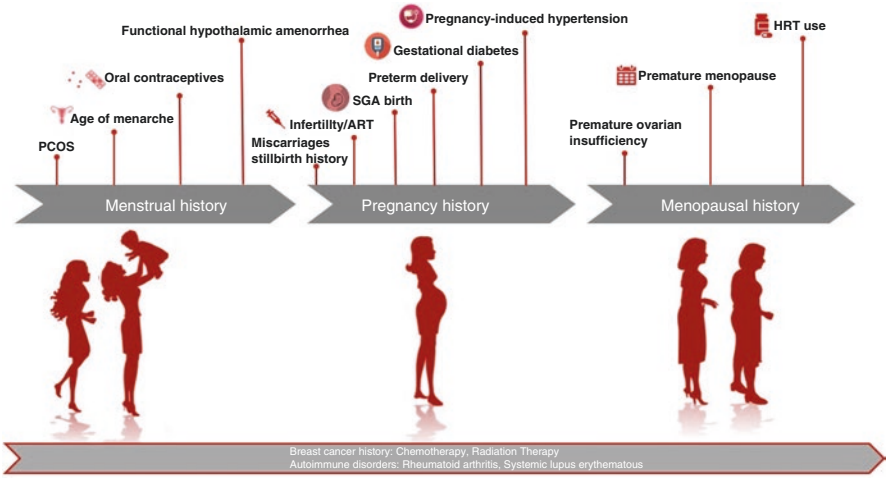

Fig. 10.2 ASCVD risk assessment in women: sex-specific and sex-predominant risk factors. ART assisted reproductive technology, HR hormone replacement therapy, PCOS polycystic ovarian syndrome, SGA small-for-gestational age

estimator of choice in the United States is the pooled cohort equations (PCEs), despite its acknowledged limitations in certain populations (Goff et al. 2014). The 2018 ACC/AHA guidelines on the treatment of blood cholesterol to reduce ASCVD in adults rely on the PCE as the initial step in ASCVD risk estimation, but now incorporate risk enhancers to refine the risk assessment, and as described above, many of the risk enhancers are sex-specific for women (Grundy et al. 2019). Risk-enhancing factors allow women to be reclassified, and this includes the sex-specific and sex-predominant risk enhancers that impact women specifically (Fig. 10.2).

Disclosures None.

References

Arora S, Stouffer GA, Kucharska-Newton AM, et al. Twenty year trends and sex differences in young adults hospitalized with acute myocardial infarction. Circulation. 2019;139:1047–56.

Asgharvahedi F, Gholizadeh L, Siabani S. The risk of cardiovascular disease in women with a history of miscarriage and/or stillbirth. Health Care Women Int. 2019;40:1117–31.

Bairey Merz CN, Andersen H, Sprague E, et al. Knowledge, attitudes, and beliefs regarding cardiovascular disease in women: the Women's Heart Alliance. J Am Coll Cardiol. 2017;70:123–32.

Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ. 2007;335:974.

Ben-Ami S, Oron G, Ben-Haroush A, Blickstein D, Hod M, Bar J. Primary atherothrombotic occlusive vascular events in premenopausal women with history of adverse pregnancy outcome. Thromb Res. 2010;125:124–7.

Boggia J, Thijs L, Hansen TW, et al. Ambulatory blood pressure monitoring in 9357 subjects from 11 populations highlights missed opportunities for cardiovascular prevention in women. Hypertension. 2011;57:397–405.

Bradshaw PT, Stevens J, Khankari N, Teitelbaum SL, Neugut AI, Gammon MD. Cardiovascular disease mortality among breast cancer survivors. Epidemiology. 2016;27:6–13.

Brown DW, Dueker N, Jamieson DJ, et al. Preeclampsia and the risk of ischemic stroke among young women: results from the Stroke Prevention in Young Women Study. Stroke. 2006;37:1055–9.

Bukowski R, Davis KE, Wilson PW. Delivery of a small for gestational age infant and greater maternal risk of ischemic heart disease. PLoS One. 2012;7:e33047.

Bushnell C, McCullough LD, Awad IA, et al. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45:1545–88.

Campos-Rodriguez F, Martinez-Garcia MA, de la Cruz-Moron I, Almeida-Gonzalez C, Catalan-Serra P, Montserrat JM. Cardiovascular mortality in women with obstructive sleep apnea with or without continuous positive airway pressure treatment: a cohort study. Ann Intern Med. 2012;156:115–22.

Carroll MD, Fryar CD. Total and high-density lipoprotein cholesterol in adults: United States, 2015–2018. In: Statistics NCfH, editor. Hyattsville, 2020.

Carroll MD, Fryar CD, Nguyen DT. Total and high-density lipoprotein cholesterol in adults: United States. NCHS Data Brief. 2015-2016;2017:1–8.

Chen J, Long JB, Hurria A, Owusu C, Steingart RM, Gross CP. Incidence of heart failure or cardiomyopathy after adjuvant trastuzumab therapy for breast cancer. J Am Coll Cardiol. 2012;60:2504–12.

Chomistek AK, Manson JE, Stefanick ML, et al. Relationship of sedentary behavior and physical activity to incident cardiovascular disease: results from the Women's Health Initiative. J Am Coll Cardiol. 2013;61:2346–54.

Christ J, Gunning M, Palla G, et al. Prolonged estrogen deprivation is associated with increased cardiovascular disease risk among women with primary ovarian insufficiency. Fertil Steril. 2017;108:e392.

Clayton JA, Collins FS. Policy: NIH to balance sex in cell and animal studies. Nature. 2014;509:282–3.

Control CfD. Participation in leisure-time aerobic and muscle-strengthening activities that meet the federal 2008 Physical Activity Guidelines for Americans among adults aged 18 and over, by selected characteristics: United States, selected years 1998–2017. 2017.

Cook NR, Buring JE, Ridker PM. The effect of including C-reactive protein in cardiovascular risk prediction models for women. Ann Intern Med. 2006;145:21–9.

Creamer MR, Wang TW, Babb S, et al. Tobacco product use and cessation indicators among adults – United States, 2018. MMWR Morb Mortal Wkly Rep. 2019;68:1013–9.

Curtis KM, Jatlaoui TC, Tepper NK, et al. U.S. selected practice recommendations for contraceptive use, 2016. MMWR Recomm Rep. 2016;65:1–66.

Cushman M, Shay CM, Howard VJ, et al. Ten-year differences in women's awareness related to coronary heart disease: results of the 2019 American Heart Association National Survey: a special report from the American Heart Association. Circulation. 2021;143:CIR0000000000000907.

Daan NMP, Muka T, Koster MPH, et al. Cardiovascular risk in women with premature ovarian insufficiency compared to premenopausal women at middle age. J Clin Endocrinol Metabol. 2016;101:3306–15.

Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med. 2013;368:987–98.

del Rincon I, Polak JF, O'Leary DH, et al. Systemic inflammation and cardiovascular risk factors predict rapid progression of atherosclerosis in rheumatoid arthritis. Ann Rheum Dis. 2015;74:1118–23.

Drazner MH. The progression of hypertensive heart disease. Circulation. 2011;123:327–34.

Ewing AC, Ellington SR, Shapiro-Mendoza CK, Barfield WD, Kourtis AP. Full-term small-for-gestational-age newborns in the U.S.: characteristics, trends, and morbidity. Matern Child Health J. 2017;21:786–96.

Exploring the biological contributions to human health: does sex matter? Washington, D.C.: The National Academies Press, 2001.

Faccini A, Kaski JC, Camici PG. Coronary microvascular dysfunction in chronic inflammatory rheumatoid diseases. Eur Heart J. 2016;37:1799–806.

Flegal KM, Graubard BI, Williamson DF, Gail MH. Cause-specific excess deaths associated with underweight, overweight, and obesity. JAMA. 2007;298:2028–37.

Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. JAMA. 2013;309:71–82.

Franklin KA, Lindberg E. Obstructive sleep apnea is a common disorder in the population-a review on the epidemiology of sleep apnea. J Thorac Dis. 2015;7:1311–22.

Fryar CD, Ostchega Y, Hales CM, Zhang G, Kruszon-Moran D. Hypertension prevalence and control among adults: United States, 2015–2016. NCHS Data Brief. 2017;289:1–8.

Gami AS, Witt BJ, Howard DE, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. J Am Coll Cardiol. 2007;49:403–14.

Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63:2935–59.

Goueslard K, Cottenet J, Mariet AS, et al. Early cardiovascular events in women with a history of gestational diabetes mellitus. Cardiovasc Diabetol. 2016;15:15.

Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice guidelines. J Am Coll Cardiol. 2019;73:e285–350.

Gulati M, Mulvagh SL. The connection between the breast and heart in a woman: breast cancer and cardiovascular disease. Clin Cardiol. 2018;41:253–7.

Gulati M, Pandey DK, Arnsdorf MF, et al. Exercise capacity and the risk of death in women: the St James Women Take Heart Project. Circulation. 2003;108:1554–9.

Gulati M, Black HR, Shaw LJ, et al. The prognostic value of a nomogram for exercise capacity in women. N Engl J Med. 2005;353:468–75.

Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity and severe obesity among adults: United States, 2017–2018. NCHS data brief. Hyattsville: National Center for Health Statistics; 2020.

Hall PS, Nah G, Vittinghoff E, et al. Relation of pregnancy loss to risk of cardiovascular disease in parous postmenopausal women (From the Women's Health Initiative). Am J Cardiol. 2019;123:1620–5.

Hirode G, Wong RJ. Trends in the prevalence of metabolic syndrome in the United States, 2011–2016. JAMA. 2020;323:2526–8.

Honigberg MC, Zekavat SM, Aragam K, et al. Long-term cardiovascular risk in women with hypertension during pregnancy. J Am Coll Cardiol. 2019;74:2743–54.

Huxley RR, Peters SA, Mishra GD, Woodward M. Risk of all-cause mortality and vascular events in women versus men with type 1 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2015;3:198–206.

Ji H, Kim A, Ebinger JE, et al. Sex differences in blood pressure trajectories over the life course. JAMA Cardiol. 2020;5:19.

Kramer CK, Campbell S, Retnakaran R. Gestational diabetes and the risk of cardiovascular disease in women: a systematic review and meta-analysis. Diabetologia. 2019;62:905–14.

Lakoski SG, Cushman M, Criqui M, et al. Gender and C-reactive protein: data from the Multiethnic Study of Atherosclerosis (MESA) cohort. Am Heart J. 2006;152:593–8.

Lee JJ, Cook-Wiens G, Johnson BD, et al. Age at menarche and risk of cardiovascular disease outcomes: findings from the National Heart Lung and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation. J Am Heart Assoc. 2019;8:e012406.

Maas AH, van der Schouw YT, Atsma F, et al. Breast arterial calcifications are correlated with subsequent development of coronary artery calcifications, but their aetiology is predominantly different. Eur J Radiol. 2007;63:396–400.

Mannisto T, Mendola P, Vaarasmaki M, et al. Elevated blood pressure in pregnancy and subsequent chronic disease risk. Circulation. 2013;127:681–90.

Margolies L, Salvatore M, Hecht HS, et al. Digital mammography and screening for coronary artery disease. JACC Cardiovasc Imaging. 2016;9:350–60.

Mason JC, Libby P. Cardiovascular disease in patients with chronic inflammation: mechanisms underlying premature cardiovascular events in rheumatologic conditions. Eur Heart J. 2015;36:482–9c.

McKee SA, Smith PH, Kaufman M, Mazure CM, Weinberger AH. Sex differences in varenicline efficacy for smoking cessation: a meta-analysis. Nicotine Tob Res. 2016;18:1002–11.

Merz CN, Johnson BD, Berga S, Braunstein G, Reis SE, Bittner V. Past oral contraceptive use and angiographic coronary artery disease in postmenopausal women: data from the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation. Fertil Steril. 2006;85:1425–31.

Merz CNB, Andersen H, Keida M, et al. Women speak up about heart health action: a Women's Heart Alliance Research report. J Am Coll Cardiol. 2016;67:2039.

Michos ED, Vasamreddy CR, Becker DM, et al. Women with a low Framingham risk score and a family history of premature coronary heart disease have a high prevalence of subclinical coronary atherosclerosis. Am Heart J. 2005;150:1276–81.

Mora S, Otvos JD, Rifai N, Rosenson RS, Buring JE, Ridker PM. Lipoprotein particle profiles by nuclear magnetic resonance compared with standard lipids and apolipoproteins in predicting incident cardiovascular disease in women. Circulation. 2009;119:931–9.

Mora S, Buring JE, Ridker PM, Cui Y. Association of high-density lipoprotein cholesterol with incident cardiovascular events in women, by low-density lipoprotein cholesterol and apolipoprotein B100 levels: a cohort study. Ann Intern Med. 2011;155:742–50.

Moradi M, Adibi A, Abedi M. Relationship between breast arterial calcification on mammography with CT calcium scoring and coronary CT angiography results. Adv Biomed Res. 2014;3:79.

Moran LJ, Misso ML, Wild RA, Norman RJ. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update. 2010;16:347–63.

Mosca L, Hammond G, Mochari-Greenberger H, Towfighi A, Albert MA. Fifteen-year trends in awareness of heart disease in women: results of a 2012 American Heart Association national survey. Circulation. 2013;127:1254–63. e1–29

Muka T, Oliver-Williams C, Kunutsor S, et al. Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality: a systematic review and meta-analysis. JAMA Cardiol. 2016;1:767–76.

Nanna MG, Wang TY, Xiang Q, et al. Sex differences in the use of statins in community practice. Circ Cardiovasc Qual Outcomes. 2019;12:e005562.

National Center for Health Statistics (US). Health, United States, 2016: with chartbook on long-term trends in health. Hyattsville (MD), 2017.

Newallo D, Meinel FG, Schoepf UJ, et al. Mammographic detection of breast arterial calcification as an independent predictor of coronary atherosclerotic disease in a single ethnic cohort of African American women. Atherosclerosis. 2015;242:218–21.

Ngo AD, Roberts CL, Chen JS, Figtree G. Delivery of a small-for-gestational-age infant and risk of maternal cardiovascular disease–a population-based record linkage Study. Heart Lung Circ. 2015;24:696–704.

Ohkuma T, Komorita Y, Peters SAE, Woodward M. Diabetes as a risk factor for heart failure in women and men: a systematic review and meta-analysis of 47 cohorts including 12 million individuals. Diabetologia. 2019;62:1550–60.

Oliver-Williams C, Vassard D, Pinborg A, Schmidt L. Risk of cardiovascular disease for women with polycystic ovary syndrome: results from a national Danish registry cohort study. Eur J Prev Cardiol. 2020; https://doi.org/10.1177/2047487320939674.

Olson MB, Shaw LJ, Kaizar EE, et al. Obesity distribution and reproductive hormone levels in women: a report from the NHLBI-sponsored WISE Study. J Womens Health (Larchmt). 2006;15:836–42.

Ostchega Y, Fryar CD, Nwankwo T, Nguyen DT. Hypertension prevalence among adults aged 18 and over: United States, 2017–2018. Hyattsville: National Center for Health Statistics; 2020.

Palmer J, Lloyd A, Steele L, et al. Differential risk of ST-segment elevation myocardial infarction in male and female smokers. J Am Coll Cardiol. 2019;73:3259–66.

Parker DR, Lu B, Sands-Lincoln M, et al. Risk of cardiovascular disease among postmenopausal women with prior pregnancy loss: the women's health initiative. Ann Fam Med. 2014;12:302–9.

Paynter NP, Chasman DI, Pare G, et al. Association between a literature-based genetic risk score and cardiovascular events in women. JAMA. 2010;303:631–7.

Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation. 2003;107:499–511.

Peters SA, Woodward M. Women's reproductive factors and incident cardiovascular disease in the UK Biobank. Heart. 2018;104:1069–75.

Pirie K, Peto R, Reeves GK, Green J, Beral V, Million Women Study C. The 21st century hazards of smoking and benefits of stopping: a prospective study of one million women in the UK. Lancet. 2013;381:133–41.

Polotsky HN, Polotsky AJ. Metabolic implications of menopause. Semin Reprod Med. 2010a;28:426–34.

Polotsky HN, Polotsky AJ. Metabolic implications of menopause. Semin Reprod Med. 2010b;28:426–34.

Prasad M, Hermann J, Gabriel SE, et al. Cardiorheumatology: cardiac involvement in systemic rheumatic disease. Nat Rev Cardiol. 2015;12:168–76.

Professional Practice Committee: Standards of Medical Care in Diabetes-2020. Diabetes Care. 2020;43:S3.

Regensteiner JG, Golden S, Huebschmann AG, et al. Sex differences in the cardiovascular consequences of diabetes mellitus: a scientific statement from the American Heart Association. Circulation. 2015;132:2424–47.

Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. Circulation. 2003;107:391–7.

Roeters van Lennep JE, Heida KY, Bots ML, Hoek A, collaborators of the Dutch Multidisciplinary Guideline Development Group on Cardiovascular Risk Management after Reproductive D. Cardiovascular disease risk in women with premature ovarian insufficiency: a systematic review and meta-analysis. Eur J Prev Cardiol. 2016;23:178–86.

Romundstad PR, Magnussen EB, Smith GD, Vatten LJ. Hypertension in pregnancy and later cardiovascular risk: common antecedents? Circulation. 2010;122:579–84.

Rosenberg L, Palmer JR, Rao RS, Shapiro S. Low-dose oral contraceptive use and the risk of myocardial infarction. Arch Intern Med. 2001;161:1065–70.

Savitz DA, Danilack VA, Elston B, Lipkind HS. Pregnancy-induced hypertension and diabetes and the risk of cardiovascular disease, stroke, and diabetes hospitalization in the year following delivery. Am J Epidemiol. 2014;180:41–4.

Scheuner MT, Setodji CM, Pankow JS, Blumenthal RS, Keeler E. Relation of familial patterns of coronary heart disease, stroke, and diabetes to subclinical atherosclerosis: the multi-ethnic study of atherosclerosis. Genet Med. 2008;10:879–87.

Schmidt J, Landin-Wilhelmsen K, Brannstrom M, Dahlgren E. Cardiovascular disease and risk factors in PCOS women of postmenopausal age: a 21-year controlled follow-up study. J Clin Endocrinol Metab. 2011;96:3794–803.

Shaw LJ, Bairey Merz CN, Azziz R, et al. Postmenopausal women with a history of irregular menses and elevated androgen measurements at high risk for worsening cardiovascular event-free survival: results from the National Institutes of Health–National Heart, Lung, and Blood Institute sponsored Women's Ischemia Syndrome Evaluation. J Clin Endocrinol Metab. 2008;93:1276–84.

Shufelt CL, Bairey Merz CN. Contraceptive hormone use and cardiovascular disease. J Am Coll Cardiol. 2009;53:221–31.

Sinicato NA, da Silva Cardoso PA, Appenzeller S. Risk factors in cardiovascular disease in systemic lupus erythematosus. Curr Cardiol Rev. 2013;9:15–9.

Teede H, Deeks A, Moran L. Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. BMC Med. 2010;8:41.

Thomopoulos C, Tsioufis C, Michalopoulou H, Makris T, Papademetriou V, Stefanadis C. Assisted reproductive technology and pregnancy-related hypertensive complications: a systematic review. J Hum Hypertens. 2013;27:148–57.

Udell JA, Lu H, Redelmeier DA. Long-term cardiovascular risk in women prescribed fertility therapy. J Am Coll Cardiol. 2013;62:1704–12.

Udell JA, Lu H, Redelmeier DA. Failure of fertility therapy and subsequent adverse cardiovascular events. CMAJ. 2017;189:E391–7.

US UDoHaHS, Department of Health and Human Services PHS, Centers for Disease Control and Prevention NCfC, Disease Prevention and Health Promotion OoSa, Health. 2004 Surgeon General's report: the health consequences of smoking. Atlanta, 2004.

Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke Statistics-2020 update: a report from the American Heart Association. Circulation. 2020;141:e139–596.

Wessel TR, Arant CB, Olson MB, et al. Relationship of physical fitness vs body mass index with coronary artery disease and cardiovascular events in women. JAMA. 2004;292:1179–87.

Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018;71:e127–248.

Wilmot KA, O'Flaherty M, Capewell S, Ford ES, Vaccarino V. Coronary heart disease mortality declines in the United States from 1979 through 2011: evidence for stagnation in young adults, especially women. Circulation. 2015;132:997–1002.

Wu P, Gulati M, Kwok CS, et al. Preterm delivery and future risk of maternal cardiovascular disease: a systematic review and meta-analysis. J Am Heart Assoc. 2018;7:e007809.

Yoon YE, Kim KM, Han JS, et al. Prediction of subclinical coronary artery disease with breast arterial calcification and low bone mass in asymptomatic women: registry for the women health cohort for the BBC Study. JACC Cardiovasc Imaging. 2019;12:1202–11.

Chapter 11
Ethnic Factors in the Assessment of Cardiovascular Risk for Primary Prevention

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Introduction

The United States is becoming more ethnically diverse, and care of patients should take ethnic factors into account when providing recommendations for primary prevention of cardiovascular disease (CVD). However, there is a lack of clinical trial data for primary prevention of CVD in diverse populations. Large multiethnic cohorts have developed over time and have shown that the prevalence of disease and risk factors, association of risk factors with disease, and amount of risk accounted for by risk factors are all affected by ethnicity. A comprehensive understanding of the interaction between ethnicity and cardiovascular risk is needed to care for a diverse patient population. This chapter will review the differences in cardiovascular disease, traditional risk factors, and novel risk factors by ethnicity.

In the United States, the percentage of non-Hispanic White individuals in the population is steadily decreasing, while the proportion of Hispanic/Latino, African American/Black, Asian, and Native American/Alaska Native individuals is increasing (Fig. 11.1) (Humes et al. 2010; U.S. Census Bureau U.S. Census Bureau QuickFacts: United States 2020). From 2000 to 2019, non-Hispanic White individuals decreased from 69.1% to 60.1%, Hispanic/Latino individuals increased from 12.5% to 18.5%, African American/Black individuals increased from 12.3% to 13.4%, Asian individuals increased from 3.6% to 5.9%, and Native American/

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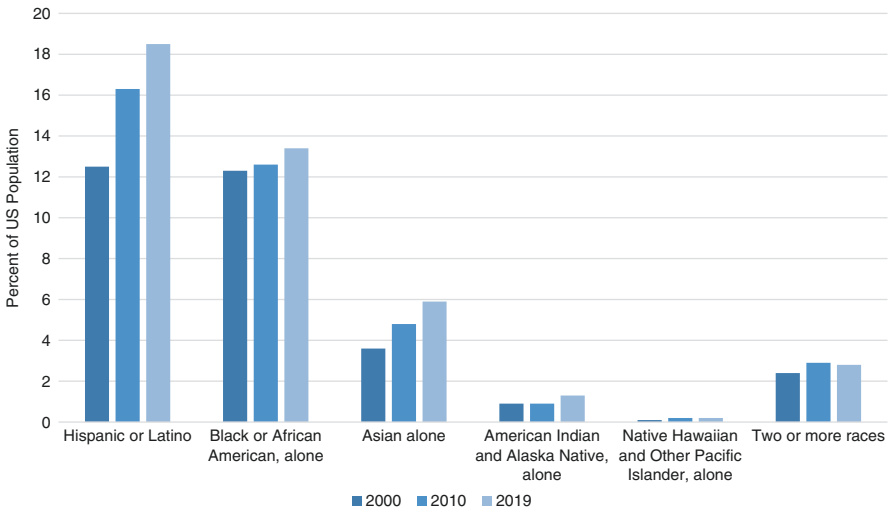

Fig. 11.1 Proportion of racial and ethnic minorities in the United States, 2000–2019. (Adapted from the United States Census Bureau. Percentage of White, alone: 75.1% (2000), 72.4% (2010), 76.3% (2019). Percentage of White, non-Hispanic, or Latino: 69.1% (2000), 63.7% (2010), 60.1% (2019) (Humes et al. 2010; U.S. Census Bureau U.S. Census Bureau QuickFacts: United States 2020))

Alaska Native individuals increased from 0.9% to 1.3% (Humes et al. 2010; U.S. Census Bureau U.S. Census Bureau QuickFacts: United States 2020) (Fig. 11.1). European countries are also becoming more ethnically diverse with minorities being disproportionately affected by CVD risk factors (Dal Canto et al. 2018). Given this increasing diversity, there is a greater need for scientific literature that reflects the changing demographics.

The prevalence of CVD (coronary heart disease (CHD), heart failure, stroke, and hypertension) in adults at least 20 years of age, based on data from 2013 to 2016, is 48% in the overall US population, with increasing prevalence with age, and highest in African American/Black individuals and lowest in Asian individuals, with limited data available on Native Americans (Virani et al. 2020). Death due to CVD progressively rose from the 1900s to the 1980s, subsequently declined until 2010, and now has started to rise again. Coronary heart disease is the leading cause of cardiovascular death, followed by stroke, hypertension, and heart failure. A significant portion of cardiovascular disease mortality can be prevented through optimization of known risk factors, and there is significant variation in risk factors based on race/ethnicity and socioeconomic factors. There remains a disparity in life expectancy between White and African American/Black males, although it is decreasing (Virani et al. 2020).

Despite the growing diversity in the United States, clinical trials, including primary prevention trials, which guide care and risk assessment of patients, have not consistently reflected that diversity. In a study of pivotal clinical trials for novel

cardiometabolic drugs studied from 2008 to 2017, White individuals represented 81%, African American/Black individuals represented 4%, and Asian individuals represented 12% of the study population. Hispanic/Latino ethnicity was available in only a subset of studies and represented 11% of that population (Khan et al. 2020). Modern primary prevention trials have also underrepresented minorities (Table 11.1). In assessing statins for primary prevention, the JUPITER trial had representation of African American/Black participants similar to the overall US population but underrepresented Hispanic/Latino and Asian participants (Ridker et al. 2008a). The HOPE-3 trial had excellent representation of Chinese, South Asians, and Hispanic/Latinos but poor representation of African American/Black participants (Yusuf et al. 2016). All three modern trials of aspirin (ARRIVE, ASCEND, ASPREE) for primary prevention had poor representation of ethnic minorities with more than 90% White participants (Gaziano et al. 2018; McNeil et al. 2018; Effects of aspirin for primary prevention in persons with diabetes mellitus 2018). In one study of modern trials of antidiabetic drugs for cardiovascular outcomes, representation of African American/Black individuals was <5% in five of seven trials assessed (Hoppe and Kerr 2017). Efforts are being made to improve representation of women and minorities in clinical research. For example, the National Institutes of Health (NIH) has a mandate for the inclusion of women and minority groups in NIH-funded

Table 11.1 Ethnic representation in primary cardiovascular disease prevention clinical trials

Year	Trial	Topic	Representation
2008	JUPITER (Ridker et al. 2008a)	Statins for primary prevention	71.2% White 12.7% Hispanic/Latino 12.5% African American/Black 3.6% Other
2016	HOPE-3 [7]	Statins for primary prevention	29.0% Chinese 27.5% Hispanic/Latino 20.0% White 14.6% South Asian 5.5% Other Asian 1.8% African American/Black 1.6% Other
2018	ASCEND (Effects of aspirin for primary prevention in persons with diabetes mellitus 2018)	Aspirin for primary prevention	96.5% White
2018	ARRIVE (Gaziano et al. 2018)	Aspirin for primary prevention	97.9% White
2018	ASPREE (McNeil et al. 2018)	Aspirin for primary prevention	91% White 5% African American/Black 3% Hispanic/Latino 1% Asian 1% Other

research (Inclusion of Women and Minorities as Participants in Research Involving Human Subjects 2021).

There is a need for more studies of ethnicity and cardiovascular risk factors. In a systematic review of North American studies, risk factor differences in African American/Black and White populations are the most commonly studied (79.1%), followed by those in Hispanic/Latinos and White (44.5%), Indigenous and White (23.6%), Chinese and White (20.0%), Filipino and White (15.5%), and Arab and White populations (3.6%). The authors note that much of the evidence within populations is conflicting, making it difficult to draw conclusions (Gasevic et al. 2015). Ethnicity is difficult to study due to variation in methods of identification and study types, and given that ethnicity is often self-identified (Dal Canto et al. 2018). In addition, ethnicities are not uniform. For example, among Hispanic/Latino individuals, there are varying levels of markers for cardiovascular disease as well as differences in the magnitude of association between traditional risk factors and coronary artery calcification (Gasevic et al. 2015).

Longitudinal cohort studies, particularly modern multiethnic cohort studies, have sought to fill these knowledge gaps (Table 11.2). Much of our current understanding of cardiovascular disease and risk factors comes from the Framingham Heart Study (FHS). Through the FHS, risk factors such as hypertension, hypercholesterolemia, smoking, obesity, diabetes, age, and sex were identified (Tsao and Vasan 2015). Although these findings have been shown to apply to ethnic minorities, the first three cohort generations only included White individuals and may have underappreciated specific ethnic factors (Tsao and Vasan 2015). More diverse cohorts, OMNI-1 and OMNI-2, were subsequently created to better reflect

Table 11.2 Ethnic representation in cardiovascular disease longitudinal cohort studies

Year started	Study name	Population	Area of interest
1948 (original) 1994 (OMNI-1) 2003 (OMNI-2)	Framingham Heart Study (FHS) (Tsao and Vasan 2015)	Original: 100% European ancestry OMNI-1: 42% Hispanic/Latino 28% African American/Black 24% Asian 6% Other OMNI-2: 42% Hispanic/Latino 28% African American/Black 24% Asian 6% Other	Identification of risk factors for cardiovascular disease to guide prevention

Table 11.2 (continued)

Year started	Study name	Population	Area of interest
1986	Atherosclerosis Risk in Communities (ARIC) (The atherosclerosis risk in communit (aric) stui)y: design and objectwes 1989; Cohort Description|Atherosclerosis Risk in Communities 2020)	73% White 27% Non-White (predominantly African American/Black)	Variation in cardiovascular risk factors, medical care, and disease by demographics and identification of the etiology of atherosclerosis and its clinical consequences
1988	Strong Heart Study (Lee et al. 1990)	100% Native American	Cardiovascular disease burden, mortality, and risk factors in Native Americans
1993	Northern Manhattan Stroke Study (NOMAS) (Sacco et al. 1998)	64% Hispanic/ Latino 22% White 13% African American/Black	Stroke incidence for White individuals, African American/Black individuals, and Hispanic/Latino individuals in an urban community
1998	The Jackson Heart Study of Cardiovascular Disease Among African Americans (Fuqua et al. 2005)	100% African American/Black	Long-term observation of CVD risk factors in African American/Black individuals as an outgrowth of ARIC
2000	Multi-Ethnic Study of Atherosclerosis (MESA) (Bild et al. 2002)	38% White 28% African American/Black 23% Hispanic/ Latino 11% Chinese	Subclinical CVD prevalence, measures, and progression
2003	REasons for Geographic and Racial Differences in Stroke (REGARDS) (Howard et al. 2005; Shikany et al. 2015)	58% White 42% African American/Black	Assess causes for excess stroke mortality in southeastern United States and in the African American/Black population
2008	Hispanic Community Health Study/Study of Latinos (HCHS/SOL) (LaVange et al. 2010)	100% Hispanic/ Latino	Risk factors for disease and association between risk factors and disease outcomes in Hispanics/ Latinos
2010	Mediators of Atherosclerosis in South Asians Living in America (MASALA) (Kanaya et al. 2013)	100% South Asian	Subclinical CVD prevalence, measures, and outcomes in South Asians in the United States

increasing racial and ethnic diversity with significant proportions of African American/Black individuals, Hispanic/Latino Americans, and Asian Americans and to understand how race and ethnicity interact with traditional and nontraditional risk factors (Tsao and Vasan 2015). Other multiethnic cohorts have also been developed to better understand cardiovascular disease in minority groups, such as the Multi-Ethnic Study of Atherosclerosis (MESA) (Bild et al. 2002), Atherosclerosis Risk in Communities (ARIC) (The atherosclerosis risk in communit (aric) stui)y: design and objectwes 1989), REasons for Geographic and Racial Differences in Stroke (REGARDS) (Howard et al. 2005), the Northern Manhattan Study (NOMAS) (Sacco et al. 1998), Hispanic Community Health Study/Study of Latinos (HCHS/SOL) (LaVange et al. 2010), Mediators of Atherosclerosis in South Asians Living in America (MASALA) (Kanaya et al. 2013), the Jackson Heart Study of Cardiovascular Disease Among African Americans (Fuqua et al. 2005), and the Strong Heart Study (Lee et al. 1990). These studies included ethnically diverse populations to bridge gaps in understanding cardiovascular risk in ethnic groups (Table 11.2).

Additionally, many risk assessment tools used in modern practices are not based on ethnically diverse samples (Table 11.3). The Framingham Risk Score for CHD

Table 11.3 Ethnic representation in development of cardiovascular disease risk assessment tools

Year	Tool	Topic	Representation
1991–1998	Framingham risk score (Tsao and Vasan 2015; Wilson et al. 1998)	Coronary heart disease	100% European ancestry
2006	Strong Heart Study (Lee et al. 2006)	Coronary heart disease	100% Native American
2007–2008	Reynolds risk score (Ridker et al. 2007; Ridker et al. 2008b)	Cardiovascular disease risk	95% White women, 5% primarily White men
2010	CHA_2DS_2VASc Score (Lip et al. 2010)	Thromboembolism with atrial fibrillation	European Cohort, race/ethnicity data not available
2014	ACC/AHA Pooled Cohorts Equation (Goff et al. 2014)	Cardiovascular disease risk	83% White 17% African American/Black
2015	MESA Risk Score (McClelland et al. 2015)	Coronary heart disease	39% white 28% African American/Black 22% Hispanic/Latino 12% Chinese
2017	QRISK3 Calculator (Hippisley-Cox et al. 2017)	Cardiovascular disease risk	89% White 2% Black African 1% Black Caribbean 2% Indian 1% Pakistani 1% Bangladeshi 1% Chinese 1% Other Asian 2% Other

was developed through the Framingham Heart Study, which was initiated in a single geographic area and contained only participants of European ancestry (Tsao and Vasan 2015; Wilson et al. 1998). The Reynolds Risk Score for cardiovascular risk was developed and validated in cohorts that had poor representation of minority groups. Specifically, the Reynolds Risk Score developed initially for women included over 95% White female participants (Ridker et al. 2007; Ridker et al. 2008b). Due to these limitations, the ACC/AHA Pooled Cohorts Equation for CVD risk was developed using multiple diverse cohorts and included White and African American/Black participants but did not have representative samples of other minority groups (Goff et al. 2014). The CHA_2DS_2VASc score for assessment of thromboembolic risk in atrial fibrillation was developed from a subset of a European cohort of patients without available data on race/ethnicity and did not account for race/ethnicity (Lip et al. 2010). It has subsequently been shown that the addition of ethnicity to the score would improve risk prediction (Kabra et al. 2016). There remains a need for tools for risk assessment in more ethnically diverse populations. For example, none of the major risk assessment tools are derived from or prospectively validated in South Asians in the United States (Volgman et al. 2018). More recently, newer scores have been developed as part of more ethnically diverse cohort studies. The MESA 10-year coronary heart disease (CHD) risk score was developed using the previously described MESA cohort and takes into account White, Chinese, African American/Black, and Hispanic/Latino ethnicities (McClelland et al. 2015). QRISK calculators were developed using a diverse patient cohort including South Asian, East Asian, and African American/Black participants (Hippisley-Cox et al. 2017). As part of the Strong Heart Study, a risk calculator for CHD in Native Americans was developed (Lee et al. 2006). The 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease lists high-risk ethnicity (such as South Asian) as a risk-enhancing factor as well as considering waist circumferences, using ethnically specific cutpoints, as a risk factor given ethnic differences in body mass index (BMI) for risk assessment (Arnett et al. 2019).

In general, traditional cardiovascular risk factors, especially modifiable risk factors, are extremely important in all ethnic groups. The majority of excess risk in minority groups is explained by traditional risk factors and socioeconomic factors (Volgman et al. 2018; Henderson et al. 2007; Thomas et al. 2005; Safford et al. 2012; Tajeu et al. 2020; Matthews et al. 2005; Bravata et al. 2005). When risk factors are addressed in clinical trial settings, for example, mortality is similar in minorities and White participants (Beohar et al. 2013). Immigrants experience different patterns of disease than in their countries of origin, likely related to modifiable risk factors such as higher degrees of obesity (Dal Canto et al. 2018). The INTERHEART study demonstrated that, in general, lipids, smoking, and psychosocial factors were the most important global risk factors; however, regional differences in risk factors were noted. In INTERHEART, apoB/apoA1 ratio, hypertension, diabetes mellitus, abdominal obesity, psychosocial factors, lack of fruit and vegetable intake, regular alcohol use, and lack of regular physical activity accounted for more than 90% of the risk associated with acute myocardial infarction in the general population and in most racial/regional subgroups (Yusuf et al. 2004). However, excess risk for CVD persists in ethnic minorities after accounting for traditional risk

factors in many studies (Dal Canto et al. 2018; Henderson et al. 2007; Hurley et al. 2010).

Significant opportunities exist for optimization of risk factors in ethnic groups. Ethnic and regional differences are associated with differences in risk factor burden, knowledge of risk factors, and the strength of the association between risk factors and cardiovascular disease. Minorities, in general, are more likely to have CVD risk factors compared with White individuals (Mensah et al. 2005). Minorities are often less likely to be aware of their risk factors and associated cardiovascular risk (Kim et al. 2017; Fussman et al. 2009; Hertz et al. 2007). They are less likely to have their diabetes, blood pressure, and lipids well-controlled (Parrinello et al. 2015; Wang et al. 2014; Holland et al. 2013; Chatterji et al. 2012; Egede et al. 2011; Winston et al. 2009; Chowdhury et al. 2006). African American/Black individuals, in particular, are more likely to have multiple risk factors as compared to White individuals (Frierson et al. 2013; Leifheit-Limson et al. 2013; Hayes et al. 2006; Sharma et al. 2004) and other ethnic groups (Hayes et al. 2006; Sharma et al. 2004). Minorities are also less likely to be offered preventive measures including antihypertensive and lipid-lowering medications, aspirin, and smoking cessation therapies (Winston et al. 2009; Leifheit-Limson et al. 2013).

Table 11.4 Most significant cardiovascular disease risk factors and targets for intervention by ethnic group

Ethnic group	Most significant cardiovascular disease risk factors
Hispanic/Latino	Diabetes Dyslipidemia (low HDL, high TG) Obesity
African American/black	Hypertension Diabetes Central obesity/metabolic syndrome
South Asian	Diabetes Central obesity/metabolic syndrome Dyslipidemia (low HDL, high total cholesterol: HDL)
Native American (American Indian/Alaska native)	Diabetes Obesity Hypertension Smoking/toxic chemical exposure Low physical activity

Risk factors are listed in descending order based on the risk factors making the greatest contribution to CVD risk, which, therefore, may also be the most critical targets for cardiovascular disease prevention

Ethnic Groups at High Risk for Cardiovascular Disease

As discussed above, traditional risk factors explain the majority of disparity in risk in ethnic groups and significant disparities in risk factor control remain. However, in high-risk groups, the significance of individual risk factors varies (Table 11.4). This section will address high-risk ethnic groups individually in terms of relative importance of risk factors, further options for risk stratification and patient management, and needs for further study. In addition, attention is paid to East Asians, who are at a lower CVD risk overall. In general, the studies cited use White individuals as the reference group for comparison unless otherwise specified.

Hispanic/Latino Americans

Hispanic/Latino Americans are the largest and fastest growing ethnic group in the United States. They also represent the largest immigrant population in the United States. Despite this, there is inadequate literature on Hispanic/Latinos, and barriers to studying them remain, including language and the difficulty studying undocumented immigrants. In addition, most studies in the United States focus on Mexicans. Although Hispanic/Latino Americans are often treated as one group, they are made up of diverse populations from various regions and Spanish-speaking countries and education and socioeconomic status can vary by country of origin (Rodriguez et al. 2014). Different subgroups within Hispanic/Latinos (including Mexican-Americans, Dominican-Americans, Puerto Rican-Americans, and other Hispanic-Americans) have been shown, for example, to have varying strengths of association between traditional risk factors and coronary artery calcification (Allison et al. 2008).

Hispanic/Latino individuals exhibit higher rates of CVD and evidence of more severe CVD than do White individuals in several areas. In general, Hispanic/Latino individuals demonstrate lower rates of coronary artery calcification, independent of other risk factors (Budoff et al. 2006), and lower rates of premature coronary artery disease but higher rates of hospitalization for myocardial infarction than do White individuals (Rodriguez et al. 2014). The risk for ischemic stroke (Patel et al. 2017) as well as overall stroke (Rodriguez et al. 2014) is higher in Hispanic/Latino individuals than in White individuals. Among those with stroke, Hispanic/Latino individuals are more likely to have diabetes and be overweight and less likely to have coronary disease; the association with hypertension has been inconsistent depending on the population studied (McGruder et al. 2004; Sacco et al. 2001). Among those with atrial fibrillation, Hispanic/Latino individuals are more likely to sustain a stroke (Shih et al. 2020). Hispanic/Latino individuals have a higher risk of heart failure per number of heart failure risk factors (Breathett et al. 2018) and a higher overall incidence of heart failure compared with White individuals (Rodriguez et al. 2014). Among those hospitalized with heart failure, Hispanic/Latino individuals are younger with lower ejection fraction and more likely to have diabetes and

hypertension than White individuals (Thomas et al. 2011). Hispanic/Latino individuals demonstrate a lower risk of peripheral arterial disease (PAD) (Rodriguez et al. 2014; Allison et al. 2006). However, in those with PAD, Hispanic/Latino individuals are more likely to have diabetes and hypertension, less likely to use aspirin and statins, and more likely to need peripheral artery bypass surgery (Meadows et al. 2009).

In general, Hispanic/Latino individuals exhibit worse overall cardiovascular health based on risk factor control than do White individuals (Pool et al. 2017). Among Hispanic/Latino individuals, diabetes is a particularly important CVD risk factor. Several studies have shown that diabetes is more prevalent among Hispanic/Latino individuals compared with White individuals (Gasevic et al. 2015; Rodriguez et al. 2014; Kulick et al. 2016; Romero et al. 2012; Sundquist et al. 2001). Hispanic/Latino individuals are more likely to die from diabetes, have poorly controlled glucose levels, and go undiagnosed. Those with diabetes are more likely to have nephropathy and retinopathy and less likely to have cardiovascular complications compared with White individuals (Rodriguez et al. 2014). Additionally, family history is a stronger risk factor in Hispanic/Latino than in White individuals, particularly among lean Hispanic/Latino individuals (Sundquist et al. 2001).

Hispanic/Latino individuals have a higher prevalence of dyslipidemia, typically with lower high-density lipoprotein cholesterol (HDL-C), higher triglycerides, and comparable low-density lipoprotein cholesterol (LDL-C) to White individuals. Importantly, they have lower rates of screening for dyslipidemia than do White and African American/Black individuals (Rodriguez et al. 2014). Hispanic/Latino individuals have a lower prevalence of hypertension than the general American population, but rates are increasing (Rodriguez et al. 2014). Additionally, Hispanic/Latino individuals with hypertension are more likely to have uncontrolled blood pressure, elevated hemoglobin A1c, and albuminuria (Liu et al. 2011). Obesity is significantly more common in Hispanic/Latino individuals, particularly in Mexican-Americans, than in White individuals, and the prevalence is increasing (Rodriguez et al. 2014; Wang et al. 2017). Risk factors for obesity in Hispanic/Latino individuals include age, history of arthritis, and diabetic medication use (Wang et al. 2017).

In terms of lifestyle factors, Hispanic/Latino individuals have a lower prevalence of smoking overall (Gasevic et al. 2015; Rodriguez et al. 2014; Romero et al. 2012). However, some individual subgroups (especially Mexican and Cuban men) exceed the national average. Hispanic/Latino individuals are less likely to be offered smoking cessation and are more likely to be light or nondaily smokers, which may make screening for smoking more difficult (Rodriguez et al. 2014). Hispanic/Latino individuals have lower rates of leisurely physical activity than White individuals. However, when occupation is taken into account, overall physical activity levels are comparable (Rodriguez et al. 2014). A significant portion of the differences in risk between Hispanic/Latino individuals and White individuals is explained by socioeconomic status and geographic location (Matthews et al. 2005). There also appears to be an association between race/ethnicity and socioeconomic status, which impacts risk factors among Hispanic/Latino individuals (Rodriguez et al. 2014; Winkleby et al. 1998), covered in greater detail elsewhere in this textbook.

Interventions for primary prevention in Hispanic/Latinos should be, as with all groups, directed toward optimal risk factor control. In particular, screening for dyslipidemia, diabetes (especially with a family history of diabetes), and smoking should be emphasized. Control of hypertension, diabetes, and interventions directed toward weight loss, given high rates of obesity are particularly important. Interventions that integrate cultural values, social support, and adaptation to literacy levels have been shown to be effective (Rodriguez et al. 2014). Among those who smoke, offering smoking cessation should be a point of emphasis. Physical activity outside of occupational activity should be emphasized. The diversity of backgrounds that are included within the category of Hispanic/Latinos should be recognized. Barriers to access to health care including language, health literacy, and patient–provider relationships need to be addressed. Additionally, more studies are needed in areas such as cultural values and behaviors and their impact on risk factors, the impact of socioeconomic status, and disparities in cardiovascular disease and stroke; in particular, future studies should address individual Hispanic/Latino groups rather than treating them as a monolith (Rodriguez et al. 2014).

African American/Black Individuals

African American/Black individuals make up the second largest ethnic group in the United States. They suffer from a significant disparity in life expectancy, largely due to the higher burden of cardiovascular disease. In the United States, life expectancy for African American/Black individuals is over 3 years shorter compared with that for White individuals, with worse overall cardiovascular health characterized by a high burden of risk factors and less effective disease management (Carnethon et al. 2017). While coronary disease has declined overall, the decrease in African American/Black men is half that in White men (Carnethon et al. 2017). African American/Black men are less likely to have coronary artery calcification than are White men, while African American/Black women are more likely compared with White women (Budoff et al. 2006). The incidence, prevalence, and prognosis of heart failure among African American/Black individuals are worse, likely due to increased risk factor burden (Carnethon et al. 2017). African American/Black individuals with heart failure are more likely to have hypertension and diabetes and more likely to have more risk factors (Breathett et al. 2018; Thomas et al. 2011; Lawson et al. 2020; Kubicki et al. 2020) than White individuals. Among those hospitalized with heart failure, African American/Black individuals are younger, with lower ejection fraction than White individuals (Thomas et al. 2011). African American/Black individuals have a significant risk for stroke with higher overall risk, higher mortality, and higher risk of recurrence with intracranial stenosis (Carnethon et al. 2017; Jiménez et al. 2019; Waddy et al. 2009). Stroke in African American/Black individuals is more likely to be associated with hypertension, diabetes, and obesity and less likely to be associated with coronary disease, atrial fibrillation, smoking, or excess alcohol use (McGruder et al. 2004; Sacco et al. 2001;

Hajat et al. 2004; Dundas et al. 2001; Hajat et al. 2001). The risk for stroke is attenuated when income level is adjusted for (Bravata et al. 2005). The risk for peripheral arterial disease is higher in African American/Black individuals, even after adjustment for traditional and novel risk factors. PAD is more often associated with diabetes and hypertension in African American/Black individuals, and they are more likely to have higher blood pressure and total cholesterol, less likely to use aspirin and statins, and less likely to receive peripheral artery bypass surgery (Allison et al. 2006; Meadows et al. 2009; Carnethon et al. 2017). Although African American/Black individuals have a higher burden of risk factors for atrial fibrillation, they have a lower prevalence of atrial fibrillation, known as the atrial fibrillation paradox (Carnethon et al. 2017; Gbadebo et al. 2011; O'Neal et al. 2017; Jensen et al. 2013; Lipworth et al. 2012). This may be related to poor access to care and lower disease ascertainment (however, similar findings have been seen during hospitalizations (Rodriguez et al. 2015)), less genetic predisposition, or different responses to hypertension, such as smaller left atrial size, than in White individuals (Gbadebo et al. 2011). However, traditional risk factors for atrial fibrillation confer higher attributable risk on African American/Black individuals, and African American/Black individuals with atrial fibrillation are more likely to experience a stroke (Shih et al. 2020; O'Neal et al. 2017; Jensen et al. 2013; Lipworth et al. 2012; Rodriguez et al. 2016).

African American/Black individuals have a higher risk of hypertension, diabetes mellitus, and dyslipidemia across the age spectrum compared with White individuals (Howard et al. 2017). Important risk factors for premature coronary disease in this population include dyslipidemia, diabetes, and smoking (Amin et al. 2009). Hypertension is the most important risk factor for African American/Black individuals, given its high prevalence and contribution to disparities in CVD, and presents the greatest opportunity for prevention (Carnethon et al. 2017). Hypertension has been consistently shown to be more common in African American/Black individuals than in White individuals (Romero et al. 2012; Sundquist et al. 2001; Dundas et al. 2001; Bell et al. 2018; Cappuccio et al. 1997). Prehypertension is also more common and more strongly associated with alcohol consumption in African American/Black individuals than in White individuals (Glasser et al. 2011). Additionally, higher blood pressure levels start in childhood (Carnethon et al. 2017). While African American/Black individuals may actually be more aware of a diagnosis of hypertension and more likely to be treated, they are less likely to have adequate blood pressure control and more likely to have poorly controlled diabetes as well (Hertz et al. 2007; Liu et al. 2011; Carnethon et al. 2017). Additionally, the association between systolic blood pressure and stroke is much stronger in African American/Black individuals than in White individuals (Carnethon et al. 2017).

African American/Black individuals are at a higher risk of type 2 diabetes mellitus than White individuals (Kulick et al. 2016; Carnethon et al. 2017; Bell et al. 2018; Cappuccio et al. 1997; Bancks et al. 2017). African American/Black adolescents are more likely to develop diabetes, and those who have diabetes are less

likely to be aware of it and achieve control and more likely to have complications and die from them (Carnethon et al. 2017). Additionally, use of hemoglobin A1c may underestimate the prevalence of diabetes in this population due to the prevalence of sickle cell trait and anemia, though this remains unclear (Carnethon et al. 2017). The differences in risk of type 2 diabetes seem to be related to biological, socioeconomic, and behavioral factors (Bancks et al. 2017).

African American/Black individuals, in general, have lower total cholesterol, lower triglycerides, and HDL-C than do White individuals (Dal Canto et al. 2018; Lemic-Stojcevic et al. 2001). However, they have higher rates of atherosclerotic cardiovascular disease and mortality from coronary heart disease (Dal Canto et al. 2018; Carnethon et al. 2017). African American/Black individuals have higher levels of lipoprotein(a) and oxidized phospholipids, which may explain some of the increased risks (Tsimikas et al. 2009; Palaniappan et al. 2002). They are also less likely to be aware of dyslipidemia and to have it under control, likely due to lower rates of prescription of lipid-lowering therapies (Carnethon et al. 2017).

African American/Black individuals have a higher prevalence of obesity than do White and Hispanic/Latino individuals (Romero et al. 2012; Wang et al. 2017; Carnethon et al. 2017; Bell et al. 2018). Risk factors for obesity in African American/Black individuals include female gender, low physical activity, smoking, binge drinking, and use of antidiabetic medications (Wang et al. 2017). Body mass index, however, is less predictive of risk for diabetes, hypertension, and dyslipidemia as well as events in this population, possibly due to variation in weight distribution with larger waist circumference and more visceral fat (Carnethon et al. 2017; Taylor et al. 2010). African American/Black individuals have a higher prevalence of risk factors at nearly all BMIs compared with White individuals (Taylor et al. 2010). Abdominal fat is associated with hypertension in African American/Black individuals and White individuals (Harris et al. 2000), and ethnicity-specific weight circumference may be a better measure than BMI (Zhu et al. 2005). Fat distribution appears to vary by gender; there is an increased prevalence of abdominal obesity in African American/Black women with a lower prevalence in African American/Black men (Sundquist et al. 2001; Després et al. 2000), and the lower prevalence in men has been proposed to explain generally more favorable lipid profiles (Després et al. 2000). Weight loss in African American/Black individuals is associated with improvement in hypertension in both men and women (Juhaeri et al. 2003). Genetic factors may play a role in the increased risk of CVD in African American/Black individuals, including genetic variants for C-reactive protein (CRP), and the notion of increased family prevalence of hypertension, but further study is needed (Carnethon et al. 2017).

General cardiovascular health, as assessed by modifiable risk factor control, is worse in African American/Black individuals than in White individuals (Pool et al. 2017). African American/Black individuals, regardless of geographic location, are more likely to consume a southern diet (characterized by added fats, fried food,

organ meats, processed meats, eggs and egg dishes, and sugar-sweetened beverages), which is associated with elevated risks for coronary disease and stroke (Carnethon et al. 2017; Shikany et al. 2015). They are more likely to have low physical activity, leading to CVD (Sundquist et al. 2001; Carnethon et al. 2017; Palaniappan et al. 2002; Zaninotto et al. 2007). They have similar rates of smoking and the magnitude of associated risk but are more at risk for environmental smoke exposure and are less likely to quit smoking (Carnethon et al. 2017). They are more likely to have obstructive sleep apnea associated with higher rates of coronary disease and stroke mortality (Carnethon et al. 2017).

Overall, African American/Black individuals have lower socioeconomic status than White individuals by several measures including income, wealth, poverty rate, level of education, and occupation (Rodriguez et al. 2014). However, higher BMI, waist circumference, and lower HDL-C are associated with higher socioeconomic status in this group overall (Waldstein et al. 2016), but this relationship appears to be modified by gender as African American/Black women appear to have a lower burden of cardiovascular risk factors with higher socioeconomic status (Boykin et al. 2011). Socioeconomic status explains some of the increased risks of hypertension, diabetes, and dyslipidemia (Whitty et al. 1999). When socioeconomic status and risk factors are combined, much of the higher cardiovascular mortality in African American/Black individuals is explained (Tajeu et al. 2020). Risk of stroke is also attenuated after adjustment for income (Bravata et al. 2005). African American/Black individuals are more likely to have a high school education than Hispanic/Latino individuals, but less likely than White individuals, and more education is associated with a lower risk (Sharma et al. 2004; Rodriguez et al. 2014).

Cardiovascular disease prevention in African American/Black individuals should focus on guideline-driven optimization of modifiable risk factors. Hypertension appears to be the most important risk factor and opportunity for risk prevention. Diabetes and obesity are also important risk factors, leading to disparities in healthcare outcomes. When assessing risks, calcium scoring may underestimate the risk in African American/Black individuals due to the lower degree of coronary artery calcification in this population (Carnethon et al. 2017). The ACC/AHA Pooled Cohorts Equation was developed with a large number of African America/Black individuals and is the best available risk score for these patients (Carnethon et al. 2017). Medical management is generally similar compared with other ethnic groups with notable exceptions. For the management of hypertension, calcium channel blockers and thiazide diuretics are specifically recommended; for heart failure with reduced ejection fraction, hydralazine and nitrates in addition to angiotensin-converting enzyme inhibitors/angiotensin receptor blockers are beneficial (Carnethon et al. 2017). Public health interventions on a larger scale are needed, given the disparities in income level and lack of available preventive services. The social and cultural environment may be used as an opportunity for targeted interventions (Carnethon et al. 2017). For example, in an interventional randomized trial of African American/Black individuals with hypertension recruited from African

American-owned barbershops, there was a significant reduction in systolic blood pressure with a pharmacist-led intervention focused around barbershops (Victor et al. 2018).

Future studies should focus on studying cardiovascular risks and interventions in diverse populations, including a representative sample of African American/Black individuals. More studies are needed to better understand the potential contribution of inherited/genetic risks for CVD in African American/Black individuals. Further studies regarding targeted interventions, which address barriers to care and take into account social and cultural factors, such as the barbershop study, are needed. Broader reform in the United States to reduce health disparities among African American/Black individuals, including cardiovascular disease risk, is also needed.

South Asians

South Asians make up one-quarter of the world's population and are one of the fastest growing ethnic groups in the United States. The group comprises people from Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, and Sri Lanka with diverse cultural and religious practices and languages. In the United States in 2010, there were 3.4 million South Asians, and 80% were of Indian origin. National surveys, however, have only recently started classifying Asian Americans into separate subgroups (Volgman et al. 2018).

In general, South Asians have increased frequency and severity of cardiovascular disease compared with other groups. South Asians have increased risk of premature cardiovascular disease with increased risk of poorer outcomes from revascularization and higher mortality compared with Whites and other Asian groups (Volgman et al. 2018; Gupta and Brister 2006). South Asians are more likely to have more severe coronary artery disease, with greater degree of stenosis and involvement of multiple vessels as well as smaller luminal diameter of coronary arteries (Vasudev et al. 2020; Hasan et al. 2011). Bangladeshis appear to be at a particularly high risk (Vasudev et al. 2020). South Asians are also more likely to have elevated coronary artery calcium scores compared with African American/Blacks and Hispanic/Latinos and similar to White individuals (Volgman et al. 2018). Those who suffer strokes are younger, with higher rates of diabetes mellitus and higher blood pressure and glucose compared with other ethnic groups, despite comparable socioeconomic status to White individuals and higher antidiabetic and antiplatelet medication use (Gezmu et al. 2014). They also have higher rates of peripheral arterial disease (Volgman et al. 2018). Despite higher rates of associated risk factors, South Asians appear to have less risk of atrial fibrillation than White individuals (Gillott et al. 2017). Among those who develop heart failure, South Asians are more likely to have ischemic heart disease, hypertension, and diabetes compared with Whites (Lawson et al. 2020).

Among South Asians, traditional risk factors account for a large portion of the increased cardiovascular risk but do not fully explain it (Volgman et al. 2018; Yusuf et al. 2004; Gupta and Brister 2006). Genetic risk factors for CVD may play a role, but there is a need for further study (Volgman et al. 2018). In particular, diabetes and fat distribution appear to be the most important risk factors in South Asians. South Asians have increased prevalence of type 2 diabetes compared with other ethnic groups (Volgman et al. 2018; Cappuccio et al. 1997; Gupta and Brister 2006; Rabanal et al. 2013) even at lower BMI levels and younger ages (Virani et al. 2020). Additionally, there appears to be an increased risk of gestational diabetes in Indians (Seshiah et al. 2004), which is associated with an increased risk of developing overt diabetes mellitus (Feig et al. 2008) and cardiovascular disease later in life (Tobias et al. 2017). Diabetes in South Asians has been associated with lower income and education, psychological comorbidities, and low physical activity (Shah et al. 2015). However, there also appears to be increased genetic susceptibility (Kooner et al. 2011) and South Asians have been observed to have increased insulin resistance and reduced fat oxidation (Hall et al. 2010), especially among those with metabolic syndrome (Ajjan et al. 2007), which may explain some of the increased risk for diabetes. Importantly, Indians and Bangladeshis with diabetes are more likely to have cardiovascular disease, an association not seen in Black Caribbean, Pakistani, or Chinese participants in a study in the UK (Zaninotto et al. 2007), and Indians with diabetes, compared with nondiabetics, have a stronger association with severe coronary artery disease than White individuals (Gijsberts et al. 2015).

Obesity, in general, is less prevalent in South Asians (Gupta and Brister 2006). However, distribution of fat appears to be a more significant risk factor in this population. South Asians have lower BMI, body weight, and waist circumference than most other groups. However, they have increased abdominal obesity at any degree of BMI, which is associated with increased insulin resistance (Volgman et al. 2018; Gupta and Brister 2006). South Asians have a higher waist/hip ratio than other ethnic groups (Rabanal et al. 2013), and this appears to be a better predictor of cardiovascular risk than BMI (Volgman et al. 2018; Zaninotto et al. 2007). Given these data, the ADA (American Diabetes Association), AHA, ACC and World Health Organization (WHO) recommended reducing BMI cutoffs for South Asians to better identify risks (Volgman et al. 2018; Grundy et al. 2005) and the ACC/AHA primary prevention guidelines recommend considering waist circumference as a risk factor for minority groups (Arnett et al. 2019).

In South Asians, dyslipidemia occurs at lower levels of BMI and body fat than in White individuals (Dal Canto et al. 2018). In general, South Asians have lower HDL-C, higher triglycerides, and a higher cholesterol to HDL-C ratio with similar LDL-C and total cholesterol compared with other groups, though LDL particles have been observed to be smaller, which is an artherosclerotic CVD (ASCVD) risk factor (Volgman et al. 2018; Gupta and Brister 2006; Rabanal et al. 2013). Lower HDL-C and higher cholesterol: HDL-C ratio appear to be important risk factors in this population (Game and Jones 2000). Additionally, several studies have observed higher levels of lipoprotein(a) in South Asians (Palaniappan et al. 2002; Anand et al. 2000; Kamath et al. 1999; Anand and Yusuf 1997). Although there are no reasons to

suspect that statins would be less effective in South Asians, data on statin efficacy in this population are extremely limited (Volgman et al. 2018). Hypertension is also common in South Asians and appears to be an important risk factor, but it is less well studied (Volgman et al. 2018). South Asians have also been observed to have higher high-sensitivity C-reactive protein levels than do White individuals (Gupta and Brister 2006).

In terms of lifestyle factors, some South Asian groups have lower levels of physical activity, which may be related to diabetes risk, but data are limited (Volgman et al. 2018; Palaniappan et al. 2002; Zaninotto et al. 2007). Pakistanis who are moderate drinkers and Indians who are heavy drinkers are more likely to have cardiovascular disease than other ethnic groups (Zaninotto et al. 2007). South Asians in the United States have similar or lower rates of smoking than those in the general population (Volgman et al. 2018). However, those with a history of smoking are also more likely to have cardiovascular disease than other ethnic groups (Zaninotto et al. 2007). Diet is likely an important risk factor; truncal obesity may be related to diets high in carbohydrates and saturated fats (Volgman et al. 2018). However, diet varies based on region, while cardiovascular risk remains consistent (Gupta and Brister 2006).

Patient management should center around management of diabetes and central obesity. Tailored interventions in the context of cultural customs appear to be the most effective and should focus on the use of whole grains and carbohydrate substitutes such as couscous and quinoa, as well as addressing barriers to physical activity (Volgman et al. 2018). The AHA statement on South Asians recommends focusing on insulin resistance and using race-specific cutoffs for metabolic syndromes, closely monitoring those with a history of gestational diabetes, implementing educational efforts centered around community gatherings such as temples and cultural events, and improving cultural competency regarding medications, diet, and lifestyle modifications (Volgman et al. 2018). Additionally, the Pooled Cohorts Equation is recommended for risk stratification, but the UK QRISK calculator is another tool for cardiovascular risk assessment, which specifically includes South Asians (Volgman et al. 2018; Hippisley-Cox et al. 2017).

There are many needs to further understand CVD risk in South Asians, including inclusion in primary prevention studies and understanding the use of statins in this population. South Asians should be studied separately rather than included with East Asians as a larger group of Asians. Certain South Asian groups may be at more risk than others, and further study is needed to target interventions. Further understanding of disease risk includes identifying environmental, biological, and psychosocial risk factors as well as underlying potential genetic risk factors for CVD. Of particular importance is identifying specific cutpoints for waist circumference and BMI in South Asians, as well as understanding risks associated with low HDL-C and high triglycerides. Additional CVD risk calculators should be studied and validated in South Asians. Research on barriers to improved physical activity is also needed.

Native Americans (American Indians/Alaska Natives)

The Native American population in the United States is growing, increasing by 39% from 2000 to 2010 to make up 1.7% of the total population. Cardiovascular disease is the leading cause of death among Native Americans (Breathett et al. 2020). Native Americans have higher rates of CVD in younger people and risk for developing CVD at an earlier age than White individuals. Importantly, there is significant regional and tribal variability in CVD. Native Americans also have the highest reported rate of stroke among ethnic groups (Breathett et al. 2020). There are important barriers to care and study of this population, and rates of disease are believed to be underreported (Breathett et al. 2020).

Diabetes appears to be the most significant CVD risk factor in this population. Native Americans have higher rates of diabetes compared to other major ethnic groups, and, among adults with diabetes, they have the highest prevalence of hypercholesterolemia (Gasevic et al. 2015; Harjo et al. 2011). On average, they have lower LDL-C and HDL-C than White individuals. Lipoprotein(a) is generally low and not independently predictive (Breathett et al. 2020). Hypertension is common, and Native Americans may have a higher prevalence of hypertension overall (Gasevic et al. 2015; Breathett et al. 2020). They also have a higher prevalence of obesity and abdominal obesity (Gasevic et al. 2015; Breathett et al. 2020). Additionally, renal disease is common (Breathett et al. 2020). They have a higher prevalence of smoking and exposure to toxic chemicals such as arsenic and cadmium, and the rates have not significantly improved over the last 20 years (Gasevic et al. 2015; Breathett et al. 2020). They also have a high prevalence of low physical activity (Breathett et al. 2020). The interplay of genetic risks and environmental factors leading to obesity, dyslipidemia, hypertension, and diabetes may put this population at particularly high risk (Breathett et al. 2020). Socioeconomic status is an important contributor to health as a quarter of Native Americans live below the federal poverty line and there is a high prevalence of uninsured status (Breathett et al. 2020). Access to medical care can also be challenging, given that Native Americans may live in relatively remote regions in the United States where traveling long distances is required to obtain medical care.

In addition to the established guidelines for management and risk stratification of these patients, complementary risk scores derived from the Strong Heart Study (which included data from 13 Native American tribes and communities in Arizona, North and South Dakota, and Oklahoma) are available (Lee et al. 2006). Diabetes and obesity are the most important risk factors to address. Hypertension, smoking, and low physical activity are also important factors. Community-based programs are needed with tribal and organizational support to address barriers to care, develop relationships with communities, and improve access and education. The CDC developed the REACH program to improve disease management, which has demonstrated improved adherence to antihypertensive medications. Cultural competency and implicit bias training among providers are essential (Breathett et al. 2020).

East Asians

In contrast to the racial and ethnic groups previously covered, East Asians represent a lower risk group overall (Volgman et al. 2018). Asian individuals have lower rates of hypertension and stroke mortality than other ethnic groups (Virani et al. 2020). East Asians are less likely to develop coronary calcification (Budoff et al. 2006), carotid atherosclerosis (Anand et al. 2000), and peripheral arterial disease (Allison et al. 2006) than White individuals. East Asians have similar lipid profiles as White individuals (Anand et al. 2000), lower rates of smoking (Gasevic et al. 2015), and lower prevalence of obesity (Gasevic et al. 2015; Wang et al. 2017). Chinese people, however, have a higher percentage of total body fat and central fat in studies in Canada and China (Lesser et al. 2013; Wang et al. 2011) and the waist–hip ratio is predictive of cardiovascular disease risk in this population (Zaninotto et al. 2007). There is a need for further study in East Asians, and guidance on management, but this population appears to be at lower CVD risk overall compared with other ethnic groups in the United States.

Table 11.5 Recommendations for an approach to patient management, which considers racial/ethnic factors in cardiovascular disease risk

Recommendations for patient management
Risk assessment
Screen for risk factors in all patients
Use ACC/AHA pooled cohorts equation for CVD risk assessment
Consider MESA risk score, especially for Hispanic/Latino and Chinese patients
Consider UK QRISK calculator for south Asian patients
Consider strong heart study risk score for native American patients
Traditional cardiovascular disease risk factors
Ethnicity may inform the priority of risk factors
Recommend lifestyle modifications, offer culturally sensitive dietary counseling and smoking cessation to all patients, and recommend physical activity
Control of traditional risk factors, including hypertension, diabetes, dyslipidemia, and obesity
Primary prevention with statins and aspirin as recommended by primary prevention of CVD guidelines
Address barriers to care
Language barriers
Cost of medical therapy
Access to regular physician follow-up
Community-based interventions (if available)
Focus on cultural competency and addressing barriers unique to each ethnic group

ACC American College of Cardiology, *AHA* American Heart Association, *CVD* cardiovascular disease, *MESA* Multi-Ethnic Study of Atherosclerosis

Overview of Patient Management (Table 11.5)

In general, screening for risk factors should be offered to all patients. The ACC/AHA Pooled Cohorts Equation is recommended for risk stratification for all ethnicities, but adjunctive calculators (such as the MESA risk score, UK QRISK calculator, and Strong Heart Study Risk Score) with more race-specific information can also be considered based on the ethnic group. Patient management should focus on guideline-driven optimization of traditional risk factors, as these address most of the disparities in risks. However, ethnicity may inform the priority of risk factors and help tailor management. All patients should be counseled on lifestyle modifications, including heart-healthy diet patterns, smoking cessation, and increased physical activity. Traditional risk factors should be controlled as much as possible, and primary prevention should be offered as recommended by the guidelines. Individual barriers to care should be addressed when possible. Racial and ethnic minorities are less likely to report having a physician and medical follow-up (Edelman et al. 2008). As such, there should be a focus on ensuring regular follow-up with a health care provider and it is also imperative to increase diversity among healthcare professionals in the United States. Finally, community-based interventions, where available, have shown benefits for treatment of risk factors.

Future Directions (Table 11.6)

Further study is needed to understand risk factors in all ethnic groups and to tailor medical therapy for diverse populations. In future research, individual ethnic groups should be evaluated rather than using large aggregate designations such as Asians or

Table 11.6 Future directions and needs to improve prevention of cardiovascular disease among diverse racial/ethnic groups

Future directions and research needs
Areas of research
Studies of more specific ethnic groups rather than considering combined groups (e.g., avoid treating all Hispanic/Latinos or Asians as monolithic groups)
Risk factors in all ethnic groups
Cultural values and behaviors that impact risk factors
Genetic risk factors
Race-specific cutpoints for risk factors
Risk assessment tools accounting for diverse populations
Diverse representation in primary CVD prevention clinical trials
Other future directions
Community-based interventions for individual ethnic groups
Increase representation of people from diverse ethnic backgrounds among healthcare providers
Public policy to address inequity and barriers to health

Hispanic/Latinos. Further understanding of genetic risk factors, race-specific cut-points for risk factors, and cultural values and behaviors that impact risk factors is needed. Risk assessment tools should be developed with diverse populations or, at least, validated in diverse populations. Future clinical studies should include samples representative of the diverse populations in the United States. Public policy is needed to address health disparities and overarching barriers to care of minority groups.

Conclusions

The United States is becoming a progressively more ethnically diverse nation, and ethnic groups often disparately suffer from CVD. Current knowledge of CVD risk factors, tools for risk assessment, and interventions are not based on representative sample populations. However, multiethnic cohort studies have been developed to address these gaps. Traditional risk factors explain the majority of cardiovascular risk, but the importance of various risk factors varies by ethnic group, and ethnicity can be used to tailor risk assessment as well as prioritize risk factor management. Future large CVD prevention trials should include diverse populations.

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References

Ajjan R, Carter AM, Somani R, Kain K, Grant PJ. Ethnic differences in cardiovascular risk factors in healthy Caucasian and South Asian individuals with the metabolic syndrome. J Thromb Haemost. 2007;5:754–60.

Allison MA, Criqui MH, McClelland RL, et al. The effect of novel cardiovascular risk factors on the ethnic-specific odds for peripheral arterial disease in the Multi-Ethnic Study of Atherosclerosis (MESA). J Am Coll Cardiol. 2006;48:1190–7.

Allison MA, Budoff MJ, Wong ND, Blumenthal RS, Schreiner PJ, Criqui MH. Prevalence of and risk factors for subclinical cardiovascular disease in selected US Hispanic ethnic groups. Am J Epidemiol. 2008;167:962–9.

Amin AP, Nathan S, Evans AT, Attanasio S, Mukhopadhyay E, Mehta V, Kelly RF. The effect of ethnicity on the relationship between premature coronary artery disease and traditional cardiac risk factors among uninsured young adults. Prev Cardiol. 2009;12:128–35.

Anand SS, Yusuf S. Risk factors for cardiovascular disease in Canadians of South Asian and European origin: a pilot study of the Study of Heart Assessment and Risk in Ethnic Groups (SHARE). Clin Investig Med. 1997;20:204–10.

Anand SS, Yusuf S, Vuksan V, et al. Differences in risk factors, atherosclerosis, and cardiovascular disease between ethnic groups in Canada: the Study of Health Assessment and Risk in Ethnic groups (SHARE). Lancet. 2000;356:279–84.

Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;140:e596–646.

Bancks MP, Kershaw K, Carson AP, Gordon-Larsen P, Schreiner PJ, Carnethon MR. Association of modifiable risk factors in young adulthood with racial disparity in incident type 2 diabetes during middle adulthood. JAMA J Am Med Assoc. 2017;318:2457–65.

Bell CN, Thorpe RJ, Bowie JV, LaVeist TA. Race disparities in cardiovascular disease risk factors within socioeconomic status strata. Ann Epidemiol. 2018;28:147–52.

Beohar N, Sansing VV, Davis AM, Srinivas VS, Helmy T, Althouse AD, Thomas SB, Brooks MM. Race/ethnic disparities in risk factor control and survival in the bypass angioplasty revascularization investigation 2 diabetes (Bari 2d) trial. Am J Cardiol. 2013;112:1298–305.

Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol. 2002;156:871–81.

Boykin S, Diez-Roux AV, Carnethon M, Shrager S, Ni H, Whitt-Glover M. Racial/ethnic heterogeneity in the socioeconomic patterning of CVD risk factors: in the United States: the multiethnic study of atherosclerosis. J Health Care Poor Underserved. 2011;22:111–27.

Bravata DM, Wells CK, Gulanski B, Kernan WN, Brass LM, Long J, Concato J. Racial disparities in stroke risk factors: the impact of socioeconomic status. Stroke. 2005;36:1507–11.

Breathett K, Leng I, Foraker RE, et al. Risk factor burden, heart failure, and survival in women of different ethnic groups insights from the women's health initiative. Circ Hear Fail. 2018;11:e004642. https://doi.org/10.1161/CIRCHEARTFAILURE.117.004642.

Breathett K, Sims M, Gross M, Jackson EA, Jones EJ, Navas-Acien A, Taylor H, Thomas KL, Howard BV. Cardiovascular Health in American Indians and Alaska Natives: a scientific statement from the American Heart Association. Circulation. 2020;141:E948–59.

Budoff MJ, Nasir K, Mao S, Tseng PH, Chau A, Liu ST, Flores F, Blumenthal RS. Ethnic differences of the presence and severity of coronary atherosclerosis. Atherosclerosis. 2006;187:343–50.

Cappuccio FP, Cook DG, Atkinson RW, Strazzullo P. Prevalence, detection, and management of cardiovascular risk factors in different ethnic groups in South London. Heart. 1997;78:555–63.

Carnethon MR, Pu J, Howard G, et al. Cardiovascular health in African Americans: a scientific statement from the American Heart Association. Circulation. 2017;136:e393–423.

Chatterji P, Joo H, Lahiri K. Racial/ethnic- and education-related disparities in the control of risk factors for cardiovascular disease among individuals with diabetes. Diabetes Care. 2012;35:305–12.

Chowdhury TA, Lasker SS, Mahfuz R. Ethnic differences in control of cardiovascular risk factors in patients with type 2 diabetes attending an inner London diabetes clinic. Postgrad Med J. 2006;82:211–5.

Cohort Description|Atherosclerosis Risk in Communities. https://sites.cscc.unc.edu/aric/Cohort_Description. Accessed 16 Nov 2020.

Dal Canto E, Farukh B, Faconti L. Why are there ethnic differences in cardio-metabolic risk factors and cardiovascular diseases? JRSM Cardiovasc Dis. 2018;7:204800401881892.

Després JP, Couillard C, Gagnon J, Bergeron J, Leon AS, Rao DC, Skinner JS, Wilmore JH, Bouchard C. Race, visceral adipose tissue, plasma lipids, and lipoprotein lipase activity in men and women: the health, risk factors, exercise training, and genetics (HERITAGE) family study. Arterioscler Thromb Vasc Biol. 2000;20:1932–8.

Dundas R, Morgan M, Redfern J, Lemic-Stojcevic N, Wolfe C. Ethnic differences in behavioural risk factors for stroke: implications for health promotion. Ethn Health. 2001;6:95–103.

Edelman DJ, Gao Q, Mosca L. Predictors and barriers to timely medical follow-up after cardiovascular disease risk factor screening according to race/ethnicity. J Natl Med Assoc. 2008;100:534–9.

Effects of aspirin for primary prevention in persons with diabetes mellitus. N Engl J Med. 2018;379:1529–39.
Egede LE, Gebregziabher M, Lynch CP, Gilbert GE, Echols C. Longitudinal ethnic differences in multiple cardiovascular risk factor control in a cohort of US adults with diabetes. Diabetes Res Clin Pract. 2011;94:385–94.
Feig DS, Zinman B, Wang X, Hux JE. Risk of development of diabetes mellitus after diagnosis of gestational diabetes. CMAJ. 2008;179:229–34.
Frierson GM, Howard EN, DeFina LF, Powell-Wiley TM, Willis BL. Effect of race and socioeconomic status on cardiovascular risk factor burden: the Cooper Center Longitudinal study. Ethn Dis. 2013;23:35–42.
Fuqua SR, Wyatt SB, Andrew ME, Sarpong DF, Henderson FR, Cunningham MF, Taylor HA. Recruiting African-American research participation in the Jackson heart study: methods, response rates, and sample description. Ethn Dis. 2005;15:S6-18-29.
Fussman C, Rafferty AP, Reeves MJ, Zackery S, Lyon-Callo S, Anderson B. Racial disparities in knowledge of stroke and heart attack risk factors and warning signs among Michigan adults. Ethn Dis. 2009;19:128–34.
Game FL, Jones AF. Ethnicity and risk factors for coronary heart disease in diabetes mellitus. Diabetes Obes Metab. 2000;2:91–7.
Gasevic D, Ross ES, Lear SA. Ethnic differences in cardiovascular disease risk factors: a systematic review of North American evidence. Can J Cardiol. 2015;31:1169–79.
Gaziano JM, Brotons C, Coppolecchia R, et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. Lancet. 2018;392:1036–46.
Gbadebo TD, Okafor H, Darbar D. Differential impact of race and risk factors on incidence of atrial fibrillation. Am Heart J. 2011;162:31–7.
Gezmu T, Schneider D, Demissie K, Lin Y, Gizzi MS. Risk factors for acute stroke among South Asians compared to other racial/ethnic groups. PLoS One. 2014;9:e108901. https://doi.org/10.1371/journal.pone.0108901.
Gijsberts CM, Seneviratna A, De Carvalho LP, et al. Ethnicity modifies associations between cardiovascular risk factors and disease severity in parallel Dutch and Singapore coronary cohorts. PLoS One. 2015;10:e0132278. https://doi.org/10.1371/journal.pone.0132278.
Gillott RG, Willan K, Kain K, Sivananthan UM, Tayebjee MH. South Asian ethnicity is associated with a lower prevalence of atrial fibrillation despite greater prevalence of established risk factors: a population-based study in Bradford Metropolitan District. Europace. 2017;19:356–63.
Glasser SP, Judd S, Basile J, Lackland D, Halanych J, Cushman M, Prineas R, Howard V, Howard G. Prehypertension, racial prevalence and its association with risk factors: analysis of the reasons for geographic and racial differences in stroke (REGARDS) study. Am J Hypertens. 2011;24:194–9.
Goff DC, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American college of cardiology/American heart association task force on practice guidelines. Circulation. 2014;129:49–73.
Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. Circulation. 2005;112:2735–52.
Gupta M, Brister S. Is South Asian ethnicity an independent cardiovascular risk factor? Can J Cardiol. 2006;22:193–7.
Hajat C, Dundas R, Stewart JA, Lawrence E, Rudd AG, Howard R, Wolfe CDA. Cerebrovascular risk factors and stroke subtypes: differences between ethnic groups. Stroke. 2001;32:37–42.
Hajat C, Tilling K, Stewart JA, Lemic-Stojcevic N, Wolfe CDA. Ethnic differences in risk factors for ischemic stroke: a European case-control study. Stroke. 2004;35:1562–7.
Hall LML, Moran CN, Milne GR, Wilson J, Macfarlane NG, Forouhi NG, Hariharan N, Salt IP, Sattar N, Gill JMR. Fat oxidation, fitness and skeletal muscle expression of oxidative/

lipid metabolism genes in South Asians: implications for insulin resistance? PLoS One. 2010;5:e14197. https://doi.org/10.1371/journal.pone.0014197.
Harjo TC, Perez A, Lopez V, Wong ND. Prevalence of diabetes and cardiovascular risk factors among California Native American adults compared to other ethnicities: the 2005 California health interview survey. Metab Syndr Relat Disord. 2011;9:49–54.
Harris MM, Stevens J, Thomas N, Schreiner P, Folsom AR. Associations of fat distribution and obesity with hypertension in a bi-ethnic population: the ARIC study. Obes Res. 2000;8:516–24.
Hasan RK, Ginwala NT, Shah RY, Kumbhani DJ, Wilensky RL, Mehta NN. Quantitative angiography in South Asians reveals differences in vessel size and coronary artery disease severity compared to Caucasians. Am J Cardiovasc Dis. 2011;1:31–7.
Hayes DK, Denny CH, Keenan NL, Croft JB, Sundaram AA, Greenlund KJ. Racial/ethnic and socioeconomic differences in multiple risk factors for heart disease and stroke in women: behavioral risk factor surveillance system, 2003. J Women's Heal. 2006;15:1000–8.
Henderson SO, Haiman CA, Wilkens LR, Kolonel LN, Wan P, Pike MC. Established risk factors account for most of the racial differences in cardiovascular disease mortality. PLoS One. 2007;2:e377. https://doi.org/10.1371/journal.pone.0000377.
Hertz RP, McDonald M, Unger AN, Lustik MB. Racial and ethnic disparities in the prevalence and management of cardiovascular risk factors in the United States workforce. J Occup Environ Med. 2007;49:1165–75.
Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ. 2017;357:j2099. https://doi.org/10.1136/bmj.j2099.
Holland AT, Zhao B, Wong EC, Choi SE, Wong ND, Palaniappan LP. Racial/ethnic differences in control of cardiovascular risk factors among type 2 diabetes patients in an insured, ambulatory care population. J Diabetes Complicat. 2013;27:34–40.
Hoppe C, Kerr D. Minority underrepresentation in cardiovascular outcome trials for type 2 diabetes. Lancet Diabetes Endocrinol. 2017;5:13.
Howard VJ, Cushman M, Pulley LV, Gomez CR, Go RC, Prineas RJ, Graham A, Moy CS, Howard G. The reasons for geographic and racial differences in stroke study: objectives and design. Neuroepidemiology. 2005;25:135–43.
Howard G, Safford MM, Moy CS, et al. Racial differences in the incidence of cardiovascular risk factors in older black and white adults. J Am Geriatr Soc. 2017;65:83–90.
Humes KR, Jones NA, Ramirez RR. Overview of race and Hispanic origin: 2010 2010 census briefs. 2010.
Hurley LP, Dickinson LM, Estacio RO, Steiner JF, Havranek EP. Prediction of cardiovascular death in racial/ethnic minorities using Framingham risk factors. Circ Cardiovasc Qual Outcomes. 2010;3:181–7.
Inclusion of Women and Minorities as Participants in Research Involving Human Subjects|grants.nih.gov. https://grants.nih.gov/policy/inclusion/women-and-minorities.htm. Accessed 18 Feb 2021.
Jensen PN, Thacker EL, Dublin S, Psaty BM, Heckbert SR. Racial differences in the incidence of and risk factors for atrial fibrillation in older adults: the Cardiovascular Health Study. J Am Geriatr Soc. 2013;61:276–80.
Jiménez MC, Manson JAE, Cook NR, Kawachi I, Wassertheil-Smoller S, Haring B, Nassir R, Rhee JJ, Sealy-Jefferson S, Rexrode KM. Racial variation in stroke risk among women by stroke risk factors. Stroke. 2019;50:797–804.
Juhaeri SJ, Chambless LE, Nieto FJ, Jones D, Schreiner P, Arnett D, Cai J. Associations of weight loss and changes in fat distribution with the remission of hypertension in a bi-ethnic cohort: the Atherosclerosis Risk in Communities Study. Prev Med (Baltim). 2003;36:330–9.
Kabra R, Girotra S, Vaughan Sarrazin M. Refining stroke prediction in atrial fibrillation patients by addition of African-American ethnicity to CHA2DS2-VASc score. J Am Coll Cardiol. 2016;68:461–70.

Kamath SK, Hussain EA, Amin D, Mortillaro E, West B, Peterson CT, Aryee F, Murillo G, Alekel DL. Cardiovascular disease risk factors in 2 distinct ethnic groups: Indian and Pakistani compared with American premenopausal women. Am J Clin Nutr. 1999;69:621–31.

Kanaya AM, Kandula N, Herrington D, Budoff MJ, Hulley S, Vittinghoff E, Liu K. Mediators of Atherosclerosis in South Asians Living in America (MASALA) study: objectives, methods, and cohort description. Clin Cardiol. 2013;36:713–20.

Khan MS, Shahid I, Siddiqi TJ, Khan SU, Warraich HJ, Greene SJ, Butler J, Michos ED. Ten-year trends in enrollment of women and minorities in pivotal trials supporting recent US Food and Drug Administration Approval of Novel Cardiometabolic Drugs. J Am Heart Assoc. 2020;9:e015594.

Kim Y, Hogan K, D'Onofrio G, Chekijian S, Safdar B. Patient ethnicity predicts poor health access and gaps in perception of personal cardiovascular risk factors. Crit Pathw Cardiol. 2017;16:147–57.

Kooner JS, Saleheen D, Sim X, et al. Genome-wide association study in individuals of South Asian ancestry identifies six new type 2 diabetes susceptibility loci. Nat Genet. 2011;43:984–9.

Kubicki DM, Xu M, Akwo EA, Dixon D, Muñoz D, Blot WJ, Wang TJ, Lipworth L, Gupta DK. Race and sex differences in modifiable risk factors and incident heart failure. JACC Hear Fail. 2020;8:122–30.

Kulick ER, Moon YP, Cheung K, Willey JZ, Sacco RL, Elkind MSV. Racial-ethnic disparities in the association between risk factors and diabetes: the Northern Manhattan study. Prev Med (Baltim). 2016;83:31–6.

LaVange LM, Kalsbeek WD, Sorlie PD, et al. Sample design and cohort selection in the Hispanic Community Health Study/Study of Latinos. Ann Epidemiol. 2010;20:642–9.

Lawson CA, Zaccardi F, Squire I, Okhai H, Davies M, Huang W, Mamas M, Lam CSP, Khunti K, Kadam UT. Risk factors for heart failure: 20-year population-based trends by sex, socioeconomic status, and ethnicity. Circ Hear Fail. 2020;13:e006472. https://doi.org/10.1161/CIRCHEARTFAILURE.119.006472.

Lee ET, Welty TK, Fabsitz R, Cowan LD, Le NA, Oopik AJ, Cucchiara AJ, Savage PJ, Howard BV. The strong heart study a study of cardiovascular disease in American Indians: design and methods. Am J Epidemiol. 1990;132:1141–55.

Lee ET, Howard BV, Wang W, Welty TK, Galloway JM, Best LG, Fabsitz RR, Zhang Y, Yeh J, Devereux RB. Prediction of coronary heart disease in a population with high prevalence of diabetes and albuminuria: the Strong Heart Study. Circulation. 2006;113:2897–905.

Leifheit-Limson EC, Spertus JA, Reid KJ, Jones SB, Vaccarino V, Krumholz HM, Lichtman JH. Prevalence of traditional cardiac risk factors and secondary prevention among patients hospitalized for acute myocardial infarction (AMI): variation by age, sex, and race. J Women's Heal. 2013;22:659–66.

Lemic-Stojcevic N, Dundas R, Jenkins S, Rudd A, Wolfe C. Preventable risk factors for coronary heart disease and stroke amongst ethnic groups in London. Ethn Health. 2001;6:87–94.

Lesser IA, Gasevic D, Lear SA. The effect of body fat distribution on ethnic differences in cardiometabolic risk factors of Chinese and Europeans. Appl Physiol Nutr Metab. 2013;38:701–6.

Lip GYH, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. Chest. 2010;137:263–72.

Lipworth L, Okafor H, Mumma MT, Edwards TL, Roden DM, Blot WJ, Darbar D. Race-specific impact of atrial fibrillation risk factors in blacks and whites in the southern community cohort study. Am J Cardiol. 2012;110:1637–42.

Liu X, Liu M, Tsilimingras D, Schiffrin EL. Racial disparities in cardiovascular risk factors among diagnosed hypertensive subjects. J Am Soc Hypertens. 2011;5:239–48.

Matthews KA, Sowers MF, Derby CA, Stein E, Miracle-McMahill H, Crawford SL, Pasternak RC. Ethnic differences in cardiovascular risk factor burden among middle-aged women: Study of Women's Health Across the Nation (SWAN). Am Heart J. 2005;149:1066–73.

McClelland RL, Jorgensen NW, Budoff M, et al. 10-year coronary heart disease risk prediction using coronary artery calcium and traditional risk factors derivation in the MESA (Multi-Ethnic Study of Atherosclerosis) with validation in the HNR (Heinz Nixdorf Recall) study and the DHS (Dallas Heart Study). J Am Coll Cardiol. 2015;66:1643–53.

McGruder HF, Malarcher AM, Antoine TL, Greenlund KJ, Croft JB. Racial and ethnic disparities in cardiovascular risk factors among stroke survivors: United States 1999 to 2001. Stroke. 2004;35:1557–61.

McNeil JJ, Wolfe R, Woods RL, et al. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. N Engl J Med. 2018;379:1509–18.

Meadows TA, Bhatt DL, Hirsch AT, et al. Ethnic differences in the prevalence and treatment of cardiovascular risk factors in US outpatients with peripheral arterial disease: insights from the Reduction of Atherothrombosis for Continued Health (REACH) Registry. Am Heart J. 2009;158:1038–45.

Mensah GA, Mokdad AH, Ford ES, Greenlund KJ, Croft JB. State of disparities in cardiovascular health in the United States. Circulation. 2005;111:1233–41.

O'Neal WT, Judd SE, Limdi NA, McIntyre WF, Kleindorfer DO, Cushman M, Howard VJ, Howard G, Soliman EZ. Differential impact of risk factors in blacks and whites in the development of atrial fibrillation: the Reasons for Geographic And Racial Differences in Stroke (REGARDS) Study. J Racial Ethn Heal Disparities. 2017;4:718–24.

Palaniappan L, Anthony MN, Mahesh C, Elliott M, Killeen A, Giacherio D, Rubenfire M. Cardiovascular risk factors in ethnic minority women aged ≤30 years. Am J Cardiol. 2002;89:524–9.

Parrinello CM, Rastegar I, Godino JG, Miedema MD, Matsushita K, Selvin E. Prevalence of and racial disparities in risk factor control in older adults with diabetes: the atherosclerosis risk in communities study. Diabetes Care. 2015;38:1290–8.

Patel RC, Sánchez BN, Morgenstern LB, Li C, Lisabeth LD. Impact of stroke risk factors on ethnic stroke disparities among midlife Mexican Americans and non-hispanic whites. Stroke. 2017;48:2872–4.

Pool LR, Ning H, Lloyd-Jones DM, Allen NB. Trends in racial/ethnic disparities in cardiovascular health among US adults from 1999-2012. J Am Heart Assoc. 2017;6:e006027. https://doi.org/10.1161/JAHA.117.006027.

Rabanal KS, Lindman AS, Selmer RM, Aamodt G. Ethnic differences in risk factors and total risk of cardiovascular disease based on the Norwegian CONOR study. Eur J Prev Cardiol. 2013;20:1013–21.

Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. J Am Med Assoc. 2007;297:611–9.

Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008a;359:2195–207.

Ridker PM, Paynter NP, Rifai N, Gaziano JM, Cook NR. C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds risk score for men. Circulation. 2008b;118:2243–51.

Rodriguez CJ, Allison M, Daviglus ML, et al. Status of cardiovascular disease and stroke in hispanics/latinos in the United States: a science advisory from the american heart association. Circulation. 2014;130:593–625.

Rodriguez CJ, Soliman EZ, Alonso A, Swett K, Okin PM, Goff DC, Heckbert SR. Atrial fibrillation incidence and risk factors in relation to race-ethnicity and the population attributable fraction of atrial fibrillation risk factors: the Multi-Ethnic Study of Atherosclerosis. Ann Epidemiol. 2015;25:71–76.e1.

Rodriguez F, Stefanick ML, Greenland P, et al. Racial and ethnic differences in atrial fibrillation risk factors and predictors in women: findings from the Women's Health Initiative. Am Heart J. 2016;176:70–7.

Romero CX, Romero TE, Shlay JC, Ogden LG, Dabelea D. Changing trends in the prevalence and disparities of obesity and other cardiovascular disease risk factors in three racial/ethnic groups of USA adults. Adv Prev Med. 2012;2012:1–8.

Sacco RL, Boden-Albala B, Gan R, Chen X, Kargman DE, Shea S, Paik MC, Hauser WA. Stroke incidence among white, black, and Hispanic residents of an urban community: the Northern Manhattan Stroke Study. Am J Epidemiol. 1998;147:259–68.

Sacco RL, Boden-Albala B, Abel G, Lin IF, Elkind M, Hauser WA, Paik MC, Shea S. Race-ethnic disparities in the impact of stroke risk factors the Northern Manhattan stroke study. Stroke. 2001;32:1725–31.

Safford MM, Brown TM, Muntner PM, et al. Association of race and sex with risk of incident acute coronary heart disease events. JAMA J Am Med Assoc. 2012;308:1768–74.

Seshiah V, Balaji V, Balaji MS, Sanjeevi CB, Green A. Gestational diabetes mellitus in India. J Assoc Physicians India. 2004;52:707–11.

Shah AD, Vittinghoff E, Kandula NR, Srivastava S, Kanaya AM. Correlates of prediabetes and type II diabetes in US South Asians: findings from the Mediators of Atherosclerosis in South Asians Living in America (MASALA) study. Ann Epidemiol. 2015;25:77–83.

Sharma S, Malarcher AM, Giles WH, Myers G. Racial, ethnic and socioeconomic disparities in the clustering of cardiovascular disease risk factors. Ethn Dis. 2004;14:43–8.

Shih T, Ledezma K, McCauley M, Rehman J, Galanter WL, Darbar D. Impact of traditional risk factors for the outcomes of atrial fibrillation across race and ethnicity and sex groups. IJC Hear Vasc. 2020;28:100538. https://doi.org/10.1016/j.ijcha.2020.100538.

Shikany JM, Safford MM, Newby PK, Durant RW, Brown TM, Judd SE. Southern dietary pattern is associated with hazard of acute coronary heart disease in the reasons for geographic and Racial Differences in Stroke (REGARDS) study. Circulation. 2015;132:804–14.

Sundquist J, Winkleby MA, Pudaric S. Cardiovascular disease risk factors among older black, Mexican-American, and white women and men: an analysis of NHANES III, 1988-1994. J Am Geriatr Soc. 2001;49:109–16.

Tajeu GS, Safford MM, Howard G, Howard VJ, Chen L, Leann Long D, Tanner RM, Muntner P. Black–white differences in cardiovascular disease mortality: a prospective US study, 2003–2017. Am J Public Health. 2020;110:696–703.

Taylor HA, Coady SA, Levy D, Walker ER, Vasan RS, Liu J, Akylbekova EL, Garrison RJ, Fox C. Relationships of BMI to cardiovascular risk factors differ by ethnicity. Obesity. 2010;18:1638–45.

The atherosclerosis risk in communit (aric) stui)y: design and objectwes. Am J Epidemiol. 1989;129:687–702.

Thomas AJ, Eberly LE, Smith GD, Neaton JD, Stamler J. Race/ethnicity, income, major risk factors, and cardiovascular disease mortality. Am J Public Health. 2005;95:1417–23.

Thomas KL, Hernandez AF, Dai D, Heidenreich P, Fonarow GC, Peterson ED, Yancy CW. Association of race/ethnicity with clinical risk factors, quality of care, and acute outcomes in patients hospitalized with heart failure. Am Heart J. 2011;161:746–54.

Tobias DK, Stuart JJ, Li S, Chavarro J, Rimm EB, Rich-Edwards J, Hu FB, Manson JE, Zhang C. Association of history of gestational diabetes with long-term cardiovascular disease risk in a large prospective cohort of US women. JAMA Intern Med. 2017;177:1735–42.

Tsao CW, Vasan RS. Cohort profile: the Framingham Heart Study (FHS): overview of milestones in cardiovascular epidemiology. Int J Epidemiol. 2015;44:1800–13.

Tsimikas S, Clopton P, Brilakis ES, Marcovina SM, Khera A, Miller ER, De Lemos JA, Witztum JL. Relationship of oxidized phospholipids on apolipoprotein B-100 particles to race/ethnicity, apolipoprotein(a) isoform size, and cardiovascular risk factors results from the Dallas heart study. Circulation. 2009;119:1711–9.

U.S. Census Bureau U.S. Census Bureau QuickFacts: United States. https://www.census.gov/quickfacts/fact/table/US/PST120219. Accessed 13 Nov 2020.

Vasudev R, Shah P, Patel J, et al. Should Bangladeshi race be considered as an independent risk factor for multi vessel coronary artery disease? Vasc Health Risk Manag. 2020;16:143–7.

Victor RG, Lynch K, Li N, et al. A cluster-randomized trial of blood-pressure reduction in black barbershops. N Engl J Med. 2018;378:1291–301.

Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke statistics—2020 update: a report from the American Heart Association. Circulation. 2020;141:E139–596.

Volgman AS, Palaniappan LS, Aggarwal NT, et al. Atherosclerotic Cardiovascular Disease in South Asians in the United States: epidemiology, risk factors, and treatments: a scientific statement from the American Heart Association. Circulation. 2018;138:e1–e34.

Waddy SP, Cotsonis G, Lynn MJ, Frankel MR, Chaturvedi S, Williams JE, Chimowitz M. Racial differences in vascular risk factors and outcomes of patients with intracranial atherosclerotic arterial stenosis. Stroke. 2009;40:719–25.

Waldstein SR, Moody DLB, McNeely JM, Allen AJ, Sprung MR, Shah MT, Al'Najjar E, Evans MK, Zonderman AB. Cross-sectional relations of race and poverty status to cardiovascular risk factors in the Healthy Aging in Neighborhoods of Diversity across the Lifespan (HANDLS) study. BMC Public Health. 2016;16:258. https://doi.org/10.1186/s12889-016-2945-9.

Wang D, Li Y, Lee SG, Wang L, Fan J, Zhang G, Wu J, Ji Y, Li S. Ethnic differences in body composition and obesity related risk factors: study in chinese and white males living in China. PLoS One. 2011;6:e19835. https://doi.org/10.1371/journal.pone.0019835.

Wang Y, Katzmarzyk PT, Horswell R, Zhao W, Li W, Johnson J, Ryan DH, Hu G. Racial disparities in cardiovascular risk factor control in an underinsured population with type 2 diabetes. Diabet Med. 2014;31:1230–6.

Wang L, Southerland J, Wang K, Bailey BA, Alamian A, Stevens MA, Wang Y. Ethnic differences in risk factors for obesity among adults in California, the United States. J Obes. 2017;2017:2427483. https://doi.org/10.1155/2017/2427483.

Whitty CJM, Brunner EJ, Shipley MJ, Hemingway H, Marmot MG. Differences in biological risk factors for cardiovascular disease between three ethnic groups in the Whitehall II study. Atherosclerosis. 1999;142:279–86.

Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97:1837–47.

Winkleby MA, Kraemer HC, Ahn DK, Varady AN. Ethnic and socioeconomic differences in cardiovascular disease risk factors: findings for women from the third national health and nutrition examination survey, 1988-1994. J Am Med Assoc. 1998;280:356–62.

Winston GJ, Barr RG, Carrasquillo O, Bertoni AG, Shea S. Sex and racial/ethnic differences in cardiovascular disease risk factor treatment and control among individuals with diabetes in the Multi-Ethnic Study of Atherosclerosis (MESA). Diabetes Care. 2009;32:1467–9.

Yusuf PS, Hawken S, Ôunpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364:937–52.

Yusuf S, Bosch J, Dagenais G, et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med. 2016;374:2021–31.

Zaninotto P, Mindell J, Hirani V. Prevalence of cardiovascular risk factors among ethnic groups: results from the Health Surveys for England. Atherosclerosis. 2007;195:e48. https://doi.org/10.1016/j.atherosclerosis.2007.02.017.

Zhu S, Heymsfield SB, Toyoshima H, Wang ZM, Pietrobelli A, Heshka S. Race-ethnicity-specific waist circumference cutoffs for identifying cardiovascular disease risk factors. Am J Clin Nutr. 2005;81:409–15.

Chapter 12
Triglyceride-Rich Lipoproteins

Najdat Bazarbashi and Michael Miller

Abbreviations

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ANCHOR	Effect of AMR101 (Ethyl Icosapentate) on Triglyceride Levels in Patients on Statins with High TG Levels (>200 and <500 mg/dL)
ANGPTL3	Angiopoietin-Like Protein 3
Apo	Apolipoprotein
APPROACH	A Study of Volanesorsen in Patients with Familial Chylomicronemia Syndrome
ASCVD	Atherosclerotic Cardiovascular Disease
CVD	Cardiovascular Disease
DHA	Docosahexaenoic Acid
EPA	Eicosapentaenoic Acid
FFA	Free Fatty Acid
HDL-C	High-Density Lipoprotein Cholesterol
HF	Heart Failure
HTG	Hypertriglyceridemia
IPE	Icosapent Ethyl
JELIS	Japan Eicosapentaenoic Acid Lipid Intervention Study
LDL-C	Low-Density Lipoprotein Cholesterol
LPL	Lipoprotein Lipase
MARINE	Efficacy and Safety of AMR101 (Ethyl Icosapentate) in Patients with Fasting Triglyceride (TG) Levels >500 and <2000 mg/dL
OM3FA	Omega-3 Fatty Acids

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OMEMI	Omega-3 Fatty Acids in Elderly Patients with Myocardial Infarction
PPARα	Peroxisome Proliferator-Activated Receptor Alpha
PROMINENT	Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes
REDUCE-IT	Reduction of Cardiovascular Events with Icosapent Ethyl – Intervention Trial
RRR	Relative Risk Reduction
STRENGTH	STatin Residual Risk Reduction with EpaNova in HiGh CV Risk PatienTs with Hypertriglyceridemia
T2DM	Type 2 Diabetes Mellitus
TG	Triglyceride
TRL	Triglyceride-Rich Lipoprotein
VLDL	Very-Low-Density Lipoprotein

Introduction

Epidemiology of Hypertriglyceridemia

Elevated plasma triglycerides (TGs) are among the most common lipid abnormalities encountered in clinical practice. As elaborated upon in the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) and the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines, hypertriglyceridemia (HTG) is classified as borderline high at TG levels of 150–199 mg/dL, mild to moderately high at TG levels of 200–499 mg/dL, and very/severely high at TG levels greater than 500 mg/dL (Grundy et al. 2004, 2019). The prevalence of HTG is approximately 10% of the adult population in Europe (Laufs et al. 2020; Hegele et al. 2014). However, a study of the National Health and Nutrition Examination Survey (NHANES) conducted between 2007 and 2014 estimated an overall prevalence of HTG in the United States to be considerably higher (25.9%); this includes 12.3 million statin-treated patients with TGs ≥ 150 mg/dL (Fan et al. 2020). Of these, 6.4 million had concomitant type 2 diabetes mellitus (T2DM) or atherosclerotic cardiovascular disease (ASCVD). Whilst mild to moderately high TG levels are common, very high HTG (TGs ≥ 500 mg/dL) is rare, representing only 1.6% of the US population (Christian et al. 2011).

Hypertriglyceridemia as a Risk Enhancer

It is well established that HTG is associated with an increased risk of developing ASCVD (Miller et al. 2011; Hulley et al. 1980). For many years, the extent to which HTG promoted coronary atherosclerosis was difficult to reconcile because TGs per

se are not taken up by vascular wall macrophages (Peng et al. 2017; Thomsen et al. 2014; Jorgensen et al. 2013). Rather, the lipoprotein complex containing TGs, or triglyceride-rich lipoproteins (TRLs), become atherogenic following hydrolysis by lipoprotein lipase (LPL), due to formation of cholesterol-enriched by-products; these smaller particles, referred to as remnants (Do et al. 2013), are easily transported across the endothelium (Fogelstrand and Boren 2012). TRL remnants are highly atherogenic because they carry more cholesterol per molecule than LDL and thus do not need to be modified for uptake by macrophages (in contrast to LDL) (Nordestgaard and Varbo 2014), thereby facilitating foam cell formation and atherosclerotic plaque deposition (Zilversmit 1979). In addition, TG hydrolysis facilitates free fatty acid (FFA) release; in the vascular endothelium, this may result in local inflammation and injury (Saraswathi and Hasty 2006). Taken together, HTG is a marker for elevated concentrations of atherogenic cholesterol-enriched remnant particles that perpetuate low-grade inflammation, foam cell formation, and atherosclerotic plaques that contribute to elevated risk of CVD (Nordestgaard and Varbo 2014).

Observational studies have examined HTG as an independent risk factor for coronary atherosclerosis (Miller et al. 2002). A meta-analysis of 21 studies involving 57,077 patients across multiple countries demonstrated the consistency of an association between elevated TG levels and risk of CVD (Austin et al. 1998). In univariate analysis, each 1-mmol increase in TGs was associated with a relative risk (RR) of 1.32 (95% confidence interval (CI), 1.26–1.39) and 1.76 (95% CI, 1.50–2.02) in men and women, respectively, after adjustment for high-density lipoprotein cholesterol (HDL-C) (Austin et al. 1998). A subsequent meta-analysis of 68 studies from the Emerging Risk Factors Collaboration evaluated 302,430 individuals without known vascular disease at baseline. Their observation noted a gradual association between elevated TGs and ischemic stroke and CVD; however, following adjustment for HDL-C and non-HDL-C, the association was no longer statistically significant (Emerging Risk Factors C et al. 2009). Furthermore, Tirosh et al. followed 13,953 healthy, untreated, young men (aged 25–34 years) with TG levels <300 mg/dL for 10.5 years to assess the association between changes over time in fasting TG and CVD risk (Tirosh et al. 2007). At baseline, TG levels in the top quintile were associated with a fourfold increase of CVD compared to those in the lowest TG quintile, even after adjustment for HDL-C and other CVD risk factors (Tirosh et al. 2007). These findings support HTG as a biomarker of elevated CVD risk.

Metabolism and Atherogenic Potential of Triglyceride-Rich Lipoproteins

Biochemical/Regulatory Pathways of TGs and Lipoproteins

Triglyceride-rich lipoproteins are macromolecular complexes consisting of core lipids, most commonly cholesteryl esters and triglycerides, enveloped by a single layer of phospholipids, apolipoproteins, and variable amounts of free cholesterol (Ginsberg

2002). Circulating TRLs consist of very-low-density lipoproteins (VLDLs), VLDL remnants, chylomicrons, and intermediate-density lipoproteins (IDLs). The lipoprotein core is composed of hydrophobic TGs and cholesterol esters (CEs), whereas the hydrophilic surface consists of phospholipids, free cholesterol, and apolipoproteins (apos) that play a key role in plasma lipid regulation (Miller et al. 2011). Chylomicrons are the largest TRLs obtained from dietary fat and consist of numerous apos (A-I, A-II, A-IV, A-V, B-48, C-II, E) (Feingold and Grunfeld 2000a) with apolipoprotein B48 (ApoB-48) viewed as an essential protein vital for secretion into the lymphatic system prior to release into the systemic circulation (Feingold and Grunfeld 2000a).

VLDLs are composed of apolipoprotein B100 (ApoB-100) and triglycerides. They are synthesized by hepatocytes and secreted into the systemic circulation whereupon LPL-mediated hydrolysis results in the release of FFAs that are utilized as an energy source by the peripheral muscle or stored in adipose tissue reserves for subsequent utilization (Miller et al. 2011; Feingold and Grunfeld 2000a; Dallinga-Thie et al. 2010).

Metabolic Consequences and Impact of TRLs on ASCVD

Hypertriglyceridemia ensues from increased production or decreased catabolism of TRLs. This, in turn, impacts the metabolism of LDL and HDL (Miller et al. 2011). Hepatic overproduction of VLDL activates cholesterol ester transfer protein (CETP) to facilitate the transfer of TG from VLDL to LDL (and HDL) in exchange for cholesteryl ester. The resulting by-products, TG-enriched LDL particles, are avidly hydrolyzed by hepatic triglyceride lipase (HTGL) (Fig. 12.1).

These small, dense LDL particles traverse the endothelium where they do not bind as well to high-affinity LDL receptors compared to normal-sized LDL particles, are more susceptible to oxidation, and exhibit preferential and unregulated uptake by macrophages (Fig. 12.2) (Laufs et al. 2020; Miller et al. 2011; Chait and Eckel 2019; Mudd et al. 2007).

Increased VLDL production as a result of excess insulin and fatty acid secretion is also observed in HTG states where increased concentration of ApoC-III, an inhibitor of LPL, may upregulate proinflammatory signaling pathways that also contribute to atherosclerosis (Stahel et al. 2018; Xiao et al. 2016).

In clinical studies, TRLs are consistently associated with elevated ASCVD risk, independent of coexisting metabolic derangements (Nordestgaard and Varbo 2014; Ganda et al. 2018; Jepsen et al. 2016; Varbo et al. 2013, 2015). For example, The Copenhagen General Population Study examined 58,547 individuals initially free of ASCVD, diabetes, and statin use. They found that statin-noneligible individuals with TGs > 264 mg/dL demonstrated similar risk of ASCVD compared with statin-eligible patients with lower TGs (Madsen et al. 2018). Fasting TG levels were also

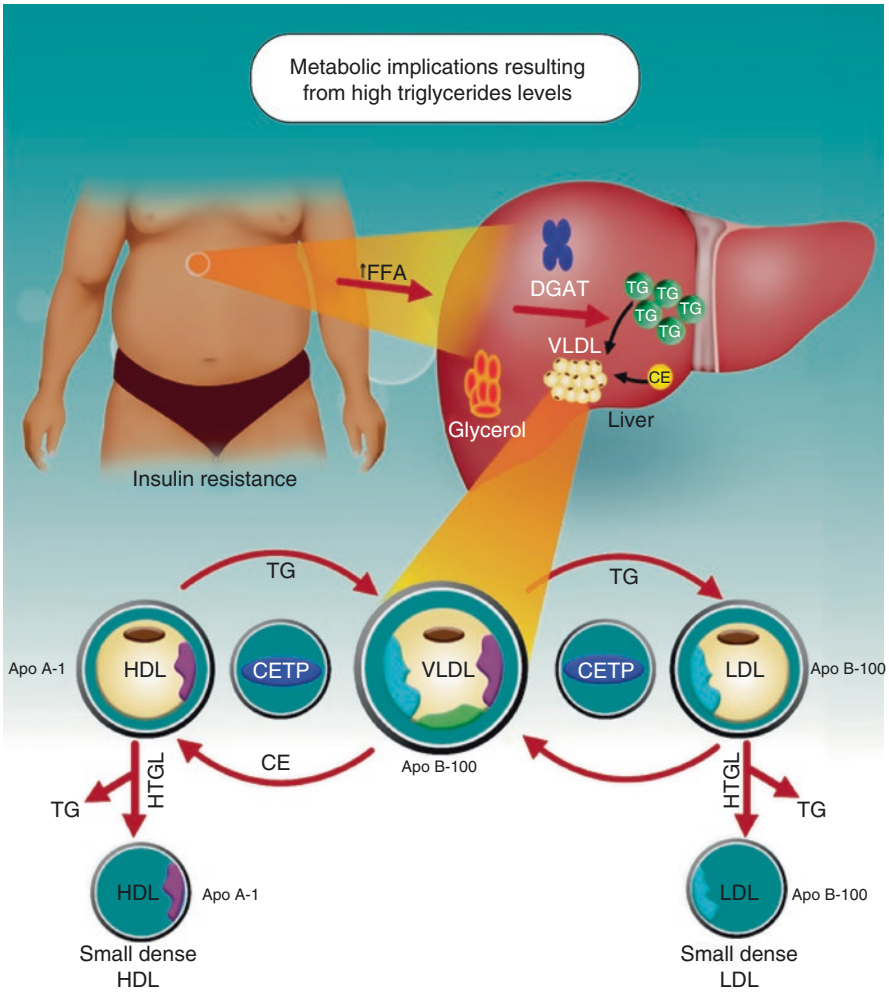


Fig. 12.1 Metabolic implications resulting from high triglycerides. Apo A-1 apolipoprotein A-1, Apo B-100 apolipoprotein B-100, CE cholesteryl ester, CETP cholesteryl ester transfer protein, DGAT diacylglycerol acyltransferase, FFA free fatty acid, HDL high-density lipoprotein, HTGL hepatic triglyceride lipase, LDL low-density lipoprotein, TG triglyceride, VLDL very low density lipoprotein. (Adapted from Miller et al. 2011)

found to predict long- and short-term cardiovascular risks after acute coronary syndrome (ACS) in the dal-OUTCOMES study. Specifically, subjects with the lowest TG levels (~100 mg/dL) at baseline also experienced the lowest likelihood of CVD events (Schwartz et al. 2015, 2012), consistent with previous observations made in the PROVEIT-TIMI 22 trial (Miller et al. 2008).

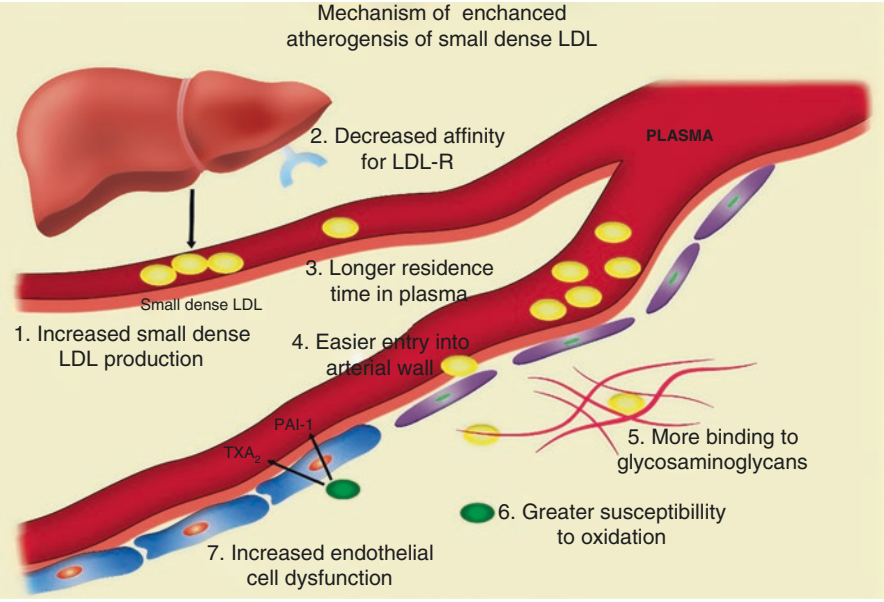


Fig. 12.2 Mechanisms of enhanced atherogenesis of small, dense LDL. LDL-R low-density lipoprotein receptor, TXA2 thromboxane A2, PAI-1 plasminogen activator inhibitor-1. (Reproduced from Elsevier as Open Access Content from Mudd et al. 2007)

Landmark Clinical Trials of TRLs and ASCVD

Based on accumulating data in support of HTG as a biomarker of CVD risk, studies have been conducted in recent years to evaluate TG-lowering therapies with respect to (1) efficacy in reducing TGs without raising LDL and (2) extent of ASCVD reduction. In part, this reflects data from prior studies that demonstrated TG-lowering therapies to raise LDL-C levels in patients with very high TGs (greater than 500 mg/dL) or not to have evaluated CVD risk in an exclusive HTG cohort (Skulas-Ray et al. 2019). To address these issues, three clinical trials were designed. The TG-lowering therapies tested were (1) omega-3 fatty acids containing eicosapentaenoic acid (EPA) with or without docosahexaenoic acid (DHA) and (2) fibrates.

Prior to launching the Reduction of Cardiovascular Events with Icosapent Ethyl – Intervention Trial (REDUCE-IT), icosapent ethyl (IPE), a highly purified formulation of eicosapentaenoic acid (EPA), patients with moderate HTG (baseline levels, 200–499 mg/dL) and severe HTG (baseline levels, 500–2000 mg/dL) were evaluated. Not only was there a significant reduction in median TGs (22% and 33%, respectively) but there was also no rise in LDL-C in either study (Bays et al. 2011; Ballantyne et al. 2012). Previously, the Japan EPA Lipid Intervention Study (JELIS) assessed the role of purified EPA (1.8 g) administered daily to patients with hypercholesterolemia (total cholesterol >6.5 mmol/L or 250 mg/dL) but without HTG (median baseline TGs ~150 mg/dL), who were also receiving low-dose pravastatin

or simvastatin (Yokoyama et al. 2007). Overall, there was an 18% reduction in CVD events in the group who received purified EPA. However, a post hoc analysis of the subgroup with baseline TGs ≥150 mg/dL demonstrated a more robust reduction by 53% in CVD events in subjects assigned to EPA (Saito et al. 2008). This observation builds upon prior data from fibrate studies (Sacks et al. 2010) that found that patients with dyslipidemia, defined by HTG (≥204 mg/dL) and low HDL-C (≤34 mg/dL), exhibited benefits compared to subjects without dyslipidemia.

Thus, these trials paved the way for testing the hypothesis as to whether patients with HTG would benefit from these therapies with respect to CVD outcomes.

REDUCE-IT

REDUCE-IT was a phase III double-blind, randomized, placebo-controlled trial to evaluate CVD outcomes in 8179 patients with established CVD or in high-risk primary prevention patients aged 50 years and older with T2DM and at least 1 additional risk factor, fasting TGs (135–499 mg/dL) and LDL-C (41–100 mg/dL on statin therapy) (Bhatt et al. 2019a). Enrolled patients were randomized to either IPE 4 g/day or mineral oil placebo and were followed up for a median of 4.9 years. At the end of 1 year of IPE treatment, serum TGs and LDL-C were reduced by 19.7% and 6.6%, respectively, compared to placebo treatment ($p < 0.001$ for both). Additionally, patients receiving IPE experienced a significant reduction of 39.9% in baseline high-sensitivity C-reactive protein (hsCRP) ($p < 0.0001$) (Bhatt et al. 2019a; Bazarbashi and Miller 2020a). Primary endpoints such as CVD death, nonfatal myocardial infarction (MI), nonfatal stroke, unstable angina, and coronary revascularization occurred in 23% of patients receiving IPE versus 28.3% in the placebo arm (hazard ratio (HR) 0.75 (0.68–0.83), $p < 0.001$), with a number needed to treat (NNT) of 21 patients over the study duration to prevent 1 event (95% CI, 15–33) (Bhatt et al. 2019a) (Fig. 12.3).

In addition to the primary endpoint, prespecified hierarchical testing revealed significant improvement in the key secondary composite endpoint (CVD death, nonfatal MI, stroke), with individual endpoints including CVD death and the composite of total mortality, nonfatal MI, or nonfatal stroke. Finally, there was a 13% reduction in all-cause mortality that trended toward, but did not attain, statistical significance (Fig. 12.4).

Subgroup analysis of the trial (REDUCE-IT REVASC) examined total on-trial coronary revascularization procedures as well as recurrent revascularization procedures and subtypes. Patients allocated to IPE experienced a 34% reduction in initial coronary revascularization compared to that of placebo ($p < 0.0001$; NNT, 24), with similar results observed for recurrent revascularization intervention (Peterson et al. 2021). Overall, initial as well as repeat (second, third, and fourth) CVD events were reduced, yielding a 31% reduction in total events (Fig. 12.5) (Bhatt et al. 2019b).

Notably, while on treatment, TGs accounted for only a small proportion of the benefits observed (Miller 2019) and EPA levels were a robust predictor of multiple

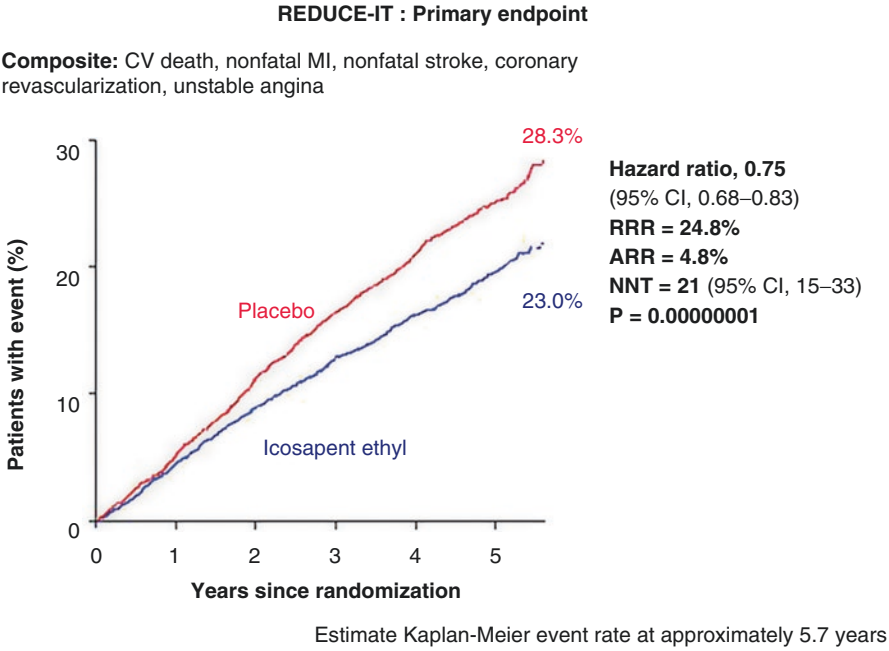


Fig. 12.3 The REDUCE-IT trial primary endpoint. HR hazard ratio, RRR relative risk reduction, ARR absolute risk reduction, NNT number needed to treat. (From Bhatt et al. 2019a. Copyright © (2019) Massachusetts Medical Society. Reprinted with permission)

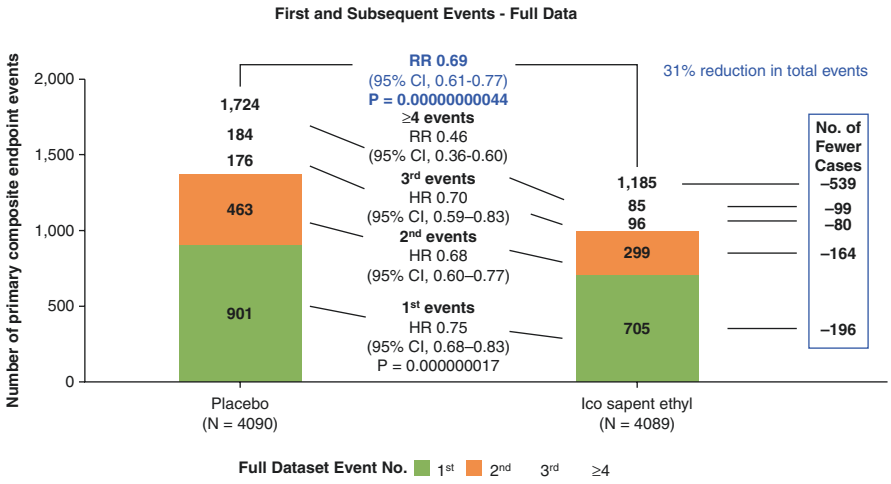
REDUCE-IT : Prespecified hierarchical endpoint testing

Endpoint	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Hazard Ratio (95%CI)	RRR	P-Value
Primary Composite (ITT)		705/4089 (17.2%)	901/4089 (22.0%)	0.75 (0.68–0.83)	25% ▼	<0.001
Key Secondary Composite (ITT)		459/4089 (11.2%)	606/4089 (14.8%)	0.74 (0.65–0.83)	26% ▼	<0.001
Cardiovascular Death or Nonfatal Myocardial Infarction		392/4089 (9.6%)	507/4089 (12.4%)	0.75 (0.66–0.86)	25% ▼	<0.001
Fatal or Nonfatal Myocardial Infarction		250/4089 (6.1%)	355/4089 (8.7%)	0.69 (0.58–0.81)	31% ▼	<0.001
Urgent or Emergent Revascularization		216/4089 (5.3%)	321/4089 (7.8%)	0.65 (0.55–0.78)	35% ▼	<0.001
Cardiocvascular Death		174/4089 (4.3%)	213/4089 (5.2%)	0.80 (0.66–0.98)	20% ▼	0.03
Hospitalization for Unstable Angina		108/4089 (2.6%)	157/4089 (3.8%)	0.68 (0.53–0.87)	32% ▼	0.002
Fatal or Nonfastal Stroke		98/4089 (2.4%)	134/4089 (3.3%)	0.72 (0.55–0.93)	28% ▼	0.01
Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke		549/4089 (13.4%)	690/4089 (16.9%)	0.77 (0.69–0.86)	23% ▼	<0.001
		274/4089 (6.7%)	310/4089 (7.8%)	0.87 (0.74-1.02)	13% ▼	0.09

0.4 Icosapent Ethyl Better
1.0
1.4 Placebo Better

RRR denotes relative risk reduction

Fig. 12.4 The REDUCE-IT trial prespecified hierarchical endpoint. RRR relative risk reduction, CI confidence interval. (From Bhatt et al. 2019a. Copyright © (2019) Massachusetts Medical Society. Reprinted with permission)



Note: WLW method for the 1st events, 2nd events, and 3rd events categories: Negative binomial model for 4th events and overall treatment comparison.

Fig. 12.5 The REDUCE-IT trial first and subsequent events. RR relative risk, HR hazard ratio, CI confidence interval. (Reproduced from Elsevier as Open Access Content from Bhatt et al. 2019b)

CVD endpoints in the REDUCE-IT trial (Bhatt et al. 2020). Taken together, a high daily intake of purified EPA improved CVD risk in patients with HTG at an increased risk of CVD.

STRENGTH

The STRENGTH (Statin Residual Risk Reduction with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia) trial was a double-blinded, randomized, multicenter trial of 13,078 participants designed to examine omega-3 carboxylic acids (CAs), EPA, and DHA, in statin-treated patients at high CVD risk (defined as 1) the presence of established ASCVD in coronary, peripheral, carotid, or aortic regions, (2) T1DM or T2DM aged 40 or older for men or aged 50 and older for woman with at least one risk factor, including smoking, hypertension, hsCRP 2 mg/dL or higher, or high albuminuria, with HTG (200–500 mg/dL) and low HDL-C. Enrolled patients were randomized to receive 4 g/d of omega-3 CAs or corn oil and followed up for a median period of 42 months. The study was terminated on January 8, 2020 after a prespecified interim analysis reported study futility, despite favorable reductions in TGs, non-HDL, and hsCRP (−19%, −6.1%, and −20%, respectively, $p < 0.001$ compared to placebo) (Nicholls et al. 2020). Additionally, the levels of apolipoprotein C-III were decreased in the omega-3 CA arm but not in

placebo (−7% vs +5.9%, $p < 0.001$). Unfortunately, no differences were observed in the primary endpoint of CV death, MI, stroke, coronary revascularization, or unstable angina requiring hospitalization (12% on omega-3 CAs vs 12.2% on placebo (HR 0.99 (95% CI, 0.90–1.09, $p = 0.84$))). Similarly, there were no statistically significant differences in the secondary endpoint (CV death, stroke, or MI) or in all-cause mortality (Nicholls et al. 2020).

Why Were Results of REDUCE-IT and STRENGTH Discrepant?

Despite similar reductions in triglyceride levels in the two studies, REDUCE-IT exhibited higher circulating levels of EPA compared to STRENGTH (89.6 vs 144 micrograms/mL), and this finding may have contributed to the benefits observed in REDUCE-IT but not in STRENGTH. Alternatively, DHA may have blunted the CVD benefits in STRENGTH. Another study, the Omega-3 Fatty Acids in Elderly Patients with Myocardial Infarction (OMEMI) trial, did not show clinical benefits on CVD outcomes (nonfatal MI, unscheduled revascularization, stroke, hospitalization for HF, or all-cause mortality) in post-MI seniors (70 years and older) assigned to 1.8 g/day of EPA/DHA vs placebo over a 2-year period (Kalstad et al. 2020).

In addition to the favorable results obtained in two clinical trials (JELIS and REDUCE-IT), experimental evidence has also demonstrated a beneficial role for EPA in endothelial function, cellular inflammation, oxidative stress, and platelet aggregation (Borow et al. 2015). Moreover, EPA improves HDL functionality by upregulating cholesterol efflux and inhibiting cytokine-mediated adhesion molecule expression (Tanaka et al. 2018). Finally, EPA reduces the expressions of proinflammatory genes and microRNAs that influence atherogenic metabolic signaling pathways (Mason et al. 2020; Bazarbashi and Miller 2020b). In contrast, DHA increases membrane fluidity and promotes lipid domain changes and disordering effects (Mason et al. 2020) that may partially temper the benefits of EPA.

PROMINENT

The PROMINENT (Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes) is an ongoing randomized, double-blind, placebo-controlled multicenter trial evaluating the selective peroxisome proliferator-activated receptor alpha (PPARα) modulator, pemafibrate (K-877), in high-risk patients (i.e., T2DM with or without preexisting CVD) with mild to moderate HTG (200–499 mg/dL) and low HDL-C (≤40 mg/dL) receiving statins and other standard-of-care therapies (NCT03071692) (Pradhan et al. 2018). The study is fully enrolled ($n = 10{,}391$) with patients randomized to either pemafibrate 0.2 mg twice a day or placebo. The mean follow-up duration is 4 years with an estimated completion date in 2022. The primary outcome measure is time to first occurrence of a composite of

the following endpoints: MI, ischemic stroke, unstable angina requiring unplanned coronary revascularization, and cardiovascular death. Secondary outcomes include all-cause mortality, hospitalization for heart failure, any coronary revascularization, and new or worsening peripheral arterial disease (PAD) (Pradhan et al. 2018).

Current Treatments for HTG

Lifestyle Modifications

Because HTG may result from unhealthy dietary habits associated with visceral obesity and metabolic syndrome, the primary strategy with mild to moderate HTG (200–499 mg/dL) is lifestyle intervention. In patients with very high TGs (fasting levels equal to or greater than 500 mg/dL), pharmacological therapy is combined with lifestyle intervention (Miller et al. 2011).

The ACC/AHA and the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines address the management of lifestyle factors that promote physical activity and weight loss as critical components for the management of HTG (Grundy et al. 2019; Mach et al. 2020). Physical activity as recommended by the ACC/AHA (COR 1, LOE B) consists of 150 mins per week or more of moderate intensity (e.g., brisk walking at a rate of 3–4 miles per hour) or 75 mins per week of more vigorous intensity. For each kilogram of weight loss achieved, there is an approximate 8 mg/dL decrease in TGs (Arnett et al. 2019). Dietary recommendations include vegetables, fruits, legumes, nuts, whole grains, and fish as is the custom of the Mediterranean diet that is associated with 10–15% reduction in TGs and decreased ASCVD risk (COR 1, LOE B) (Miller et al. 2011; Arnett et al. 2019). Replacing saturated fats with dietary monounsaturated and polyunsaturated fats may also contribute to TG and ASCVD reduction (COR IIa, LOE B) (Arnett et al. 2019).

Traditional TG-Lowering Therapies

Statins remain a treatment of choice in high-risk patients (e.g., CVD, T2DM) with mild to moderate HTG. On average, statins reduce TG levels by 10–30%, depending upon the statin used and the associated baseline TGs (Miller et al. 2011; Stein et al. 1998). Niacin inhibits hepatic diacylglycerol acetyltransferase 2 (DGAT2) and VLDL synthesis, resulting in 20% or more decreases in plasma TG levels (Feingold and Grunfeld 2000b; Kamanna et al. 2013; Birjmohun et al. 2005). However, niacin is rarely used due to its unfavorable side effect profile and failure to reduce CVD events in clinical trials (Group HTC 2013). Fibrates are the most potent TG-lowering therapies currently available with ~20–50% reductions via PPARα-mediated activation of LPL (Group AS et al. 2010). Results from the Action to Control Cardiovascular Risk in Diabetes (ACCORD), a large randomized controlled trial (RCT) comparing

fenofibrate and statin therapy to statin monotherapy, did not demonstrate clinical benefits in patients with T2DM (Group AS et al. 2010). However, a prespecified analysis in patients with TGs >200 mg/dL and HDL <35 mg/dL did show a trend toward statistical significance (p = 0.06) (Elam et al. 2011). As illustrated in Fig. 12.3, other fibrate trials have suggested clinical benefits of fibrates in patients with HTG and low HDL-C. Consequently, the results of PROMINENT are expected to provide more conclusive data as to whether fibrate therapy may play an important role in CVD risk reduction for high-risk patients with HTG. Fibrate therapy is generally well tolerated, although the combination of gemfibrozil and statins is not recommended due to the increased risk of myopathy and caution should be exercised when combining fenofibrate with statins (Kamanna et al. 2013; Zhao et al. 2016).

Omega-3 Fatty Acids

Both EPA and DHA reduce TG levels to a similar extent (~5–10% per gram), although differential effects have been observed on other lipoprotein lipids and metabolic biomarkers (Borow et al. 2015; Mori et al. 2000; Sahebkar et al. 2018). As noted above, IPE is an ultra-purified prescription form of EPA (>96% purity) and was initially approved as an add-on therapy in patients with very high TGs (≥500 mg/dL). Other prescription OM3s (e.g., omega-3 acid ethyl esters) that contain EPA and DHA have also been approved for very high TGs.

Based upon the results of the REDUCE-IT trial, the Food and Drug Administration (FDA) has recently approved IPE as an adjunctive therapy for the management of patients with TGs (150–499 mg/dL) and CVD or DM and at least one additional CVD risk factor (Bazarbashi and Miller 2020a; FDA approves use of drug to reduce risk of cardiovascular events in certain adult patient groups 2019; Orringer et al. 2019; VASCEPA 2019). Concurrently, the National Lipid Association, the European Society of Cardiology, the American Association of Clinical Endocrinologists/American College of Endocrinology, and the American Diabetes Association also released updates to their standard-of-medical-care guidelines and now recommend IPE to prevent CVD in high-risk patients with elevated TGs (135–500 mg/dL) (Mach et al. 2020; Orringer et al. 2019; American Diabetes A 2019).

Novel and Future Therapies

Apo-CIII Inhibition

While apolipoprotein C-III is known to inhibit LPL and function as a regulator of TG metabolism, several therapies aimed at regulating ApoC-III concentrations have emerged. Small antisense oligonucleotides (ASOs), small interfering RNAs

(siRNAs), and monoclonal antibodies are among the therapies developed to specifically inhibit ApoC-III (Taskinen et al. 2019). Volanesorsen is an anti-ApoC-III antisense oligonucleotide administered subcutaneously every 2 weeks. In the APPROACH (A Study of Volanesorsen in Patients with Familial Chylomicronemia Syndrome) trial, volanesorsen reduced TGs by 77% in patients with familial chylomicronemia syndrome (FCS) (Witztum et al. 2019). However, a major and unanticipated adverse event, thrombocytopenia, halted its approval by the FDA for FCS. By contrast, the European Medicine Agency granted volanesorsen an indication within the orphan drug designation. A second-generation ASO directed against ApoC-III may be more promising as thrombocytopenia has not occurred in early-phase studies. Further testing of AKCEA-APOCIII-LR, an *N*-acetylgalactosamine (GalNac)-conjugated anti-ApoC-III ASO, is anticipated in high-risk patients with HTG.

Angiopoietin-Like Protein 3 (ANGPTL3) Inhibition

Angiopoietin-like protein 3 (ANGPTL3) is a circulating protein synthesized and secreted by the liver (Koishi et al. 2002). ANGPTL3 has been shown to play an integral role in the regulation of lipid and glucose metabolism, in part via inhibition of lipoprotein lipase (Mattijssen and Kersten 2012). Inhibition of ANGPTL3 has been demonstrated pharmacologically using the monoclonal antibody evinacumab. In healthy volunteers with mild to moderate elevation in TGs (150–450 mg/dL) or LDL-C (100 mg/dL or greater), evinacumab (administered subcutaneously or intravenously) reduced TGs and LDL-C by 76% and 23%, respectively (Dewey et al. 2017). ANGPTL3 can also be inhibited by gene-targeted inactivation of messenger RNA (mRNA) via antisense oligonucleotides (ASOs). In a study of 43 participants randomized to multiple doses of the IONIS-ANGPTL3-LRx ASO, decreases in TGs (33.2%–63.1%), LDL-C (1.3%–32.9%), VLDL-C (27.9%– 60%), non-HDL-C (10%–35.6%), and apoB (3.4%–25.7%) were observed compared to placebo (Graham et al. 2017). Both medications were well tolerated without any major serious adverse events reported during early testing.

Gemcabene

Gemcabene is a dialkyl ether dicarboxylic acid lipid-regulating compound that enhances the clearance of VLDLs via reduction of hepatic ApoC-III messenger RNA (mRNA), thereby playing a potential therapeutic role in reducing TGs at levels of 200 mg/dL or higher (Bays et al. 2003; Stein et al. 2016). Gemcabene was licensed from Pfizer Inc. by Gemphire Therapeutics Inc. in 2011 for the treatment of patients with hypercholesterolemia or HTG who were otherwise unable to effectively lower LDL or TGs or were intolerant to standard therapies. In 2015, a new IND (Investigational New Drug) application for gemcabene was filed. In 2016,

gemcabene was studied in COBALT-1, an open-label trial of patients with homozygous familial hypercholesterolemia (HoFH), and demonstrated a dose-dependent change in the mean percentage and absolute changes in LDL (Gaudet et al. 2019). Most recently, results of a 12-week study to assess the efficacy, safety, and tolerability of gemcabene in subjects with severe hypertriglyceridemia (INDIGO-1) (NCT02944383) have demonstrated a 47% reduction in TGs for patients taking gemcabene 600 mg daily when compared with placebo (27%). This compound has not yet received FDA approval.

Fibroblast Growth Factor 21 (FGF21)

Fibroblast growth factor 21 is a cytokine with biological pleiotropic properties including, but not limited to, regulating cell growth, differentiation, and metabolism. FGF21 is mainly regulated by PPARα in the liver and PPARζ in adipocytes. Therapy with FGF21 analogues alleviate dyslipidemia and increase adiponectin levels. Four different FGF21 therapies have emerged (LY2405319, PF-05231023, AMG876/AKR-001, pegbelfermin) with demonstrated reductions in serum TG levels in humans (Geng et al. 2020). To date, none of the FGF21 analogues have been approved by the FDA and the majority are currently in preclinical animal models. However, pegbelfermin, an FGF21 analogue, was recently studied in a 16-week randomized, double-blinded, phase 2a clinical trial in human patients with nonalcoholic steatohepatitis. The results showed a significant decrease in absolute hepatic fat fraction in the group receiving 10 mg pegbelfermin daily (−6.8% vs −1.3%; $p = 0.0004$) compared with placebo (Sanyal et al. 2019). Most recently, AKR-001, a long-acting human immunoglobulin 1 (IgG1) Fc–FGF21 fusion protein, was studied in patients with type 2 diabetes over 4 weeks of treatment. Markers of lipid metabolism were analyzed and demonstrated a trend toward improvement in the lipoprotein profile. A maximal reduction in fasting TGs of 69% and 55% in 1- and 2-week dosing, respectively, was observed (Kaufman et al. 2020). Other FGF21 candidates (e.g., BIO89-100) are currently under evaluation for patients with severe HTG (equal to or greater than 500 mg/dL) (NCT04541186).

Current Recommendations

The 2018 ACC/AHA guideline on the management of blood cholesterol places very little emphasis on HTG (Grundy et al. 2019). They define HTG as fasting or nonfasting levels between 175 and 499 mg/dL and recommend lifestyle therapy as the cornerstone of management, similar to recommendations based on the 2011 AHA Statement (Miller et al. 2011). In patients with HTG and a high estimated 10-year risk of ASCVD (7.5% likelihood of an ASCVD event over 10 years), the recommendation is to initiate or intensify statin therapy (Fig. 12.6) (Grundy et al. 2019). It remains to be determined whether IPE therapy will be prioritized for treatment of

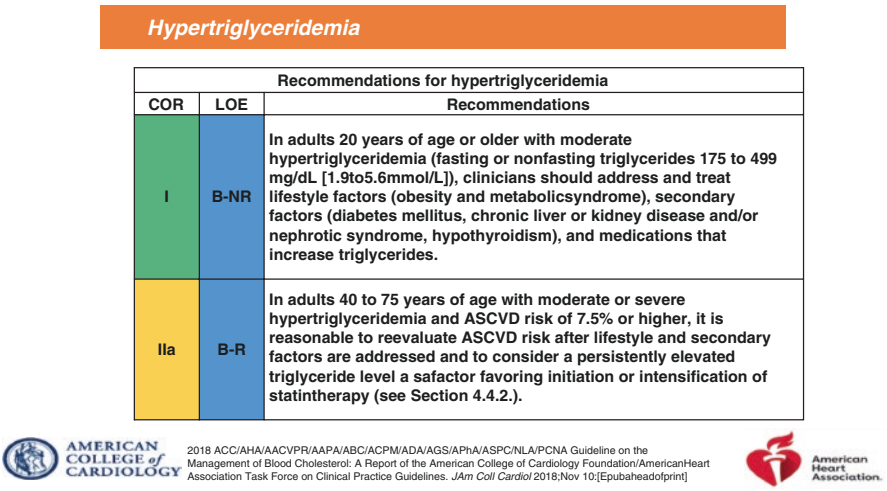


Fig. 12.6 2018 ACC/AHA guideline on the management of hypertriglyceridemia. (Reproduced from Elsevier as PMC Open Access Content from the 2018 ACC/AHA Guideline (Grundy et al. 2019)

mild to moderate HTG in future guidelines, though as noted earlier, multiple professional guidelines endorse the use of high-dose IPE for high-risk patients with elevated TG (135–500 mg/dL).

Summary

While TRLs contribute to elevated CVD risk in patients with HTG, only recently has evidence emerged that lowering TGs may translate into reduced CVD risk. While we await the results of the soon-to-be completed clinical trials (e.g., PROMINENT) and continue to investigate novel therapies, it is clear that the persistently elevated risk in this group despite statin therapy may be amenable to effective therapies (e.g., IPE) that help mitigate this risk.

References

American Diabetes A. 10. Cardiovascular disease and risk management: standards of medical care in diabetes-2019. Diabetes Care. 2019;42(Suppl 1):S103–S23.

Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. J Am Coll Cardiol. 2019;74(10):e177–232.

Austin MA, Hokanson JE, Edwards KL. Hypertriglyceridemia as a cardiovascular risk factor. Am J Cardiol. 1998;81(4A):7B–12B.

Ballantyne CM, Bays HE, Kastelein JJ, Stein E, Isaacsohn JL, Braeckman RA, et al. Efficacy and safety of eicosapentaenoic acid ethyl ester (AMR101) therapy in statin-treated patients with persistent high triglycerides (from the ANCHOR study). Am J Cardiol. 2012;110(7):984–92.

Bays HE, McKenney JM, Dujovne CA, Schrott HG, Zema MJ, Nyberg J, et al. Effectiveness and tolerability of a new lipid-altering agent, gemcabene, in patients with low levels of high-density lipoprotein cholesterol. Am J Cardiol. 2003;92(5):538–43.

Bays HE, Ballantyne CM, Kastelein JJ, Isaacsohn JL, Braeckman RA, Soni PN. Eicosapentaenoic acid ethyl ester (AMR101) therapy in patients with very high triglyceride levels (from the multi-center, plAcebo-controlled, randomized, double-blINd, 12-week study with an open-label extension [MARINE] trial). Am J Cardiol. 2011;108(5):682–90.

Bazarbashi N, Miller M. Icosapent ethyl: drug profile and evidence of reduced residual cardiovascular risk in patients with statin-managed LDL-C cholesterol. Expert Rev Cardiovasc Ther. 2020a;18(4):175–80.

Bazarbashi N, Miller M. Icosapent ethyl: niche drug or for the masses? Curr Cardiol Rep. 2020b;22(10):104.

Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, et al. Cardiovascular risk reduction with Icosapent ethyl for hypertriglyceridemia. N Engl J Med. 2019a;380(1):11–22.

Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, et al. Effects of icosapent ethyl on total ischemic events: from REDUCE-IT. J Am Coll Cardiol. 2019b;73(22):2791–802.

Bhatt DL, Miller M, Steg G, et al. on Behalf of the REDUCE-IT Investigators. , editor EPA levels and cardiovascular outcomes in the reduction of cardiovascular events with icosapent ethyl–intervention trial. American College of Cardiology Virtual Annual Scientific Session Together with World Congress of Cardiology (ACC 2020/WCC); 2020 March 30, 2020; Chicago, United States. Online: American College of Cardiology; 2020.

Birjmohun RS, Hutten BA, Kastelein JJ, Stroes ES. Efficacy and safety of high-density lipoprotein cholesterol-increasing compounds: a meta-analysis of randomized controlled trials. J Am Coll Cardiol. 2005;45(2):185–97.

Borow KM, Nelson JR, Mason RP. Biologic plausibility, cellular effects, and molecular mechanisms of eicosapentaenoic acid (EPA) in atherosclerosis. Atherosclerosis. 2015;242(1):357–66.

Chait A, Eckel RH. The chylomicronemia syndrome is most often multifactorial: a narrative review of causes and treatment. Ann Intern Med. 2019;170(9):626–34.

Christian JB, Bourgeois N, Snipes R, Lowe KA. Prevalence of severe (500 to 2,000 mg/dl) hypertriglyceridemia in United States adults. Am J Cardiol. 2011;107(6):891–7.

Dallinga-Thie GM, Franssen R, Mooij HL, Visser ME, Hassing HC, Peelman F, et al. The metabolism of triglyceride-rich lipoproteins revisited: new players, new insight. Atherosclerosis. 2010;211(1):1–8.

Dewey FE, Gusarova V, Dunbar RL, O'Dushlaine C, Schurmann C, Gottesman O, et al. Genetic and pharmacologic inactivation of ANGPTL3 and cardiovascular disease. N Engl J Med. 2017;377(3):211–21.

Do R, Willer CJ, Schmidt EM, Sengupta S, Gao C, Peloso GM, et al. Common variants associated with plasma triglycerides and risk for coronary artery disease. Nat Genet. 2013;45(11):1345–52.

Elam M, Lovato LC, Ginsberg H. Role of fibrates in cardiovascular disease prevention, the ACCORD-lipid perspective. Curr Opin Lipidol. 2011;22(1):55–61.

Emerging Risk Factors C, Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, et al. Major lipids, apolipoproteins, and risk of vascular disease. JAMA. 2009;302(18):1993–2000.

Fan W, Philip S, Granowitz C, Toth PP, Wong ND. Prevalence of US adults with triglycerides >/= 150 mg/dl: NHANES 2007-2014. Cardiol Ther. 2020;9(1):207–13.

FDA approves use of drug to reduce risk of cardiovascular events in certain adult patient groups [press release]. U.S Food and Drug Administration Website, 2019.

Feingold KR, Grunfeld C. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, Dungan K, Grossman A, et al., editors. Triglyceride lowering drugs. South Dartmouth: Endotext; 2000a.

Feingold KR, Grunfeld C. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dungan K, et al., editors. Introduction to lipids and lipoproteins. South Dartmouth: Endotext; 2000b.

Fogelstrand P, Boren J. Retention of atherogenic lipoproteins in the artery wall and its role in atherogenesis. Nutr Metab Cardiovasc Dis. 2012;22(1):1–7.
Ganda OP, Bhatt DL, Mason RP, Miller M, Boden WE. Unmet need for adjunctive dyslipidemia therapy in hypertriglyceridemia management. J Am Coll Cardiol. 2018;72(3):330–43.
Gaudet D, Durst R, Lepor N, Bakker-Arkema R, Bisgaier C, Masson L, et al. Usefulness of gemcabene in homozygous familial hypercholesterolemia (from COBALT-1). Am J Cardiol. 2019;124(12):1876–80.
Geng L, Lam KSL, Xu A. The therapeutic potential of FGF21 in metabolic diseases: from bench to clinic. Nat Rev Endocrinol. 2020;16(11):654–67.
Ginsberg HN. New perspectives on atherogenesis: role of abnormal triglyceride-rich lipoprotein metabolism. Circulation. 2002;106(16):2137–42.
Graham MJ, Lee RG, Brandt TA, Tai LJ, Fu W, Peralta R, et al. Cardiovascular and metabolic effects of ANGPTL3 antisense oligonucleotides. N Engl J Med. 2017;377(3):222–32.
Group AS, Ginsberg HN, Elam MB, Lovato LC, Crouse JR 3rd, Leiter LA, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010;362(17):1563–74.
Group HTC. HPS2-THRIVE randomized placebo-controlled trial in 25 673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment. Eur Heart J. 2013;34(17):1279–91.
Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. J Am Coll Cardiol. 2004;44(3):720–32.
Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the Management of Blood Cholesterol: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Circulation. 2019;139(25):e1082–e143.
Hegele RA, Ginsberg HN, Chapman MJ, Nordestgaard BG, Kuivenhoven JA, Averna M, et al. The polygenic nature of hypertriglyceridaemia: implications for definition, diagnosis, and management. Lancet Diabetes Endocrinol. 2014;2(8):655–66.
Hulley SB, Rosenman RH, Bawol RD, Brand RJ. Epidemiology as a guide to clinical decisions. The association between triglyceride and coronary heart disease. N Engl J Med. 1980;302(25):1383–9.
Jepsen AM, Langsted A, Varbo A, Bang LE, Kamstrup PR, Nordestgaard BG. Increased remnant cholesterol explains part of residual risk of all-cause mortality in 5414 patients with ischemic heart disease. Clin Chem. 2016;62(4):593–604.
Jorgensen AB, Frikke-Schmidt R, West AS, Grande P, Nordestgaard BG, Tybjaerg-Hansen A. Genetically elevated non-fasting triglycerides and calculated remnant cholesterol as causal risk factors for myocardial infarction. Eur Heart J. 2013;34(24):1826–33.
Kalstad AA, Myhre PL, Laake K, Tveit SH, Schmidt EB, Smith P, et al. Effects of n-3 fatty acid supplements in elderly patients after myocardial infarction: a randomized controlled trial. Circulation. 2020;143(6):528–39.
Kamanna VS, Ganji SH, Kashyap ML. Recent advances in niacin and lipid metabolism. Curr Opin Lipidol. 2013;24(3):239–45.
Kaufman A, Abuqayyas L, Denney WS, Tillman EJ, Rolph T. AKR-001, an Fc-FGF21 Analog, showed sustained pharmacodynamic effects on insulin sensitivity and lipid metabolism in type 2 diabetes patients. Cell Rep Med. 2020;1(4):100057.
Koishi R, Ando Y, Ono M, Shimamura M, Yasumo H, Fujiwara T, et al. Angptl3 regulates lipid metabolism in mice. Nat Genet. 2002;30(2):151–7.
Laufs U, Parhofer KG, Ginsberg HN, Hegele RA. Clinical review on triglycerides. Eur Heart J. 2020;41(1):99–109c.
Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111–88.

Madsen CM, Varbo A, Nordestgaard BG. Unmet need for primary prevention in individuals with hypertriglyceridaemia not eligible for statin therapy according to European Society of Cardiology/European Atherosclerosis Society guidelines: a contemporary population-based study. Eur Heart J. 2018;39(7):610–9.

Mason RP, Libby P, Bhatt DL. Emerging mechanisms of cardiovascular protection for the omega-3 fatty acid eicosapentaenoic acid. Arterioscler Thromb Vasc Biol. 2020;40(5):1135–47.

Mattijssen F, Kersten S. Regulation of triglyceride metabolism by angiopoietin-like proteins. Biochim Biophys Acta. 2012;1821(5):782–9.

Miller M. Icosapent ethyl for hypertriglyceridemia: insights from the REDUCE-IT trial. Futur Cardiol. 2019;15(6):391–4.

Miller M, Cosgrove B, Havas S. Update on the role of triglycerides as a risk factor for coronary heart disease. Curr Atheroscler Rep. 2002;4(6):414–8.

Miller M, Cannon CP, Murphy SA, Qin J, Ray KK, Braunwald E, et al. Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial. J Am Coll Cardiol. 2008;51(7):724–30.

Miller M, Stone NJ, Ballantyne C, Bittner V, Criqui MH, Ginsberg HN, et al. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2011;123(20):2292–333.

Mori TA, Burke V, Puddey IB, Watts GF, O'Neal DN, Best JD, et al. Purified eicosapentaenoic and docosahexaenoic acids have differential effects on serum lipids and lipoproteins, LDL particle size, glucose, and insulin in mildly hyperlipidemic men. Am J Clin Nutr. 2000;71(5):1085–94.

Mudd JO, Borlaug BA, Johnston PV, Kral BG, Rouf R, Blumenthal RS, et al. Beyond low-density lipoprotein cholesterol: defining the role of low-density lipoprotein heterogeneity in coronary artery disease. J Am Coll Cardiol. 2007;50(18):1735–41.

Nicholls SJ, Lincoff AM, Garcia M, Bash D, Ballantyne CM, Barter PJ, et al. Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: the STRENGTH randomized clinical trial. JAMA. 2020;324(22):2268–80.

Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. Lancet. 2014;384(9943):626–35.

Orringer CE, Jacobson TA, Maki KC. National Lipid Association Scientific Statement on the use of icosapent ethyl in statin-treated patients with elevated triglycerides and high or very-high ASCVD risk. J Clin Lipidol. 2019;13(6):860–72.

Peng J, Luo F, Ruan G, Peng R, Li X. Hypertriglyceridemia and atherosclerosis. Lipids Health Dis. 2017;16(1):233.

Peterson BE, Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, et al. Reduction in revascularization with icosapent ethyl: insights from REDUCE-IT revascularization analyses. Circulation. 2021;143(1):33–44.

Pradhan AD, Paynter NP, Everett BM, Glynn RJ, Amarenco P, Elam M, et al. Rationale and design of the pemafibrate to reduce cardiovascular outcomes by reducing triglycerides in patients with diabetes (PROMINENT) study. Am Heart J. 2018;206:80–93.

Sacks FM, Carey VJ, Fruchart JC. Combination lipid therapy in type 2 diabetes. N Engl J Med. 2010;363(7):692–4; author reply 4-5.

Sahebkar A, Simental-Mendia LE, Mikhailidis DP, Pirro M, Banach M, Sirtori CR, et al. Effect of omega-3 supplements on plasma apolipoprotein C-III concentrations: a systematic review and meta-analysis of randomized controlled trials. Ann Med. 2018;50(7):565–75.

Saito Y, Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Ishikawa Y, et al. Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: subanalysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS). Atherosclerosis. 2008;200(1):135–40.

Sanyal A, Charles ED, Neuschwander-Tetri BA, Loomba R, Harrison SA, Abdelmalek MF, et al. Pegbelfermin (BMS-986036), a PEGylated fibroblast growth factor 21 analogue, in patients with non-alcoholic steatohepatitis: a randomised, double-blind, placebo-controlled, phase 2a trial. Lancet. 2019;392(10165):2705–17.

Saraswathi V, Hasty AH. The role of lipolysis in mediating the proinflammatory effects of very low density lipoproteins in mouse peritoneal macrophages. J Lipid Res. 2006;47(7):1406–15.
Schwartz GG, Olsson AG, Abt M, Ballantyne CM, Barter PJ, Brumm J, et al. Effects of dalcetrapib in patients with a recent acute coronary syndrome. N Engl J Med. 2012;367(22):2089–99.
Schwartz GG, Abt M, Bao W, DeMicco D, Kallend D, Miller M, et al. Fasting triglycerides predict recurrent ischemic events in patients with acute coronary syndrome treated with statins. J Am Coll Cardiol. 2015;65(21):2267–75.
Skulas-Ray AC, Wilson PWF, Harris WS, Brinton EA, Kris-Etherton PM, Richter CK, et al. Omega-3 fatty acids for the management of hypertriglyceridemia: a science advisory from the American Heart Association. Circulation. 2019;140(12):e673–e91.
Stahel P, Xiao C, Hegele RA, Lewis GF. The atherogenic dyslipidemia complex and novel approaches to cardiovascular disease prevention in diabetes. Can J Cardiol. 2018;34(5):595–604.
Stein EA, Lane M, Laskarzewski P. Comparison of statins in hypertriglyceridemia. Am J Cardiol. 1998;81(4A):66B–9B.
Stein E, Bays H, Koren M, Bakker-Arkema R, Bisgaier C. Efficacy and safety of gemcabene as add-on to stable statin therapy in hypercholesterolemic patients. J Clin Lipidol. 2016;10(5):1212–22.
Tanaka N, Irino Y, Shinohara M, Tsuda S, Mori T, Nagao M, et al. Eicosapentaenoic acid-enriched high-density lipoproteins exhibit anti-atherogenic properties. Circ J. 2018;82(2):596–601.
Taskinen MR, Packard CJ, Boren J. Emerging evidence that ApoC-III inhibitors provide novel options to reduce the residual CVD. Curr Atheroscler Rep. 2019;21(8):27.
Thomsen M, Varbo A, Tybjaerg-Hansen A, Nordestgaard BG. Low nonfasting triglycerides and reduced all-cause mortality: a mendelian randomization study. Clin Chem. 2014;60(5):737–46.
Tirosh A, Rudich A, Shochat T, Tekes-Manova D, Israeli E, Henkin Y, et al. Changes in triglyceride levels and risk for coronary heart disease in young men. Ann Intern Med. 2007;147(6):377–85.
Varbo A, Benn M, Tybjaerg-Hansen A, Nordestgaard BG. Elevated remnant cholesterol causes both low-grade inflammation and ischemic heart disease, whereas elevated low-density lipoprotein cholesterol causes ischemic heart disease without inflammation. Circulation. 2013;128(12):1298–309.
Varbo A, Freiberg JJ, Nordestgaard BG. Extreme nonfasting remnant cholesterol vs extreme LDL cholesterol as contributors to cardiovascular disease and all-cause mortality in 90000 individuals from the general population. Clin Chem. 2015;61(3):533–43.
VASCEPA. VASCEPA label 2019. Available from: https://www.vascepa.com/assets/pdf/Vascepa_PI.pdf.
Witztum JL, Gaudet D, Freedman SD, Alexander VJ, Digenio A, Williams KR, et al. Volanesorsen and triglyceride levels in familial chylomicronemia syndrome. N Engl J Med. 2019;381(6):531–42.
Xiao C, Dash S, Morgantini C, Hegele RA, Lewis GF. Pharmacological targeting of the atherogenic dyslipidemia complex: the next frontier in CVD prevention beyond lowering LDL cholesterol. Diabetes. 2016;65(7):1767–78.
Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet. 2007;369(9567):1090–8.
Zhao S, Wang F, Dai Y, Lin L, Tong Q, Liao Y, et al. Efficacy and safety of fenofibrate as an add-on in patients with elevated triglyceride despite receiving statin treatment. Int J Cardiol. 2016;221:832–6.
Zilversmit DB. Atherogenesis: a postprandial phenomenon. Circulation. 1979;60(3):473–85.

Chapter 13
Inflammatory Diseases and Risk of Atherosclerotic Cardiovascular Disease: A New Focus on Prevention

Renato Quispe, Bibin Varghese, and Erin D. Michos

Introduction

Atherosclerosis continues to be one of the main contributors to the development of the spectrum of cardiovascular disease (CVD) that includes myocardial infarction (MI), stroke, and peripheral arterial disease. During much of the twentieth century, research focused on the causal role of lipids and cholesterol, mainly low-density lipoprotein cholesterol (LDL-C), in the formation of atherosclerosis (Goldstein and Brown 2015). Later, other risk factors were identified, such as other lipoproteins, hypertension, insulin resistance, smoking, and lifestyle-related factors (Khera et al. 2016). Despite significant reduction in cardiovascular events with LDL-C lowering with mainly statin therapy, there remains a significant residual risk for incident and recurrent atherosclerotic cardiovascular disease (ASCVD) events (Fernandez-Friera et al. 2017), even among patients with well-controlled levels of LDL-C (Ridker et al. 2008a; Quispe et al. 2020). Consequently, it is now acknowledged that elevated LDL-C alone does not fully explain the entire burden of atherosclerosis, for which current research efforts are aiming to explore novel potential contributors to residual risk.

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Compelling evidence has highlighted the potential role of inflammation as a causal risk factor for atherosclerosis (Alfaddagh et al. 2020; Ridker et al. 2017). The pathobiology of inflammation that contributes to the burden of atherosclerosis, as well as its interactions with other known risk factors, is rather complex and not fully elucidated. However, promising results from recent clinical trials of anti-inflammatory agents have opened multiple new directions for therapeutic targeting as well as a clinical dialogue about personalized medicine to further reduce the risk of ASCVD (Ridker 2018; Sweeney et al. 2021).

In this book chapter, we will provide further insights into the pathophysiological role of inflammation in the development of atherosclerosis, the atherogenic risk conferred by specific inflammatory conditions, the clinical utility of markers and imaging techniques to assess inflammation, and the relevance of inflammation in decision-making for primary prevention. We will also present some current evidence evaluating the utility of anti-inflammatory agents in secondary prevention. Although this book chapter is focused on primary prevention, discussion of these secondary prevention trials offers proof of concept of the causal role of inflammation in atherothrombosis, which may eventually be translated into primary prevention strategies as well.

Inflammation in the Initiation and Propagation of Atherosclerosis

Atherosclerosis is a dynamic process, and inflammation is implicated in all stages of the formation and evolution of atherosclerotic lesions (Fig. 13.1) (Alfaddagh et al. 2020). From a pathophysiological standpoint, atherosclerosis begins with

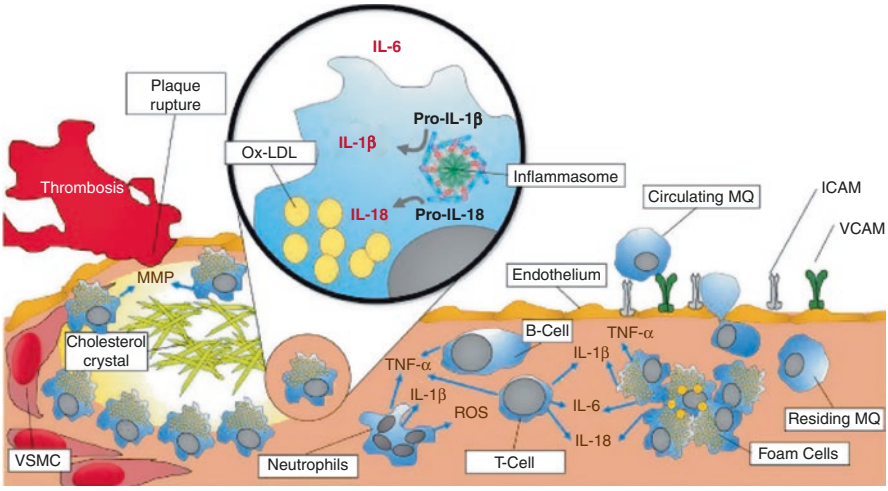

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Fig. 13.1 Mechanisms of inflammation and atherosclerotic cardiovascular disease. Reproduced with permission from Alfaddagh et al. (2020) [open access])

endothelial injury and dysfunction and subsequent accumulation of atherogenic lipoproteins in the subintimal space. Additionally, platelets in the arterial wall release protein platelet-derived growth factor (PDGF) that stimulates the migration and proliferation of smooth muscle cells (SMCs) into the intima. The extracellular matrix formed by interstitial collagens produced by SMCs entraps plasma-derived atherogenic lipoproteins, which ultimately give rise to atheroma when engulfed by arterial wall macrophages to become foam cells.

Upregulation of adhesion molecules (i.e., intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1)), in addition to a variety of selectins, promotes binding, rolling, and transmigration of inflammatory cells to early plaque initiation sites. Probing of human atherosclerotic plaques with monoclonal antibody reagents helps to better characterize and identify the different cell types that accumulate in human atherosclerotic plaques, depicting a significant inflammatory infiltrate. Different immune cells, mainly monocytes and macrophages, but also CD4+ T cells, were identified in human atherosclerotic plaques (Libby et al. 2018).

The formation of the NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasome within macrophages constitutes a key step in propagating inflammation. The NLRP3 inflammasome is a complex cytosolic multiprotein that is critical for host immune defenses against infections. It is formed when macrophages receive a second hit from either cellular hypoxia or deposition of cholesterol crystals and activates caspase-1, which cleaves pro-interleukin-1β (pro-IL-1β) into its mature and biologically active form, IL-1β. This process ultimately produces interleukin-6 (IL-6), which stimulates liver production of C-reactive protein (CRP) and further amplifies the inflammatory cascade (Libby et al. 2018).

These immune cells activate and communicate with arterial wall cells through several cytokines and cell-surface receptors. For instance, endothelial–leukocyte adhesion as well as entry of bound cells into the intima are regulated by multiple inflammatory mediators, such as cytokines and chemokines (a subset of cytokines that mediate the migration of cells in a plaque). Intrinsic arterial wall cells themselves express and respond to chemokines and cytokines, suggesting that they are also activated by inflammatory mediators. In summary, cytokines mediate the exchange of signals between immune cells (i.e., leukocytes) and intrinsic arterial wall cells. Although both leukocytes and arterial wall cells in a plaque could be considered as the protagonists in the role of inflammation during atherogenesis, cytokines and chemokines provide the dialogue through which these actors communicate (Libby et al. 2018).

Inflammation also plays a role in other features of the atherosclerotic plaque. Proinflammatory cytokines released by macrophages contribute to vascular SMC apoptosis and release of calcium-rich matrix vesicles that form the nucleation site for calcium deposition. In particular, tumor necrosis factor-α (TNF-α) has been shown to induce osteogenic differentiation of vascular SMCs into osteoblast-like cells that further accelerate intimal calcification within the plaque (Hulin et al. 2018). Interestingly, this mechanism has been postulated to also contribute to aortic valve calcification (Sverdlov et al. 2011).

As explained above, the inflammatory cascade is complex and involves multiple cytokines as well as immune cells, which additionally contribute to amplifying cytokine production. All of these steps together contribute to signaling, modulating plaque formation, and growth.

Source of Chronic Inflammation in Normal Aging: Aging as an Inflammatory "Disease"

Pathophysiologically speaking, aging in humans may be more than a simple proxy for historical exposure to cardiovascular risk factors. Aging is associated with a state of chronic, low-grade inflammation characterized by increases in the circulating levels of IL-6 and CRP (Ferrucci et al. 2005) or IL-1β (Furman et al. 2017). This link between aging and inflammation has only recently been fully elucidated and has introduced a novel concept that may explain this phenomenon.

Clonal hematopoiesis of indeterminate potential (CHIP) is an expansion of blood cell clones due to advantageous somatic mutations that can be found in up to 10% individuals 70 years or older (Jaiswal et al. 2014). Humans have an estimated 10,000–200,000 hematopoietic stem cells, and each cell acquires approximately 170 mutations in the whole genome per decade of life. Rarely can one of these mutations provide a selective advantage to a given stem cell, which leads to an expanded blood cell clone derived from a single mutated ancestor.

Recent evidence has shown that individuals who harbor these cell clones are at a higher risk of not only hematological cancers but also ASCVD (Jaiswal et al. 2014), likely because many of the genetic mutations that cause CHIP (such as TET2 or DNMT3A) (Jaiswal and Libby 2020) also lead to increased expression of inflammatory genes in innate immune cells (Zhang et al. 2015; Fuster et al. 2017). The magnitude of risk conferred by CHIP has been shown to be similar or greater than known cardiovascular risk factors. Among older individuals free of coronary artery disease (CAD), the risk of incident CAD was 1.9-fold higher in those with CHIP. Similarly, CHIP was fourfold higher in individuals with early MI (Jaiswal et al. 2017). Other studies have shown association between CHIP and ischemic heart failure (Dorsheimer et al. 2019). More details about CHIP and its link to CVD can be found in another chapter of this book.

Atherosclerosis in Specific Inflammatory Conditions

Incorporation of Inflammatory Conditions into Risk Assessment

Recent guidelines have now recognized the increased ASCVD risk among individuals with inflammatory conditions. In the 2019 guideline put forth by the American College of Cardiology (ACC) and the American Heart Association (AHA) for the

primary prevention of CVD, inflammatory conditions such as metabolic syndrome, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), psoriatic arthritis, and human immunodeficiency virus (HIV) infection were highlighted as "risk-enhancing" factors (Fig. 13.2). For those aged 40–75 years without established ASCVD, the 2019 ACC/AHA Primary Prevention Guideline recommends starting with an estimation of a 10-year risk using the pooled cohort equations (PCEs) and then characterizing individuals into low- (<5%), borderline- (5–7.4%), intermediate- (7.5–19.9%), or high-risk (≥20%) groups. Most low-risk patients can be sufficiently managed with lifestyle measures alone, whereas high-risk patients should be treated with high-intensity statins with the goal of reducing LDL-C by 50% or more, in addition to lifestyle recommendations. A shared decision-making process should be initiated for those at borderline or intermediate risk regarding the net benefits of statin therapy.

The presence of a risk-enhancing factor, such as these aforementioned inflammatory conditions, would place an individual into a higher risk category that might favor the initiation or intensification of statin therapy for prevention, particularly for those at borderline or intermediate 10-year risk (Arnett et al. 2019). If there is still uncertainty regarding the risk and net benefits of statin therapy after considering these risk-enhancing factors, a coronary artery calcium (CAC) score can be measured as a risk-decision aid to guide the clinician–patient risk discussion (Fig. 13.3). CAC, measured by noncontrast computed tomography (CT), is a surrogate marker of the total subclinical coronary atherosclerosis burden and a potent prognostic marker of future ASCVD events (Michos et al. 2017). More details about CAC can be found in another (Chap. 22) of this book. These "risk-enhancing" inflammatory conditions highlighted in the guidelines are further discussed below.

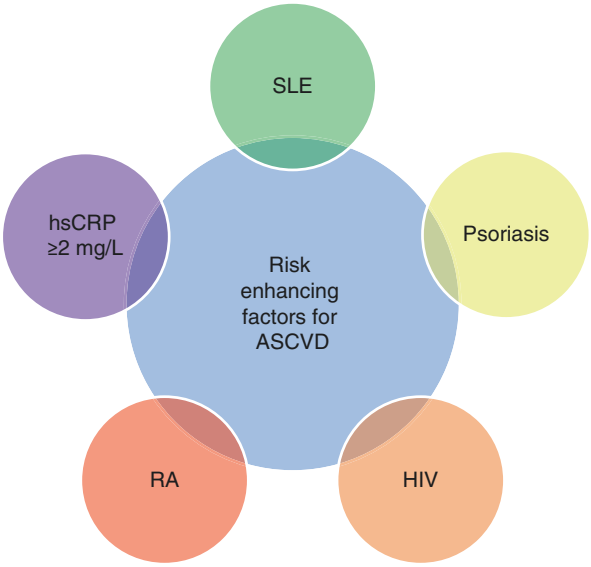

Fig. 13.2 "Risk-enhancing" factors for atherosclerotic cardiovascular disease. *Abbreviations*: ASCVD atherosclerotic cardiovascular disease, RA rheumatoid arthritis, SLE systemic lupus erythematosus, HIV human immunodeficiency virus, hsCRP high-sensitivity C-reactive protein

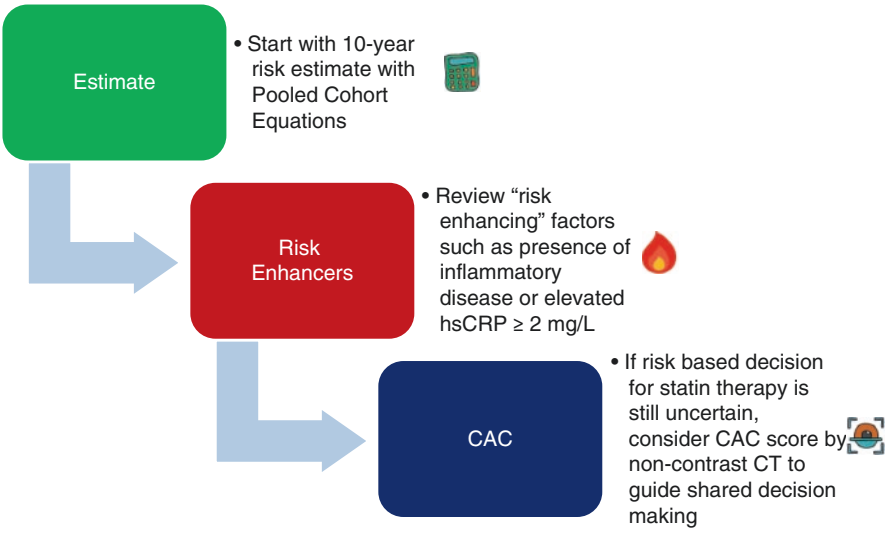

Fig. 13.3 Approach to incorporate inflammation into risk assessment. Abbreviations: ASCVD atherosclerotic cardiovascular disease, hsCRP high-sensitivity C-reactive protein, CAC coronary artery calcium, CT computed tomography

Obesity and Metabolic Syndrome

Research over the past two decades has revealed a close relationship between nutrient excess and activation of the innate immune system in most organs involved in energy homeostasis. Obesity and metabolic disorders are both accompanied by chronic low-grade inflammation (Ebron et al. 2015). Furthermore, inflammation is thought to occur as a consequence of obesity, possibly playing a role in generating insulin resistance in addition to defective insulin secretion.

Adipose depots contain multiple immune cells that maintain the integrity and hormonal sensitivity of adipocytes. However, during obesity, there is a dramatic increase in the number of macrophages, which leads to a more proinflammatory phenotype with subsequent enhanced secretion of cytokines such as TNF-α. Moreover, progressive fat deposition results in visceral obesity, causing a state of hypoxia that triggers necrosis and macrophage infiltration into the adipose tissue, leading to overproduction of adipocytokines. It has also been postulated that the initial trigger of metabolic inflammation is the disturbance of energy homeostasis and that the initial response is adaptive to relieve the anabolic pressure produced by obesity, which over time becomes maladaptive with consequent failure to resolve the initial response to the insult (Saltiel and Olefsky 2017).

Metabolic syndrome is defined as having three or more of the following five factors: increased waist circumference, elevated triglycerides, elevated blood pressure, elevated glucose, and low high-density lipoprotein cholesterol (HDL-C) (Grundy et al. 2004). The 2019 ACC/AHA Primary Prevention Guideline considers

metabolic syndrome to be a "risk-enhancing" factor that would favor initiation of statin therapy for ASCVD prevention (Arnett et al. 2019).

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a highly prevalent autoimmune inflammatory disease, more common among women, which leads to progressive destruction of the joints. RA is associated with a 1.5- to two-fold increased risk of ASCVD, including increased risk of MI and ischemic stroke (Hansildaar et al. 2020). Patients with RA have a lower survival rate compared to the general population, and this decrease in survival rate is attributed to ASCVD (Hansildaar et al. 2020). One meta-analysis including 24 studies and more than 111,000 patients found a 50% increased risk of cardiovascular mortality among patients with RA, including increased risks for both ischemic heart disease and stroke (Avina-Zubieta et al. 2008).

Although traditional cardiovascular risk factors are prevalent in RA and do play a role in the overall CVD risk, adjustments for these risk factors do not fully account for the cardiovascular risk associated with the disease (del Rincon et al. 2001). The chronic inflammation associated with the disease is thought to play a significant role in the heightened risk of ASCVD associated with RA, as patients with frequent flares and uncontrolled disease have a higher burden of ASCVD than those who stay in remission for longer.

As described previously, the pathophysiology of atherosclerosis involves endothelial dysfunction, plaque formation, and plaque destabilization and rupture. In patients with RA, evidence of endothelial dysfunction and atherosclerotic plaque is present early in the disease course (Sandoo et al. 2011). A proposed mechanism to link the exaggerated inflammatory response in RA to the development of atherosclerosis is extensive neutrophil activation via neutrophil extracellular traps (NETs) (Hansildaar et al. 2020). NETosis is a process involving neutrophil cell death in which DNA and cytoplasmic granules are released to eliminate extracellular pathogens and neutralize cytokines. NETs have been noted in atherosclerotic lesions and arterial thrombi in humans and are thought to cause endothelial dysfunction and plaque destabilization and promote thrombotic complications of CAD in many patient populations, including patients with RA (Doring et al. 2020).

Part of the challenge of identifying RA patients at risk for adverse cardiovascular outcomes is that patients with active RA have lower total cholesterol (TC) and LDL-C levels (the "lipid paradox"). The paradoxical lowering of cholesterol levels makes it difficult to estimate the ASCVD risk associated with RA, which utilizes cholesterol levels as part of the algorithm (Skeoch et al. 2017). As such, traditional risk estimation tools including the PCEs that use cholesterol levels underestimate the ASCVD risk in patients with RA. Therefore, the European League Against Rheumatism (EULAR) recommends that the risk approximated by traditional risk scores should be multiplied by 1.5 if a patient meets two out of three criteria

including seropositivity, extra-articular features, and disease duration >10 years (Peters et al. 2010). However, the accuracy of the correction factor remains to be validated.

Recent guidelines have now recognized the increased ASCVD risk among individuals with inflammatory conditions. As mentioned, in the 2019 ACC/AHA guideline for the primary prevention of CVD, RA is considered a "risk-enhancing" factor that would favor the initiation or intensification of statin therapy for ASCVD prevention (Arnett et al. 2019). Patients with RA have a greater prevalence of CAC than controls (Chung et al. 2005). Measurement of CAC in these patients to refine risk estimation can be considered if there is uncertainty regarding initiation of preventive pharmacotherapies such as aspirin and statins.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disorder, also more common in women, characterized by the production of antibodies and multisystem inflammation that damages tissue and organs throughout the body including the joints, kidneys, heart, brain, and skin. Cardiovascular disease is the most common cause of death in patients with SLE (Nossent et al. 2007). SLE patients have a two- to threefold higher risk of MI when compared to the general population (Avina-Zubieta et al. 2017) and an earlier onset of CAD (Asanuma et al. 2003). The pathogenesis of atherosclerosis likely involves an interplay of traditional risk factors and disease-specific inflammatory pathways. Part of the cardiovascular risk associated with SLE is attributable to traditional risk factors (Giannelou and Mavragani 2017). In addition to traditional dyslipidemia, HDL function is compromised with reduced cholesterol efflux capacity and formation of proinflammatory HDL. Furthermore, immunological mechanisms may play a significant role in the development of ASCVD. The initial step in the pathogenesis of atherosclerosis in SLE is thought to involve elevated type 1 interferon levels as part of the disease process, which results in endothelial injury (Liu and Kaplan 2018). In addition, autoantibodies such as anti-oxidized LDL (anti-oxLDL) and anti-β2-glycoprotein I antibodies, NETs, and other innate and adaptive cell signaling pathways may mediate accelerated vascular disease in SLE (Liu and Kaplan 2018). The mechanism and pathogenesis of atherosclerosis in SLE remains to be fully elucidated.

Similar to RA, traditional risk scores also do not account for the increased CVD risk associated with SLE and, as such, SLE is also considered a risk-enhancing factor in the most recent ACC/AHA guidelines (Arnett et al. 2019). Individuals with SLE also have higher CAC scores than individuals without SLE, even after accounting for ASCVD risk factors (Kiani et al. 2015). Thus, a CAC score could be considered to refine ASCVD risk estimation in patients with SLE if risk-based decisions to implement statin therapy were otherwise uncertain, such as those patients with SLE but without LDL-C elevation (Arnett et al. 2019).

Psoriasis

Psoriasis is an inflammatory disease of the skin that affects 2–3% of the world's population (Armstrong et al. 2013). Patients with psoriasis have increased prevalence of endothelial dysfunction and subclinical atherosclerosis (Shaharyar et al. 2014). They also have increased risk of clinical CVD with a higher risk of MI, stroke, and increased overall mortality (Armstrong et al. 2014). One meta-analysis included observational data from 201,239 patients with mild psoriasis and 17,415 with severe psoriasis (Armstrong et al. 2013). The authors reported that severe psoriasis was associated with a 39% increased risk of cardiovascular mortality, a 70% increased risk of MI, and a 56% increased risk of stroke, but even mild psoriasis was associated with a 29% increased risk of MI and a 12% increased risk of stroke (Armstrong et al. 2013).

Similar to RA and SLE, although traditional risk factors play a role, they do not fully account for the CVD risk associated with psoriasis (Takeshita et al. 2017). The overall inflammatory burden of the disease plays a significant role as more severe disease correlated with higher cardiovascular mortality than mild disease (Armstrong et al. 2014). The mechanism of accelerated atherosclerosis in patients with psoriasis is thought to include elevated Th1 and Th17 cytokine pathways (Hu and Lan 2017) and formation of oxidized lipoproteins such as oxidized LDL (oxLDL) and dysfunctional HDL with limited cholesterol efflux capability (Siddiqi and Ridker 2018). In a recent study by Sorokin et al., patients with psoriasis have been noted to have higher oxidized lipoproteins and the level of oxidized lipoproteins correlated with the burden of high-risk plaques (Sorokin et al. 2018). Treatment of psoriasis resulted in improvement of coronary plaque burden as evaluated by imaging modalities (Sorokin et al. 2018). Similar to RA and SLE, psoriasis is also considered a risk-enhancing factor in the 2019 ACC/AHA Primary Prevention Guideline (Arnett et al. 2019).

Human Immunodeficiency Virus (HIV)

With the advent of antiretroviral therapy, CVD has edged forward as the second leading cause of morbidity and mortality among the 35 million people living with HIV today (Shah et al. 2018). In a meta-analysis, patients living with HIV have a twofold greater relative risk of CVD when compared to uninfected individuals, even after accounting for traditional risk factors, lifestyle risk factors, and comorbidities (Kearns et al. 2017). Even in persons with HIV with undetectable viral loads, there is increased coronary atherosclerosis and carotid intima-media thickness with elevated inflammatory markers including high-sensitivity CRP (hsCRP), IL-6, and GlycA, which signify the importance of inflammation as the key mediation of HIV-related cardiovascular disease (Kearns et al. 2017; Tibuakuu et al. 2019). In addition, persons with HIV are noted to have a more vulnerable plaque that is more

prone to rupture, which is thought to be correlated with inflammation as opposed to other traditional risk factors (D'Ascenzo et al. 2015; Post et al. 2014). The pathogenesis of HIV-mediated atherosclerosis, although incompletely understood, likely involves CD8 T-cell activation, leading to endothelial injury, inhibition of monocyte and macrophage cholesterol efflux capacity which leads to accelerated foam cell formation, and generally increased oxidative stress, and inflammasome activation (Kearns et al. 2017).

In the Strategies for Management of Antiretroviral Therapy (SMART) trial, continuous suppression of HIV replication was associated with reduced CVD risk as opposed to intermittent therapy, suggesting a role of viral replication in HIV-related atherogenesis (Titanji et al. 2020). Several medications have been evaluated in small observational studies and randomized clinical trials (RCTs) to determine its effect on reducing inflammatory burden in persons living with HIV. Of these, statins (specifically rosuvastatin, atorvastatin, and pitavastatin), IL-1β inhibitors, and IL-6 inhibitors have suggested effects of reductions of inflammation (Titanji et al. 2020). However, the translation of the reduction in inflammation and its effects on cardiovascular outcomes remain to be elucidated in large blinded RCTs. The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) trial is currently underway and is evaluating whether pitavastatin will reduce the risk of CVD in HIV-infected individuals receiving combination antiretroviral therapy when compared to placebo (Grinspoon et al. 2019). Another RCT evaluating the benefits of canakinumab (an IL-1β inhibitor) in HIV-infected individuals (ClinicalTrials.gov Identifier: NCT02272946) is also ongoing.

Similar to inflammatory autoimmune conditions, traditional risk estimation tools like the PCE also do not adequately capture the increased CVD risk associated with HIV infection, and as such, HIV infection is also considered a "risk-enhancing" factor in the most recent ACC/AHA prevention guideline that would revise ASCVD risk estimation upward (Arnett et al. 2019).

Assessment of Inflammation: Role of Markers and Imaging

Beyond clinical diagnoses of inflammatory conditions, inflammation can be measured in various ways, including the use of plasma markers of inflammation, nuclear imaging, coronary CT angiography (CCTA), and magnetic resonance imaging (MRI) (Table 13.1). These measures are summarized below.

Inflammatory Markers

Part of the challenge of evaluating the overall cardiovascular risk for a patient is that many risk stratification tools do not account for variables, such as inflammation, which are known to play a significant role in atherogenesis. As such, the

Table 13.1 Methods for measuring inflammation

	Blood markers of inflammation	Nuclear imaging	Coronary CT Angiography	Magnetic Resonance Imaging
Prognostic and clinical utility	Independent predictors of ASCVD Represent different pathophysiological mechanisms of the disease	High sensitivity for vascular inflammation Can provide information about plaque activity and stability	Independent predictor of ASCVD Can identify anatomical markers of plaque inflammation	Can assess inflammatory activity within plaque
Limitations	Poor sensitivity for vascular inflammation	Limited availability Radiation exposure Expensive	Operator-dependent	Low sensitivity Requires gadolinium to boost sensitivity Expensive
Strengths	Supported by several epidemiological studies Inexpensive	Marker of disease activity	Widespread availability	Inflammatory activity within plaque

inflammatory biomarkers of CVD can be an additional tool in predicting cardiovascular risk (Sweeney et al. 2021).

hsCRP

The most well studied of these inflammatory biomarkers is the acute-phase reactant, hsCRP, which has been shown to add to traditional risk factors in predicting cardiovascular risk (Ridker et al. 2000; Emerging Risk Factors Collaboration et al. 2012). Indeed, hsCRP predicts ASCVD risk even when LDL-C is not very elevated (Ridker et al. 2008a, 2010; Quispe et al. 2020). The Reynolds Risk Score is a cardiovascular risk calculator that includes hsCRP (Ridker et al. 2007, 2008b). Although the PCE risk estimator does not include hsCRP, in the 2019 ACC/AHA Primary Prevention Guideline, an elevated hsCRP (≥2 mg/L) is considered a "risk-enhancing" factor (Arnett et al. 2019). The Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial demonstrated the benefits of statin therapy for primary prevention of ASCVD among adults with elevated hsCRP ≥2 mg/L but without significant hyperlipidemia (LDL-C < 130 mg/dL) (Ridker et al. 2008a). Further evidence linking hsCRP to the ASCVD risk will be discussed in detail in another chapter of this book.

Monocytes and Neutrophils

Monocytes and neutrophils are linked to CVD (Horne et al. 2005). Monocytes are thought to initiate atherogenesis by reacting with oxidized lipids within the

endothelium and transforming into foam cells. Monocyte counts have been linked to cardiovascular events in patients with CAD (Yamamoto et al. 2016). Neutrophils form NETs, which are thought to be critical to plaque formation and progression (Doring et al. 2020). Several studies have evaluated the use of NET markers, which show potential benefits in evaluating the degree of coronary atherosclerosis and risk stratification of acute coronary syndromes (ACSs) and ischemic strokes (Doring et al. 2020). A recent study used individual cell information including neutrophil and monocyte size, nuclear morphology, and cytoplasmic complexity as markers of cell age and activation state to create a mathematical model, which was then used to risk-stratify patients under evaluation for ACS (Chaudhury et al. 2017). Interestingly, this model identified >70% of patients who initially screened negative but eventually were diagnosed with ACS. This study was small with 120 patients and further work is needed to validate different risk prediction models, but it provides an example of how inflammatory cell count and morphology may be utilized as a personalized risk stratification tool in the world of personalized medicine.

Serum Amyloid A

Serum amyloid A (SAA) is an acute-phase reactant released by tissue macrophages that has been linked to cardiovascular mortality (Shridas and Tannock 2019). Animal studies have suggested that SAA is not just a biomarker but may play a causal role in atherosclerosis by increasing LDL retention in macrophages, leading to atherosclerosis (Shridas and Tannock 2019). SAA has also been linked to HDL function and hypercoagulability. However, the use of SAA remains to be validated in large population studies (Shridas and Tannock 2019).

GlycA

GlycA is a biomarker that is a composite of proton nuclear magnetic resonance (1H-NMR) spectroscopy signals from *N*-acetyl glucosamine residues on acute-phase reactant proteins such as alpha-1-acid glycoprotein (AGP), alpha-1-antitrypsin (AAT), alpha-1-antichymotrypsin (AACT), haptoglobin, and transferrin (Ballout and Remaley 2020). GlycA levels serve as a marker of chronic inflammation as glycan formation is augmented during inflammatory states. Compared to hsCRP, GlycA has less intra- and interassay variability and does not vary as significantly between the sexes as does hsCRP (Benson et al. 2018). Given that GlycA measures the extent and complexity of *N*-glycosylation of various plasma proteins, it provides insights into the overall inflammatory status in the body. As such, GlycA can be considered the inflammatory analogue that hemoglobin A1c is for glucose control (Ballout and Remaley 2020).

GlycA has been associated with increased prevalence of subclinical atherosclerosis, even after adjusting for other inflammatory markers (Tibuakuu et al. 2019; Ezeigwe et al. 2019; Fashanu et al. 2019). Several studies have linked GlycA levels

with future CVD events and CVD mortality, even after adjusting for traditional risk factors. The Women's Health Study (WHS) was the first to demonstrate a positive graded correlation between GlycA levels and future CVD events (Akinkuolie et al. 2014). Similar correlations were noted in the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study (Gruppen et al. 2015), the Multi-Ethnic Study of Atherosclerosis (MESA) study (Duprez et al. 2016), and a post host analysis of the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial (Akinkuolie et al. 2016). In the biorepository samples of the Catheterization Genetics (CATHGEN) study including over 7000 participants undergoing cardiac catheterization, GlycA levels were also correlated with the extent of CAD (McGarrah et al. 2017). In addition to ASCVD events, GlycA has been linked with incident heart failure, particularly heart failure with preserved ejection fraction (Jang et al. 2020), peripheral arterial disease (Fashanu et al. 2019), carotid plaque (Fashanu et al. 2019), valvular and aortic calcification (Ezeigwe et al. 2019), and coronary artery calcification (Tibuakuu et al. 2019). GlycA has also been linked to all-cause mortality including CVD mortality even after adjusting for other inflammatory markers such as hsCRP and IL-6 (Ballout and Remaley 2020). Future studies are needed to help define the role of GlycA testing as a predictor of cardiovascular risk in clinical practice.

Imaging

Nuclear Imaging

Uptake of radiotracers within plaques in positron emission tomography (PET)/CT imaging can provide functional information about plaque activity and stability (MacAskill et al. 2019). PET studies of inflammation have largely targeted glucose metabolism using [^{18}F]-fluorodeoxyglucose ([^{18}F]FDG), which has been shown to identify active atherosclerotic plaques within the carotid artery in symptomatic patients (MacAskill et al. 2019). In addition, [^{18}F]FDG uptake in the ascending aorta has been shown to predict development of ASCVD beyond the predictive value of the Framingham Risk Score. However, the indiscriminate nature of [^{18}F]FDG uptake by surrounding metabolically active cells limits the ability to differentiate between stable and vulnerable plaques (MacAskill et al. 2019). As such, several other tracers have been developed that may be beneficial in identifying inflammatory atherosclerosis.

The translocator protein (TSPO) is a highly expressed protein on the mitochondria of macrophages and is responsible for cholesterol transport and steroid synthesis (MacAskill et al. 2019). Targeting TSPO is one of the most widely utilized PET imaging approaches for inflammation. TSPO has been used to detect neuroinflammation, and one clinical study has shown that the [11C]PK11195 tracer can identify culprit plaques in symptomatic patients with cerebrovascular events with a sensitivity of 78% and specificity of 74% (Gaemperli et al. 2012).

^{68}Ga-DOTA-(Tyr^{3})-octreotide (^{68}Ga-DOTATATE) is a radiotracer that targets upregulated somatostatin receptor subtype 2 (SST2) on activated macrophages (Haider et al. 2021). Prior studies have shown a relationship between CVD risk factors, CAC burden, and uptake of ^{68}Ga-DOTATATE (Haider et al. 2021). In a prospective study, ^{68}Ga-DOTATATE was used to differentiate between high- and low-risk atherosclerotic plaques (Tarkin et al. 2017) and has been shown to be superior to [^{18}F]FDG-PET in identifying high-risk plaques (Tarkin et al. 2017).

PET imaging with [^{18}F]-sodium fluoride ([^{18}F]NaF) is the only modality that reliably identifies microcalcifications within plaques, which is a feature of plaque instability as opposed to macrocalcification, which confers plaque stability. Plaques that demonstrate increased [^{18}F]NaF uptake have multiple high-risk features including microcalcification, positive remodeling, and a large necrotic core. In a prospective study, [^{18}F]NaF uptake within coronary plaque was linked to a higher rate of cardiovascular events (Dweck et al. 2016). The Prediction of Recurrent Events with 18F-Flouride (PRE18FFIR) trial is currently underway and will help elucidate the link between [^{18}F]NaF uptake within coronary plaques and prediction of coronary events (Clinical Trial No. NCT02278211).

Several other radiotracer targets including chemokine receptor 4, folate receptor B, and cyclooxygenases 1 and 2 and markers of intraplaque hemorrhage may prove valuable in the detection of inflammatory atherosclerosis (MacAskill et al. 2019). Prospective trials evaluating the relationship between detection of plaque inflammation using nuclear tracers and clinical events are necessary to further improve risk prediction algorithms and for targeted treatment strategies.

Coronary CT Angiography

Coronary CT angiography has been used to identify vulnerable plaques in patients with inflammatory disease. Key features of a vulnerable plaque are inflammation, a large lipid-rich necrotic core with a thin or ruptured overlying fibrous cap, and intraplaque hemorrhage (Abdelrahman et al. 2020). The features on CCTA that correlate with the features of vulnerable plaque include positive remodeling, low-attenuation plaque, spotty calcification, and the napkin ring sign (central low-attenuation area surrounded by an open ring area of high attenuation). In persons living with HIV, a study correlated the signs of arterial inflammation as assessed by [^{18}F]FDG-PET to high-risk plaque features in CCTA (Tawakol et al. 2014).

More recently, the perivascular fat attenuation index (FAI) has been paired with CCTA to visualize and quantify inflammation in the coronary arteries, which may aid in identifying vulnerable plaques and help predict future cardiovascular events (Oikonomou et al. 2018). The perivascular FAI is based on the principle that perivascular adipocytes respond to coronary inflammation as the first step in atherogenesis by changes that inhibit adipogenesis. The FAI has been used to enhance risk

prediction models and to track changes in inflammation with treatment. As such, the FAI and CCTA may prove to be valuable tools for personalizing prevention and treatment of ASCVD. More details about CCTA can be found in another chapter in this book.

Magnetic Resonance Imaging

Magnetic resonance imaging uses the variation in the distribution of water to create high-resolution images. Although MRI has high resolution, it has low sensitivity, requiring significant differences between structures to visualize on imaging. Therefore, gadolinium is often required to boost the sensitivity of images. However, several aspects of a plaque require additional contrast agents to visualize the presence of inflammation within the plaque (Rudd et al. 2009). Given the role that macrophages play in the destabilization of plaques, contrast agents that target macrophage activity provide a window into the inflammatory activity within a plaque (Dweck et al. 2016).

Ultrasmall superparamagnetic particles of iron oxide (USPIO) is a contrast agent that is taken up by macrophages within plaques via scavenger receptors, which improves contrast on T2 images and identifies the presence of inflammation within the plaques (Tang et al. 2008). USPIO has been used to visualize inflammatory activity within carotid plaque and to show decrease in inflammatory activity with statin therapy (Tang et al. 2009). Superparamagnetic iron oxide nanoparticles that target macrophage ligands and gadolinium-loaded immunomicelles that target the macrophage scavenger receptor also have benefits in visualizing plaques. MRI using a fluorine isotope has emerged as an imaging modality with high sensitivity and specificity for imaging inflammation within plaques in preclinical studies.

Therapeutic Targeting of Inflammation for Cardiovascular Risk Reduction

In addition to several nonpharmacological options to reduce inflammation and ASCVD risk (i.e., healthy diet, regular physical activity and exercise, maintenance of a normal BMI, and smoking cessation), pharmacological therapeutics have been of recent interest (Fig. 13.4). For instance, statins are known to have pleiotropic effects and to lower inflammation dependent and independently of lipid lowering (Asher and Houston 2007). More recently, nonstatin, targeted therapeutics have gained interest and several trials have targeted inflammation via different pathways. Although these trials were conducted in a secondary prevention population, they do provide supportive evidence for the causal role of inflammation in atherogenesis.

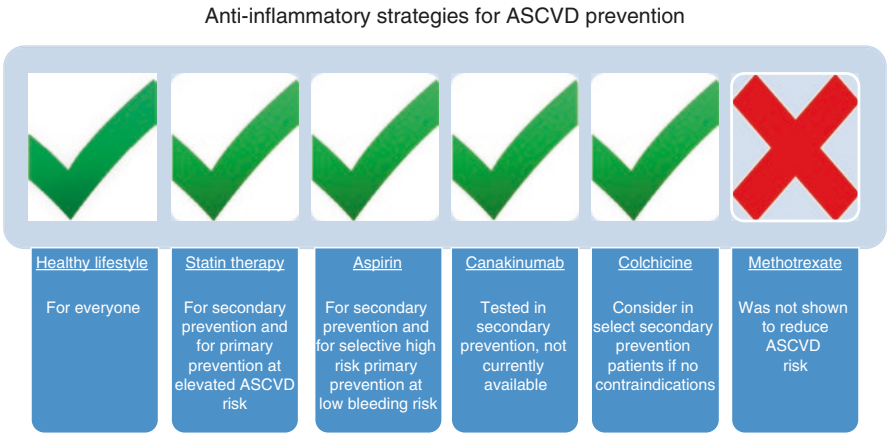

Fig. 13.4 Anti-inflammatory strategies for atherosclerotic cardiovascular disease. *Abbreviations*: ASCVD atherosclerotic cardiovascular disease

IL-1β Inhibition

IL-1β is a potent proinflammatory cytokine that promotes atherogenesis through direct vascular effects, such as leukocyte adhesion to endothelial cells, reduced smooth muscle proliferation, and production of collagenase secretion, and also by stimulating the production of IL-6, which in turn leads to the release of CRP (Ridker 2016). Canakinumab is a human monoclonal antibody that is highly specific for IL-1β and is currently approved by the Food and Drug Administration (FDA) for cryopyrin-associated periodic syndromes and systemic juvenile idiopathic arthritis.

The Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS) trial assessed whether reducing residual inflammation in patients with a prior MI would help reduce the risk of ASCVD events (Ridker et al. 2017). In CANTOS, 10,061 stable post-MI patients with subclinical inflammation (hsCRP ≥2 mg/L) treated with canakinumab had a 15% reduction in nonfatal MI, nonfatal stroke, and cardiovascular death (Ridker et al. 2017). Of note, despite the lack of reduction in LDL-C with canakinumab, the relative risk reduction observed in CANTOS was similar to that observed in the cardiovascular outcome trials of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (which reduce LDL-C by ~60%). Thus, CANTOS provided mechanistic evidence that targeting the IL-1 to IL-6 pathway of innate immunity has significant potential for targeted treatment of atherosclerosis (Ridker 2018). A post hoc analysis from CANTOS found that those patients assigned to canakinumab who achieved an on-treatment hsCRP level < 2 mg/L at 3 months had a lower risk of cardiovascular mortality and all-cause mortality than those who remained with a hsCRP ≥2 (Ridker et al. 2018), although methodological concerns were raised for a "responders" analysis and potential for residual confounding (Michos and Blumenthal 2018; Cardoso et al.

2018). Canakinumab is not FDA approved for ASCVD secondary prevention, so it likely will not be tested for primary ASCVD prevention either. However, CANTOS provided the critical proof of concept that reducing inflammation via IL-1β inhibition can reduce cardiovascular events independent of lipid lowering, reaffirming the inflammation hypothesis.

IL-6 Inhibition

Inhibition of IL-6, which is downstream from IL-1β, is also being tested as a therapeutic strategy for ASCVD prevention. In the Trial to Evaluate Reduction in Inflammation in Patients With Advanced Chronic Renal Disease Utilizing Antibody Mediated IL-6 Inhibition (*RESCUE*), the IL-6 inhibitor ziltivekimab was found to reduce markers of inflammation and thrombosis as well as lipoprotein (a) (Ridker et al. 2021). These findings have led to an ongoing cardiovascular outcome trial, which is testing whether ziltivekimab can reduce major adverse cardiovascular events among patients with chronic kidney disease (CKD), ASCVD, and hsCRP ≥2 mg/L (NCT05021835). While the ZEUS (A Research Study to Look at How Ziltivekimab Works Compared to Placebo in People With Cardiovascular Disease, Chronic Kidney Disease and Inflammation) trial is a secondary prevention trial, if the results are successful, it may be informative for other high-risk primary prevention patients such as those with CKD.

Colchicine

Colchicine dampens inflammatory pathways by inhibiting microtubule polymerization and impairing cell adhesion and activation. In addition, it modulates the gene expression of inflammasome components triggered by deposition of cholesterol crystals.

The Low-Dose Colchicine (LoDoCo) trial was a secondary prevention trial that demonstrated that patients with stable CAD who were treated with colchicine had a 67% relative risk reduction of the composite primary endpoint (incident ACS, cardiac arrest, and noncardioembolic ischemic stroke) (Nidorf et al. 2013). The LoDoCo-2 trial similarly showed that patients with stable CAD who were treated with colchicine had a 31% risk reduction in the composite primary outcome (cardiovascular death, nonprocedural MI, ischemic stroke, or ischemia-driven coronary revascularization) (Nidorf et al. 2020). In the Colchicine Cardiovascular Outcomes Trial (COLCOT) trial, patients with a recent MI (within 30 days prior to randomization) who were treated with colchicine had a 23% reduction in risk of the composite primary endpoint of cardiovascular death, cardiac arrest, MI, stroke, or urgent hospitalization for revascularization (Tardif et al. 2019).

Colchicine could therefore provide an important adjunctive therapy for high-risk patients; however, its use may be contraindicated in patients with significant kidney dysfunction given its renal excretion. While colchicine's role in primary ASCVD prevention for high-risk patients has not yet been established, these secondary prevention trials again provide supportive evidence of the causal role that inflammation plays in atherothrombosis.

Low-Dose Methotrexate

Methotrexate is a folic acid antagonist that was originally developed as a chemotherapeutic agent and used at low doses as an anti-inflammatory agent in patients with rheumatoid arthritis or psoriasis. Prior observational data showed a substantial reduction in cardiovascular mortality in patients with rheumatoid arthritis treated with methotrexate versus other conventional disease-modifying antirheumatic therapies (Choi et al. 2002; Naranjo et al. 2008).

Methotrexate was therefore postulated as a low-cost alternative to canakinumab to reduce inflammation. The Cardiovascular Inflammation Reduction Trial (CIRT) randomized 4786 patients with a history of MI or multivessel CAD and type 2 diabetes mellitus or metabolic syndrome to either low-dose methotrexate (target dose of 15–20 mg weekly) or placebo. After a median follow-up of 2.3 years, it was terminated early given that the study met a prespecified threshold for futility on the primary outcome of major adverse cardiovascular events. It was then concluded that low-dose methotrexate may not reduce the risk of incident ASCVD in patient populations other than those with rheumatologic conditions (Ridker et al. 2019).

It should be noted that low-dose methotrexate failed to reduce plasma levels of hsCRP, IL-1β, and IL-6. In addition, the CIRT included patients with lower LDL-C and lower inflammatory markers. The differing results between the trials were attributed to the differing mechanisms of action of canakinumab and methotrexate. Whereas the former directly inhibited the IL-1β pathway and reduced its downstream mediators (IL-6 and CRP), the latter reduced inflammation without effect on these cytokines. As such, the CIRT provided informative data that support the concept that adequate inhibition of the IL-1β to Il-6 pathway of innate immunity is necessary to produce long-term cardiovascular benefits.

Nonsteroidal Anti-inflammatory Drugs

While inflammation has been confirmed to be directly involved in the pathogenesis of ASCVD, not all inhibitors of inflammation can reduce ASCVD, as the CIRT demonstrated. For example, the commonly used nonsteroidal anti-inflammatory drugs (NSAIDS) and cyclooxygenase-2 inhibitors (coxibs) have been associated with increased cardiovascular risks rather than benefits (Martin Arias et al. 2019).

Conclusions

Incontrovertible evidence supports the relevance of inflammatory pathways in atherogenesis. The ASCVD risk attributed to inflammation can be most appreciated in patients with chronic inflammatory conditions. The presence of an inflammatory condition (such as RA, SLE, psoriasis, HIV infection) or the presence of an elevated hsCRP level ≥ 2 mg/L have been recently highlighted in the 2019 ACC/AHA Primary Prevention Guideline as "risk-enhancing" factors that would upgrade patients at borderline or intermediate estimated risk into a higher risk category that would favor initiation of statin therapy for ASCVD prevention, after a clinician–patient risk discussion. Inflammatory biomarkers have entered clinical practice and help refine risk estimation. Targeting inflammation is reaching clinical maturity with promising results from trials of anti-inflammatory agents that have significant potential to reduce the development of atherosclerosis and maximize risk reduction in high-risk patients. However, at this point, the use of any targeted anti-inflammatory agent should be considered only as an adjunct to statin therapy – or other more intensive LDL-C-lowering therapies in secondary prevention. Beyond statins and aspirin, no other anti-inflammatory pharmacotherapy has been demonstrated to have benefits for primary ASCVD prevention. Continued emphasis on following a healthy lifestyle throughout the lifespan is paramount to primordial, primary, and secondary prevention.

References

Abdelrahman KM, Chen MY, Dey AK, Virmani R, Finn AV, Khamis RY, et al. Coronary computed tomography angiography from clinical uses to emerging technologies: JACC state-of-the-art review. J Am Coll Cardiol. 2020;76(10):1226–43.

Akinkuolie AO, Buring JE, Ridker PM, Mora S. A novel protein glycan biomarker and future cardiovascular disease events. J Am Heart Assoc. 2014;3(5):e001221.

Akinkuolie AO, Glynn RJ, Padmanabhan L, Ridker PM, Mora S. Circulating N-linked glycoprotein side-chain biomarker, rosuvastatin therapy, and incident cardiovascular disease: an analysis from the JUPITER Trial. J Am Heart Assoc. 2016;5(7):e003822.

Alfaddagh A, Martin SS, Leucker TM, Michos ED, Blaha MJ, Lowenstein CJ, et al. Inflammation and cardiovascular disease: from mechanisms to therapeutics. Am J Prev Cardiol. 2020;4:100130.

Armstrong EJ, Harskamp CT, Armstrong AW. Psoriasis and major adverse cardiovascular events: a systematic review and meta-analysis of observational studies. J Am Heart Assoc. 2013;2(2):e000062.

Armstrong AW, Brezinski EA, Follansbee MR, Armstrong EJ. Effects of biologic agents and other disease-modifying antirheumatic drugs on cardiovascular outcomes in psoriasis and psoriatic arthritis: a systematic review. Curr Pharm Des. 2014;20(4):500–12.

Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. Circulation. 2019;140(11):e596–646.

Asanuma Y, Oeser A, Shintani AK, Turner E, Olsen N, Fazio S, et al. Premature coronary-artery atherosclerosis in systemic lupus erythematosus. N Engl J Med. 2003;349(25):2407–15.

Asher J, Houston M. Statins and C-reactive protein levels. J Clin Hypertens. 2007;9(8):622–8.

Avina-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis Rheum. 2008;59(12):1690–7.

Avina-Zubieta JA, To F, Vostretsova K, De Vera M, Sayre EC, Esdaile JM. Risk of myocardial infarction and stroke in newly diagnosed systemic lupus erythematosus: a general population-based study. Arthritis Care Res. 2017;69(6):849–56.

Ballout RA, Remaley AT. GlycA: a new biomarker for systemic inflammation and cardiovascular disease (CVD) risk assessment. J Lab Precis Med. 2020;5:17.

Benson EA, Tibuakuu M, Zhao D, Akinkuolie AO, Otvos JD, Duprez DA, et al. Associations of ideal cardiovascular health with GlycA, a novel inflammatory marker: the multi-ethnic study of atherosclerosis. Clin Cardiol. 2018;41(11):1439–45.

Cardoso R, Kaul S, Okada DR, Blumenthal RS, Michos ED. A deeper dive into the CANTOS "Responders" substudy. Mayo Clin Proc. 2018;93(7):830–3.

Chaudhury A, Noiret L, Higgins JM. White blood cell population dynamics for risk stratification of acute coronary syndrome. Proc Natl Acad Sci U S A. 2017;114(46):12344–9.

Choi HK, Hernan MA, Seeger JD, Robins JM, Wolfe F. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. Lancet. 2002;359(9313):1173–7.

Chung CP, Oeser A, Raggi P, Gebretsadik T, Shintani AK, Sokka T, et al. Increased coronary-artery atherosclerosis in rheumatoid arthritis: relationship to disease duration and cardiovascular risk factors. Arthritis Rheum. 2005;52(10):3045–53.

D'Ascenzo F, Cerrato E, Calcagno A, Grossomarra W, Ballocca F, Omede P, et al. High prevalence at computed coronary tomography of non-calcified plaques in asymptomatic HIV patients treated with HAART: a meta-analysis. Atherosclerosis. 2015;240(1):197–204.

del Rincon ID, Williams K, Stern MP, Freeman GL, Escalante A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. Arthritis Rheum. 2001;44(12):2737–45.

Doring Y, Libby P, Soehnlein O. Neutrophil extracellular traps participate in cardiovascular diseases: recent experimental and clinical insights. Circ Res. 2020;126(9):1228–41.

Dorsheimer L, Assmus B, Rasper T, Ortmann CA, Ecke A, Abou-El-Ardat K, et al. Association of mutations contributing to clonal hematopoiesis with prognosis in chronic ischemic heart failure. JAMA Cardiol. 2019;4(1):25–33.

Duprez DA, Otvos J, Sanchez OA, Mackey RH, Tracy R, Jacobs DR Jr. Comparison of the predictive value of GlycA and other biomarkers of inflammation for total death, incident cardiovascular events, noncardiovascular and noncancer inflammatory-related events, and total cancer events. Clin Chem. 2016;62(7):1020–31.

Dweck MR, Aikawa E, Newby DE, Tarkin JM, Rudd JH, Narula J, et al. Noninvasive molecular imaging of disease activity in atherosclerosis. Circ Res. 2016;119(2):330–40.

Ebron K, Andersen CJ, Aguilar D, Blesso CN, Barona J, Dugan CE, et al. A larger body mass index is associated with increased atherogenic dyslipidemia, insulin resistance, and low-grade inflammation in individuals with metabolic syndrome. Metab Syndr Relat Disord. 2015;13(10):458–64.

Emerging Risk Factors Collaboration, Kaptoge S, Di Angelantonio E, Pennells L, Wood AM, White IR, et al. C-reactive protein, fibrinogen, and cardiovascular disease prediction. N Engl J Med. 2012;367(14):1310–20.

Ezeigwe A, Fashanu OE, Zhao D, Budoff MJ, Otvos JD, Thomas IC, et al. The novel inflammatory marker GlycA and the prevalence and progression of valvular and thoracic aortic calcification: the multi-ethnic study of atherosclerosis. Atherosclerosis. 2019;282:91–9.

Fashanu OE, Oyenuga AO, Zhao D, Tibuakuu M, Mora S, Otvos JD, et al. GlycA, a novel inflammatory marker and its association with peripheral arterial disease and carotid plaque: the multi-ethnic study of atherosclerosis. Angiology. 2019;70(8):737–46.

Fernandez-Friera L, Fuster V, Lopez-Melgar B, Oliva B, Garcia-Ruiz JM, Mendiguren J, et al. Normal LDL-cholesterol levels are associated with subclinical atherosclerosis in the absence of risk factors. J Am Coll Cardiol. 2017;70(24):2979–91.

Ferrucci L, Corsi A, Lauretani F, Bandinelli S, Bartali B, Taub DD, et al. The origins of age-related proinflammatory state. Blood. 2005;105(6):2294–9.

Furman D, Chang J, Lartigue L, Bolen CR, Haddad F, Gaudilliere B, et al. Expression of specific inflammasome gene modules stratifies older individuals into two extreme clinical and immunological states. Nat Med. 2017;23(2):174–84.

Fuster JJ, MacLauchlan S, Zuriaga MA, Polackal MN, Ostriker AC, Chakraborty R, et al. Clonal hematopoiesis associated with TET2 deficiency accelerates atherosclerosis development in mice. Science. 2017;355(6327):842–7.

Gaemperli O, Shalhoub J, Owen DR, Lamare F, Johansson S, Fouladi N, et al. Imaging intraplaque inflammation in carotid atherosclerosis with 11C-PK11195 positron emission tomography/computed tomography. Eur Heart J. 2012;33(15):1902–10.

Giannelou M, Mavragani CP. Cardiovascular disease in systemic lupus erythematosus: a comprehensive update. J Autoimmun. 2017;82:1–12.

Goldstein JL, Brown MS. A century of cholesterol and coronaries: from plaques to genes to statins. Cell. 2015;161(1):161–72.

Grinspoon SK, Fitch KV, Overton ET, Fichtenbaum CJ, Zanni MV, Aberg JA, et al. Rationale and design of the randomized trial to prevent vascular events in HIV (REPRIEVE). Am Heart J. 2019;212:23–35.

Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C, American Heart A, et al. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation. 2004;109(3):433–8.

Gruppen EG, Riphagen IJ, Connelly MA, Otvos JD, Bakker SJ, Dullaart RP. GlycA, a pro-inflammatory glycoprotein biomarker, and incident cardiovascular disease: relationship with C-reactive protein and renal function. PLoS One. 2015;10(9):e0139057.

Haider A, Bengs S, Gebhard C. Imaging inflammation in atherosclerosis: exploring all avenues. J Nucl Cardiol. 2021;28(6):2514–7.

Hansildaar R, Vedder D, Baniaamam M, Tausche AK, Gerritsen M, Nurmohamed MT. Cardiovascular risk in inflammatory arthritis: rheumatoid arthritis and gout. Lancet Rheumatol. 2020;3:e58.

Horne BD, Anderson JL, John JM, Weaver A, Bair TL, Jensen KR, et al. Which white blood cell subtypes predict increased cardiovascular risk? J Am Coll Cardiol. 2005;45(10):1638–43.

Hu SC, Lan CE. Psoriasis and cardiovascular comorbidities: focusing on severe vascular events, cardiovascular risk factors and implications for treatment. Int J Mol Sci. 2017;18(10):2211.

Hulin A, Hego A, Lancellotti P, Oury C. Advances in pathophysiology of calcific aortic valve disease propose novel molecular therapeutic targets. Front Cardiovasc Med. 2018;5:21.

Jaiswal S, Libby P. Clonal haematopoiesis: connecting ageing and inflammation in cardiovascular disease. Nat Rev Cardiol. 2020;17(3):137–44.

Jaiswal S, Fontanillas P, Flannick J, Manning A, Grauman PV, Mar BG, et al. Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med. 2014;371(26):2488–98.

Jaiswal S, Natarajan P, Silver AJ, Gibson CJ, Bick AG, Shvartz E, et al. Clonal hematopoiesis and risk of atherosclerotic cardiovascular disease. N Engl J Med. 2017;377(2):111–21.

Jang S, Ogunmoroti O, Ndumele CE, Zhao D, Rao VN, Fashanu OE, et al. Association of the novel inflammatory marker GlycA and incident heart failure and its subtypes of preserved and reduced ejection fraction: the multi-ethnic study of atherosclerosis. Circ Heart Fail. 2020;13(8):e007067.

Kearns A, Gordon J, Burdo TH, Qin X. HIV-1-associated atherosclerosis: unraveling the missing link. J Am Coll Cardiol. 2017;69(25):3084–98.

Khera AV, Emdin CA, Drake I, Natarajan P, Bick AG, Cook NR, et al. Genetic risk, adherence to a healthy lifestyle, and coronary disease. N Engl J Med. 2016;375(24):2349–58.

Kiani AN, Magder LS, Post WS, Szklo M, Bathon JM, Schreiner PJ, et al. Coronary calcification in SLE: comparison with the multi-ethnic study of atherosclerosis. Rheumatology. 2015;54(11):1976–81.

Libby P, Loscalzo J, Ridker PM, Farkouh ME, Hsue PY, Fuster V, et al. Inflammation, immunity, and infection in Atherothrombosis: JACC review topic of the week. J Am Coll Cardiol. 2018;72(17):2071–81.

Liu Y, Kaplan MJ. Cardiovascular disease in systemic lupus erythematosus: an update. Curr Opin Rheumatol. 2018;30(5):441–8.

MacAskill MG, Newby DE, Tavares AAS. Frontiers in positron emission tomography imaging of the vulnerable atherosclerotic plaque. Cardiovasc Res. 2019;115(14):1952–62.

Martin Arias LH, Martin Gonzalez A, Sanz Fadrique R, Vazquez ES. Cardiovascular risk of non-steroidal anti-inflammatory drugs and classical and selective cyclooxygenase-2 inhibitors: a meta-analysis of observational studies. J Clin Pharmacol. 2019;59(1):55–73.

McGarrah RW, Kelly JP, Craig DM, Haynes C, Jessee RC, Huffman KM, et al. A novel protein glycan-derived inflammation biomarker independently predicts cardiovascular disease and modifies the association of HDL subclasses with mortality. Clin Chem. 2017;63(1):288–96.

Michos ED, Blumenthal RS. Treatment concentration of high-sensitivity C-reactive protein. Lancet. 2018;391(10118):287–9.

Michos ED, Blaha MJ, Blumenthal RS. Use of the coronary artery calcium score in discussion of initiation of statin therapy in primary prevention. Mayo Clin Proc. 2017;92(12):1831–41.

Naranjo A, Sokka T, Descalzo MA, Calvo-Alen J, Horslev-Petersen K, Luukkainen RK, et al. Cardiovascular disease in patients with rheumatoid arthritis: results from the QUEST-RA study. Arthritis Res Ther. 2008;10(2):R30.

Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL. Low-dose colchicine for secondary prevention of cardiovascular disease. J Am Coll Cardiol. 2013;61(4):404–10.

Nidorf SM, Fiolet ATL, Mosterd A, Eikelboom JW, Schut A, Opstal TSJ, et al. Colchicine in patients with chronic coronary disease. N Engl J Med. 2020;383(19):1838–47.

Nossent J, Cikes N, Kiss E, Marchesoni A, Nassonova V, Mosca M, et al. Current causes of death in systemic lupus erythematosus in Europe, 2000–2004: relation to disease activity and damage accrual. Lupus. 2007;16(5):309–17.

Oikonomou EK, Marwan M, Desai MY, Mancio J, Alashi A, Hutt Centeno E, et al. Non-invasive detection of coronary inflammation using computed tomography and prediction of residual cardiovascular risk (the CRISP CT study): a post-hoc analysis of prospective outcome data. Lancet. 2018;392(10151):929–39.

Peters MJ, Symmons DP, McCarey D, Dijkmans BA, Nicola P, Kvien TK, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Ann Rheum Dis. 2010;69(2):325–31.

Post WS, Budoff M, Kingsley L, Palella FJ Jr, Witt MD, Li X, et al. Associations between HIV infection and subclinical coronary atherosclerosis. Ann Intern Med. 2014;160(7):458–67.

Quispe R, Michos ED, Martin SS, Puri R, Toth PP, Al Suwaidi J, et al. High-sensitivity C-reactive protein discordance with Atherogenic lipid measures and incidence of atherosclerotic cardiovascular disease in primary prevention: the ARIC study. J Am Heart Assoc. 2020;9(3):e013600.

Ridker PM. From C-reactive protein to interleukin-6 to interleukin-1: moving upstream to identify novel targets for atheroprotection. Circ Res. 2016;118(1):145–56.

Ridker PM. Clinician's guide to reducing inflammation to reduce Atherothrombotic risk: JACC review topic of the week. J Am Coll Cardiol. 2018;72(25):3320–31.

Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med. 2000;342(12):836–43.

Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. JAMA. 2007;297(6):611–9.

Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008a;359(21):2195–207.

Ridker PM, Paynter NP, Rifai N, Gaziano JM, Cook NR. C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds Risk Score for men. Circulation. 2008b;118(22):2243–51.

Ridker PM, MacFadyen J, Libby P, Glynn RJ. Relation of baseline high-sensitivity C-reactive protein level to cardiovascular outcomes with rosuvastatin in the Justification for Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER). Am J Cardiol. 2010;106(2):204–9.

Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory therapy with Canakinumab for atherosclerotic disease. N Engl J Med. 2017;377(12):1119–31.

Ridker PM, MacFadyen JG, Everett BM, Libby P, Thuren T, Glynn RJ, et al. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. Lancet. 2018;391(10118):319–28.

Ridker PM, Everett BM, Pradhan A, MacFadyen JG, Solomon DH, Zaharris E, et al. Low-dose methotrexate for the prevention of atherosclerotic events. N Engl J Med. 2019;380(8):752–62.

Ridker PM, Devalaraja M, Baeres FMM, Engelmann MDM, Hovingh GK, Ivkovic M, et al. IL-6 inhibition with ziltivekimab in patients at high atherosclerotic risk (RESCUE): a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet. 2021;397(10289):2060–9.

Rudd JH, Hyafil F, Fayad ZA. Inflammation imaging in atherosclerosis. Arterioscler Thromb Vasc Biol. 2009;29(7):1009–16.

Saltiel AR, Olefsky JM. Inflammatory mechanisms linking obesity and metabolic disease. J Clin Invest. 2017;127(1):1–4.

Sandoo A, Veldhuijzen van Zanten JJ, Metsios GS, Carroll D, Kitas GD. Vascular function and morphology in rheumatoid arthritis: a systematic review. Rheumatology. 2011;50(11):2125–39.

Shah ASV, Stelzle D, Lee KK, Beck EJ, Alam S, Clifford S, et al. Global burden of atherosclerotic cardiovascular disease in people living with HIV: systematic review and meta-analysis. Circulation. 2018;138(11):1100–12.

Shaharyar S, Warraich H, McEvoy JW, Oni E, Ali SS, Karim A, et al. Subclinical cardiovascular disease in plaque psoriasis: association or causal link? Atherosclerosis. 2014;232(1):72–8.

Shridas P, Tannock LR. Role of serum amyloid A in atherosclerosis. Curr Opin Lipidol. 2019;30(4):320–5.

Siddiqi HK, Ridker PM. Psoriasis and atherosclerosis. Circ Res. 2018;123(11):1183–4.

Skeoch S, Cristinacce PLH, Williams H, Pemberton P, Xu D, Sun J, et al. Imaging atherosclerosis in rheumatoid arthritis: evidence for increased prevalence, altered phenotype and a link between systemic and localised plaque inflammation. Sci Rep. 2017;7(1):827.

Sorokin AV, Kotani K, Elnabawi YA, Dey AK, Sajja AP, Yamada S, et al. Association between oxidation-modified lipoproteins and coronary plaque in psoriasis. Circ Res. 2018;123(11):1244–54.

Sverdlov AL, Ngo DT, Chapman MJ, Ali OA, Chirkov YY, Horowitz JD. Pathogenesis of aortic stenosis: not just a matter of wear and tear. Am J Cardiovasc Dis. 2011;1(2):185–99.

Sweeney T, Quispe R, Das T, Juraschek SP, Martin SS, Michos ED. The use of blood biomarkers in precision medicine for the primary prevention of atherosclerotic cardiovascular disease: a review. Exp Rev Precis Med Drug Dev. 2021;6(4):247–58.

Takeshita J, Grewal S, Langan SM, Mehta NN, Ogdie A, Van Voorhees AS, et al. Psoriasis and comorbid diseases: epidemiology. J Am Acad Dermatol. 2017;76(3):377–90.

Tang TY, Howarth SP, Li ZY, Miller SR, Graves MJ, JM UK-I, et al. Correlation of carotid atheromatous plaque inflammation with biomechanical stress: utility of USPIO enhanced MR imaging and finite element analysis. Atherosclerosis. 2008;196(2):879–87.

Tang TY, Howarth SP, Miller SR, Graves MJ, Patterson AJ, JM UK-I, et al. The ATHEROMA (Atorvastatin Therapy: Effects on Reduction of Macrophage Activity) Study. Evaluation using

ultrasmall superparamagnetic iron oxide-enhanced magnetic resonance imaging in carotid disease. J Am Coll Cardiol. 2009;53(22):2039–50.

Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. N Engl J Med. 2019;381(26):2497–505.

Tarkin JM, Joshi FR, Evans NR, Chowdhury MM, Figg NL, Shah AV, et al. Detection of atherosclerotic inflammation by (68)Ga-DOTATATE PET compared to [(18)F]FDG PET imaging. J Am Coll Cardiol. 2017;69(14):1774–91.

Tawakol A, Lo J, Zanni MV, Marmarelis E, Ihenachor EJ, MacNabb M, et al. Increased arterial inflammation relates to high-risk coronary plaque morphology in HIV-infected patients. J Acquir Immune Defic Syndr. 2014;66(2):164–71.

Tibuakuu M, Fashanu OE, Zhao D, Otvos JD, Brown TT, Haberlen SA, et al. GlycA, a novel inflammatory marker, is associated with subclinical coronary disease. AIDS. 2019;33(3):547–57.

Titanji B, Gavegnano C, Hsue P, Schinazi R, Marconi VC. Targeting inflammation to reduce atherosclerotic cardiovascular risk in people with HIV infection. J Am Heart Assoc. 2020;9(3):e014873.

Yamamoto E, Sugiyama S, Hirata Y, Tokitsu T, Tabata N, Fujisue K, et al. Prognostic significance of circulating leukocyte subtype counts in patients with coronary artery disease. Atherosclerosis. 2016;255:210–6.

Zhang Q, Zhao K, Shen Q, Han Y, Gu Y, Li X, et al. Tet2 is required to resolve inflammation by recruiting Hdac2 to specifically repress IL-6. Nature. 2015;525(7569):389–93.

Chapter 14
Chronic Kidney Disease Is a Risk Enhancer for Cardiovascular Diseases

Kishan Padalia and Salim S. Hayek

Introduction

The connection between chronic kidney disease (CKD) and cardiovascular disease (CVD) was suggested as early as 1836 by Robert Bright. He observed that cardiac hypertrophy was often seen in those with advanced kidney disease in the absence of valvular heart disease, the predominant form of cardiac disease at the time (Bright 1836).

> The obvious structural changes in the heart have consisted chiefly of hypertrophy […] and what is most striking, out of fifty-two cases of hypertrophy […] twenty-two without any probable organic cause for the marked hypertrophy generally affecting the left ventricle. This naturally leads us to look for some less local cause […] It is observable that the hypertrophy of the heart seems in some degree to have kept pace with the advance of disease in the kidneys; for in by far the majority of cases where the muscular power of the heart was increased, the hardness and contraction of the kidney bespoke the probability of a long continuance of the disease.
>
> Robert Bright, 1836

In this chapter, we summarize the evidence surrounding CKD as a risk enhancer for CVD and its management. We review the epidemiology of CKD and CVD,

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quantify the risk of CVD in those with CKD, describe the underlying pathophysiology between CKD and CVD, and discuss management strategies to mitigate the risk of CVD in those with CKD.

Epidemiology

Definition of Chronic Kidney Disease

Chronic kidney disease is defined as a reduction in kidney function or evidence of structural kidney damage sustained over at least 3 months (Eknoyan et al. 2013). Kidney function is evaluated in terms of glomerular filtration rate (GFR), which is the total amount of fluid filtered through functioning nephrons over time. The structural integrity of the kidney is most often estimated by levels of albumin in the urine, as increased levels imply disrupted glomerular integrity. Current guidelines define CKD as GFR less than 60 mL/min per 1.73 m^2 or albuminuria greater than 30 mg/day. GFR can be estimated (eGFR) using equations that incorporate age, sex, and either serum creatinine or cystatin C. The preferred method of calculating eGFR in the population of interest is the CKD Epidemiology Collaboration equation (Table 14.1), which is more accurate, more precise, less biased, and improves risk prediction compared to the Modification of Diet in Renal Disease equation (Levey et al. 2009; Matsushita et al. 2012). Albuminuria is preferably estimated by spot urine albumin to creatinine ratio (ACR) (Eknoyan et al. 2013). Other markers of kidney damage include abnormalities in urine sediment, electrolytes, imaging, or histology. To aid in prognostication, CKD is classified into six stages based on eGFR and three stages based on albuminuria (Table 14.1).

Table 14.1 CKD staging and risk stratification

		Albuminuria categories (mg/g)		
GFR categories (mL/min per 1.73 m^2)		A1 <30	A2 30–300	A3 >300
G1	≥90	1[a]	2	3
G2	60–89	1[a]	2	3
G3a	45–59	2	3	4
G3b	30–44	3	4	4
G4	15–29	4	4	4
G5	<15	4	4	4

Numbers 1–4 reflect low, moderate, high, and very high risk of adverse clinical outcomes, respectively, as defined by consensus guidelines (Eknoyan et al. 2013)

[a]Not CKD unless other markers of kidney disease are present

Abbreviations: *CKD* chronic kidney disease; *GFR* glomerular filtration rate

Prevalence of Chronic Kidney Disease

The Global Burden of Disease CKD Collaboration evaluated CKD using data from 195 countries from 1990 to 2017 (GBD Chronic Kidney Disease Collaboration 2020). The prevalence of CKD in 2017 was 9.1%, constituting about 700 million cases, which was a 29.3% increase from 1990. The change was primarily due to population aging, as there was no significant age-standardized increase in prevalence. CKD stages 1–2, 3, 4, and 5 constituted 54.8%, 42.7%, 1.7%, and 0.8% of cases, respectively. The use of dialysis and kidney transplantation also increased from 1990 to 2017. The total incidence increased by 43.1% and 34.4%, respectively, whereas the age-standardized incidence increased by 10.7% and 12.8%, respectively. These changes suggest that both population aging and improved availability have played a role in the increasing use of renal replacement therapies. In the 2013–2016 National Health and Nutrition Examination Survey, those who were 60 years and older, diabetic, hypertensive, obese, or had a history of CVD had a CKD prevalence of 32.2%, 36.0%, 31.2%, 16.8%, and 40.3%, respectively (Saran et al. 2019).

Prevalence of Cardiovascular Disease in Chronic Kidney Disease

Cardiovascular disease is common in patients with CKD. In the 2016 National Health and Nutrition Examination Survey cohort of 178,025 CKD patients, the prevalence of CVD in those without and with CKD was 36.8% and 70.2%, respectively (Saran et al. 2019). The prevalence of CVD in those with CKD stages 1–2, 3, and 4–5 was 65.8%, 70.7%, and 77.9%, respectively. The most common CVD was coronary artery disease, which was present in 15.6% and 37.8% of those without and with CKD, respectively. This trend persisted for most major types of CVDs (Fig. 14.1). While this study uniquely provides large, granular, and comparative data, it may overestimate CVD prevalence due to the higher average age of study participants. In the United States prospective Chronic Renal Insufficiency Cohort (CRIC) study of all-age CKD patients, the prevalence of CVD was 33.4% (Shah et al. 2015). There also appears to be significant regional variability with a CVD prevalence of 9.8%, 26.8%, 39.1%, and 47.2% in cohorts of Chinese, Japanese, Spanish, and British CKD patients, respectively (Yuan et al. 2017; Iimori et al. 2015; Martínez-Castelao et al. 2011; Ritchie et al. 2013). This may be due to differences in study design, including patient recruitment and sample size, among other reasons that have not yet been investigated.

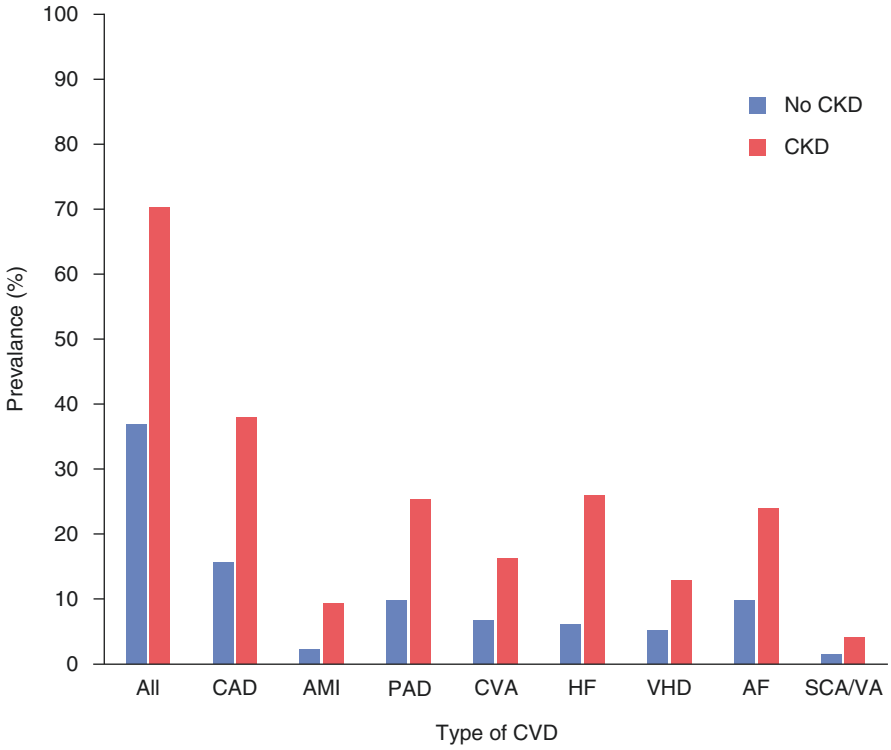

Fig. 14.1 Prevalence of CVD in CKD
Percentage of persons afflicted with common CVDs in those without and with CKD (Saran et al. 2019)
Abbreviations: CKD chronic kidney disease, CVD cardiovascular disease, CAD coronary artery disease, AMI acute myocardial infarction, PAD peripheral arterial disease, CVA cerebrovascular accident, HF heart failure, VHD valvular heart disease, AF atrial fibrillation, SCA sudden cardiac arrest, VA ventricular arrhythmia

Life Expectancy and Cause of Death in Chronic Kidney Disease

The severity of CKD corresponds with increasing mortality from CVD. In a Canadian cohort of almost one million patients, at 40 years of age without albuminuria, eGFR ≥60, 45–59, 30–44, and 15–29 corresponded with a life expectancy of 37.8, 32.8, 26.7, and 15.0 years, respectively, in women and 33.4, 30.4, 16.8, and 6.6 years, respectively, in men (Fig. 14.2a) (Turin et al. 2014). Similarly, albuminuria was associated with increased mortality independent of eGFR. The life expectancy of those with eGFR ≥60 and normal, mild, and heavy albuminuria was 37.8, 27.2, and 22.1 years, respectively, in women and 33.4, 24.8, and 19.1 years,

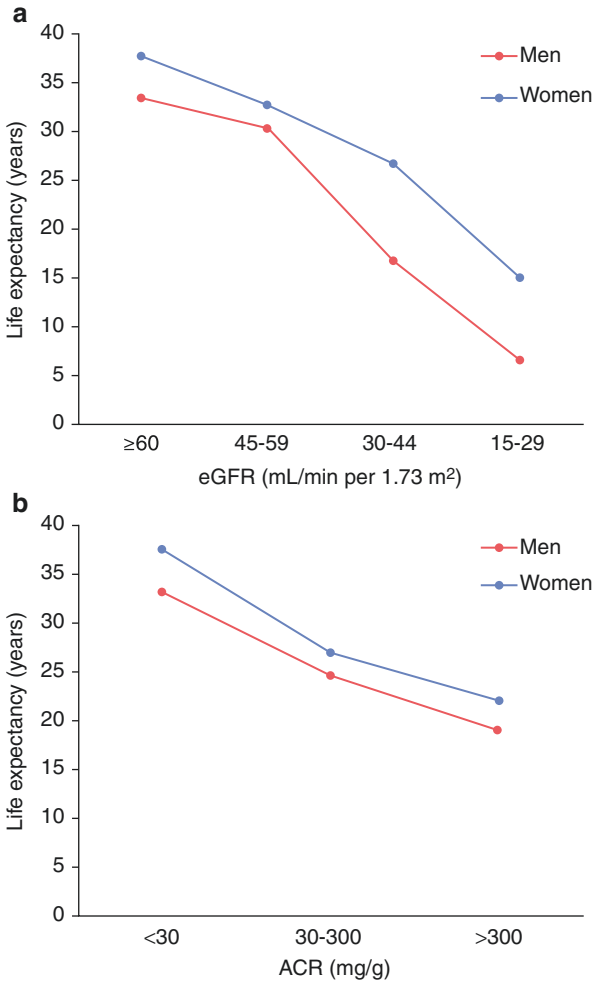

Fig. 14.2 Life expectancy in CKD
Estimated life expectancy for a 40-year-old expressed as a function of (**a**) eGFR in those with an ACR <30 mg/g and (**b**) ACR in those with eGFR ≥60 ml/min/1.73 m^2 (Turin et al. 2014)
Abbreviations: CKD chronic kidney disease, eGFR estimated glomerular filtration rate, ACR albumin creatinine ratio

respectively, in men (Fig. 14.2b). The most common cause of death in those without CKD was cancer accounting for 38.1% of deaths, whereas CVD accounted for only 24.4% of deaths (Thompson et al. 2015). The most common cause of death in those with eGFR 45–59, 30–44, and 15–29 was CVD, which accounted for 36.8%, 41.2%, and 43.7% of deaths, respectively. Most CVD-related deaths were due to ischemic heart disease, which accounted for 52.0–58.0% of CVD-related deaths in each eGFR group. A similar relationship between CKD severity and CVD mortality was found in a Taiwanese general population cohort of 462,293 patients (Wen et al. 2008).

Mortality, Morbidity, and Disability in Chronic Kidney Disease

In the Global Burden of Disease study, CKD is estimated to have directly caused 1.2 million deaths globally in 2017, reflecting a 41.5% increase in all-age and a 2.8% increase in age-standardized mortality rates since 1990 (GBD Chronic Kidney Disease Collaboration 2020). This led to CKD moving from the 17th to the 12th leading cause of death globally. Mortality due to CKD more than doubles when the number of CVD-related deaths attributed to CKD is considered. There were a total of 1.4 million CVD-related deaths due to CKD accounting for 7.6% of the total CVD-related deaths. The total 2.6 million indirect CVD-related and direct deaths due to CKD accounted for 4.6% of total global mortality (Fig. 14.3a).

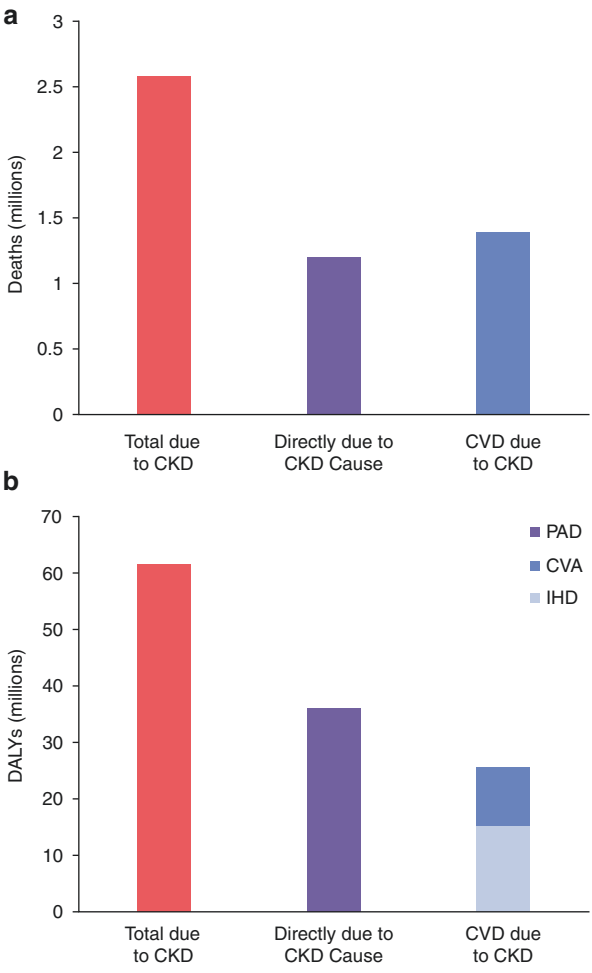

Fig. 14.3 (**a**) Mortality attributable to chronic kidney disease (**b**) Disability-adjusted life year loss attriubted to kidney disease. Mortality and DALYs due to CKD Global estimates of the number of deaths and DALYs caused by CKD directly and indirectly (GBD Chronic Kidney Disease Collaboration **2020**)
Abbreviations: CKD chronic kidney disease, CVD cardiovascular disease, DALY disability-adjusted life **year**

To provide a population-level composite measure of mortality, morbidity, and disability, the Global Burden of Disease study also calculated disability-adjusted life years in CKD patients (GBD Chronic Kidney Disease Collaboration 2020). This measure combines the years of life lost from premature mortality with years lived with disability. Chronic kidney disease caused 61.3 million disability-adjusted life years of which 58.4% were due to direct effects of CKD and 41.6% were due to CVD. Most CVD disability-adjusted life years were accounted for by ischemic heart disease making up 58.8%, followed by stroke making up 40.2%, and the remaining by peripheral arterial disease making up 1.0% (Fig. 14.3b). Although the CVD burden of CKD remains high, the age-standardized rate of CVD disability-adjusted life years due to CKD has decreased by 29.4% since 1990. In the absence of a corresponding decrease in CKD mortality or prevalence, this reflects CKD occurring at older ages and a lower average severity of nonfatal CKD. Notably, the Global Burden of Disease study likely underestimates disability-adjusted life years by using a limited definition of CVD, which excludes heart failure, valvular heart disease, and arrhythmias among other cardiac conditions.

Risk of Cardiovascular Disease

Cardiovascular Mortality

The CKD Prognosis Consortium conducted meta-analyses to study the risk of CVD mortality conferred by CKD in 21 general population cohorts with 1.2 million patients and in 10 high-risk cohorts with 266,975 patients with hypertension, diabetes, or CVD (Matsushita et al. 2010; van der Velde et al. 2011). After adjusting for traditional CVD risk factors, both cohorts found comparable increased risk of CVD mortality proportional to the severity of CKD. There was an increased risk of 1.4-, 2.0-, and 2.7-fold in those with eGFR 60, 45, and 15, respectively. There was no increased risk in those with an eGFR >75 (Fig. 14.4a). Risk of CVD mortality also increased linearly with albuminuria by 1.8- and 2.4-fold in those with ACR 30 mg/g and 300 mg/g, respectively (Fig. 14.4b). Interestingly, there was no threshold effect observed, so even those with an ACR <30 mg/g at the upper limit of normal had an increased risk of CVD mortality. The association between the risk of CVD mortality and each category of eGFR was similar across all levels of albuminuria and vice versa. This suggests that both eGFR and ACR are independent, multiplicative risk factors for CVD mortality. As eGFR declines, nonatherosclerotic CVD events, like sudden cardiac death, assume a higher proportion of the total CVD events, and the risk of fatality after a CVD event accordingly increases (Wanner et al. 2016).

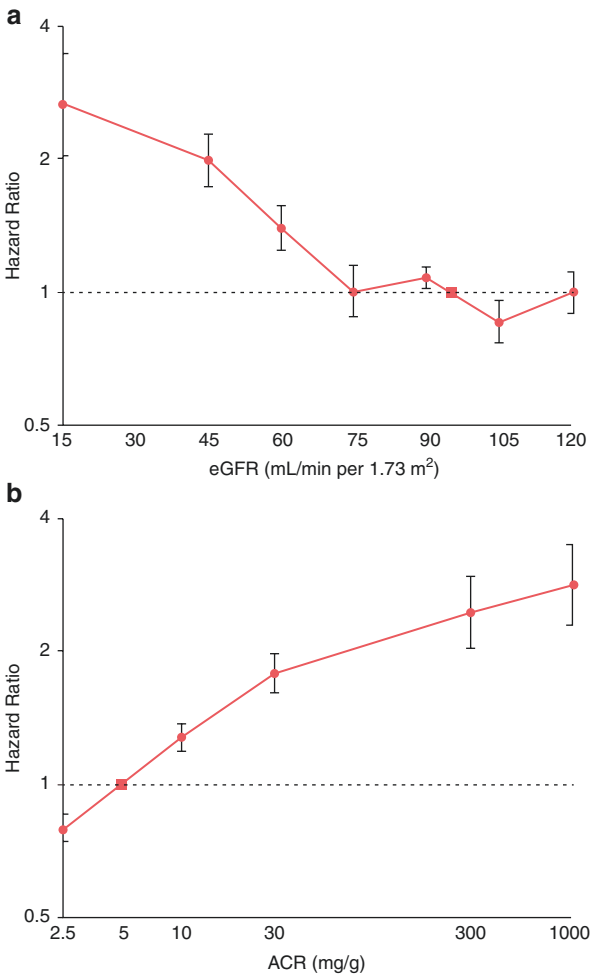

Fig. 14.4 Association between CKD and CVD mortality
Hazard ratios with **95**% confidence intervals for CVD mortality expressed as a function of spline (**a**) eGFR and (**b**) ACR adjusted for each other and traditional cardiovascular risk factors. Squares represent reference values for eGFR and ACR, which are **95** ml/min/**1.73** m² and **5** mg/g, respectively (Matsushita et al. **2010**)
Abbreviations: CKD chronic kidney disease, CVD cardiovascular disease, eGFR estimated glomerular filtration rate, ACR albumin creatinine **ratio**

Myocardial Infarction and Coronary Artery Disease

The risk of myocardial infarction and coronary heart disease increases with severity of CKD. In a meta-analysis of 26 cohorts with almost two million patients, there was an increased risk of 1.2-, 1.4-, and 1.9-fold in those with eGFR 60–90, 30–59, and < 15, respectively (Vashistha et al. 2016). In a separate meta-analysis of 26 cohorts with 169,949 patients, the risk of coronary heart disease, including myocardial infarction, increased by 1.5- and 2.2-fold in those with microalbuminuria and macroalbuminuria, respectively (Perkovic et al. 2008).

Peripheral Arterial Disease

The risk of peripheral arterial disease increases with severity of CKD. In a meta-analysis of 21 cohorts with 817,084 patients conducted by the CKD Prognosis Consortium, there was an increased risk of 1.2-, 1.7-, and 2.1-fold in those with eGFR 45, 30, and 15, respectively (Matsushita et al. 2017). There was no increased risk in those with an eGFR >60. In the same study, the risk of peripheral arterial disease also increased by 1.5- and 2.3-fold in those with ACR 30 mg/g and 300 mg/g, respectively. The relationship was linear and without evidence of a threshold effect. Both eGFR and ACR were independent, multiplicative risk factors for peripheral arterial disease.

Stroke

The risk of stroke increases with severity of CKD. In a meta-analysis of 85 cohorts with 3.4 million patients, there was an increased risk of 1.2- and 1.5-fold in those with eGFR 30–59 and < 30, respectively (Kelly and Rothwell 2019). There was no increased risk in those with eGFR >60. In a separate meta-analysis of 37 cohorts with almost 1.3 million patients, risk of stroke increased by 1.7-, 1.5-, and 1.9-fold in those with albuminuria, microalbuminuria, and macroalbuminuria, respectively (Masson et al. 2015). There was no difference between the association of eGFR or albuminuria with the risk of either ischemic or hemorrhagic stroke.

Heart Failure

The risk of developing heart failure in CKD patients is difficult to study as the two conditions often present similarly, coexist, and occur bidirectionally. This makes it difficult to retroactively ascertain which disease is primary and which is secondary. In a meta-analysis of 8 cohorts with 105,127 patients without baseline heart failure conducted by the CKD Prognosis Consortium, the risk of heart failure hospitalization or death increased by 1.2-, 2.2-, 2.5-, and 2.7-fold in those with eGFR 60, 45, 30, and 15, respectively (Matsushita et al. 2015). There was no increased risk in those with eGFR >75, and the risk plateaued at eGFR <30. In the same study, the risk of heart failure hospitalization or death also increased by 1.5- and 2.9-fold in those with ACR 30 mg/g and 300 mg/g, respectively. The relationship was linear and without evidence of a threshold effect. A secondary analysis of the smaller CRIC study had similar findings and additionally found no difference between the association of eGFR or albuminuria with the risk of hospitalization for heart failure with preserved or reduced ejection fraction (Bansal et al. 2019a).

Valvular Disease

The risk of incident aortic stenosis and mitral regurgitation increases with severity of renal dysfunction. In a cohort of 1.1 million Stockholm patients, the risk of incident aortic stenosis increased by 1.1-, 1.2-, and 1.6-fold in those with eGFR 60–90, 30–59, and < 30, respectively (Vavilis et al. 2019). In an echocardiographic database of 78,059 patients, the risk of mild and moderate aortic stenoses similarly increased by 1.3- and 1.2-fold, respectively, in those with an eGFR <60 (Samad et al. 2017). There was no increased risk of severe aortic stenosis. In the same database, the risk of mild, moderate, and severe mitral regurgitation increased by 1.3-, 1.8-, and 1.8-fold, respectively, in those with an eGFR <60.

Arrhythmia

The risk of incident atrial fibrillation increases with severity of CKD. In a meta-analysis of 3 prospective cohorts with 16,769 patients without atrial fibrillation, there was an increased risk of 1.2-, 1.6-, and 2.0-fold in those with eGFR 45–59, 30–44, and < 30, respectively (Bansal et al. 2017). There was no increased risk in those with an eGFR ≥60. In the same study, the risk of atrial fibrillation also increased by 1.5- and 1.8-fold in those with ACR 30–299 mg/g and ≥ 300 mg/g, respectively. There was no increased risk in those with ACR <30 mg/g. The risk of thromboembolism is also higher in patients who have both atrial fibrillation and CKD. In a meta-analysis of 18 cohorts with 538,479 patients, there was an increased risk of 1.6-fold in those who had both atrial fibrillation and eGFR <60 compared to atrial fibrillation alone (Zeng et al. 2015).

The risk of sudden cardiac death also increases with severity of CKD. In a large community cohort of 27,296 patients, there was an increased risk of 1.4- and 1.9-fold in those with eGFR 45–59 and < 45, respectively (Deo et al. 2017). There was no increased risk in those with eGFR ≥60. In the same study, risk of sudden cardiac death also increased by 1.7-fold in those with ACR >30 mg/g. In another community cohort of 15,792 patients, risk of sudden cardiac death increased by 3.7-fold in those with eGFR <45 (Suzuki et al. 2016).

Risk Assessment

Traditional and Nontraditional Risk Factors

CKD and CVD share common risk factors such as diabetes mellitus and hypertension, which cause 30–60% of CKD cases (Webster et al. 2017). However, these shared risk factors only partially account for the co-occurrence of CKD and

CVD. As the above studies demonstrate, CKD is associated with CVD even after adjusting for traditional cardiovascular risk factors. This suggests that CVD in CKD patients is driven by a combination of both traditional and nontraditional risk factors with the latter becoming more prominent in later stages of CKD.

In a meta-analysis of 21 cohorts with 27,465 CKD patients, a total of 66 traditional and nontraditional risk factors were identified of which 29 were found to be routinely collected and studied in multivariable models that controlled for other traditional CVD risk factors (Major et al. 2018). Traditional risk factors that increased the risk for CVD events – acute coronary syndrome, heart failure, and stroke – included age, male sex, smoking, diabetes mellitus, mean arterial blood pressure, total cholesterol, left ventricular hypertrophy, and established history of CVD (Fig. 14.5a). Other traditional risk factors such as body mass index, low-density

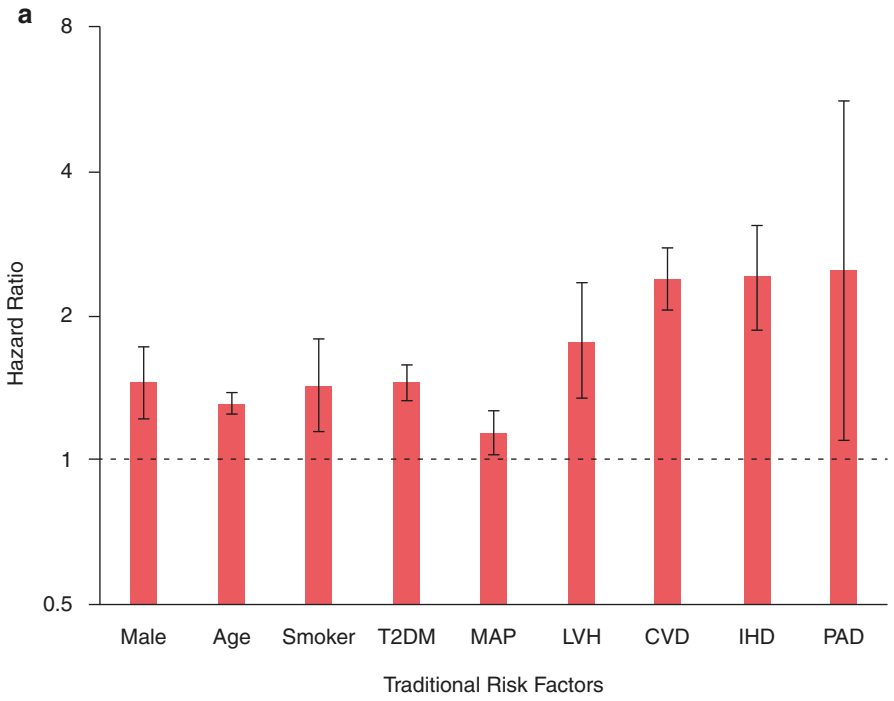

Fig. 14.5 Risk factors for CVD in CKD
Pooled hazard ratios with 95% confidence intervals for CVD events expressed as a function of (**a**) traditional risk factors and (**b**) nontraditional risk factors variably adjusted for other traditional cardiovascular risk factors. Only risk factors with significant associations found are shown. Continuous variables assessed include: age per 10 years, MAP per 10 mmHg, albumin per g/dL, Hb per g/dL, phosphate per mg/dL, sodium per mmol/L, urate per mg/dL, and BUN per 5 mg/dL. All other variables were categorical (Major et al. 2018)
Abbreviations: CKD chronic kidney disease, CVD cardiovascular disease, T2DM type 2 diabetes mellitus, MAP mean arterial pressure, LVH left ventricular hypertrophy, IHD ischemic heart disease, PAD peripheral artery disease, Hb hemoglobin, BUN blood urea nitrogen

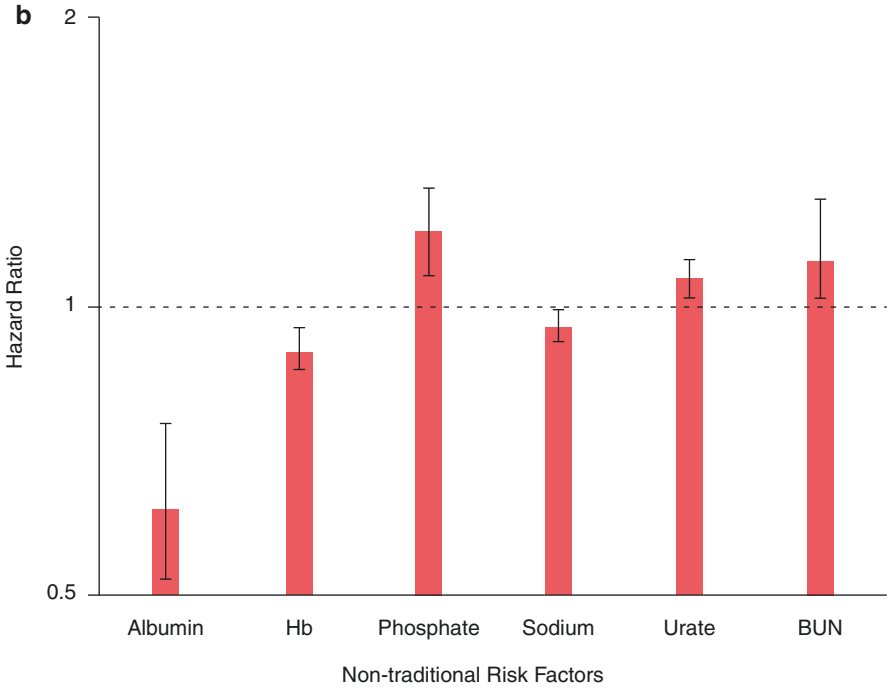

Fig. 14.5 (continued)

lipoprotein (LDL), and systolic/diastolic blood pressure did not increase the risk of CVD events. Race was not evaluated as it was not often reported and was homogeneous in those studies that did. Nontraditional risk factors that increased the risk for CVD events included serum sodium, phosphate, urate, urea nitrogen, albumin, and hemoglobin (Fig. 14.5b). Serum calcium and parathyroid hormone levels, implicated in the pathogenesis of cardiac disease in CKD, were not associated with increased risk of CVD events. Outside of an established history of CVD, left ventricular hypertrophy was the strongest risk factor for CVD, increasing risk by 1.8-fold.

Another meta-analysis of 28 cohorts with 185,024 patients with eGFR <30 was conducted by the CKD Prognosis Consortium to evaluate the relationship between traditional risk factors and CVD events in advanced CKD (Evans et al. 2018). The risk of CVD events increased by 1.3-fold for every 10-year increase in age, 1.1-fold for male sex, 2.6-fold for history of CVD, 1.1-fold for every 20 mmHg increase in systolic blood pressure over 140 mmHg, and 1.4-fold for diabetes mellitus. The risk associated with systolic blood pressure is U-shaped, with a blood pressure of 140 mmHg associated with a 11% lower risk, compared to 120 mmHg. Smoking and race were not associated with the risk of CVD events. Cholesterol and body mass index were not evaluated. Overall, these studies emphasize important differences in the impact of various CVD risk factors according to the presence and severity of CKD.

Biomarkers

Many novel biomarkers have been investigated to help predict CVD morbidity and mortality in patients with CKD. This section will provide a broad overview of those with the strongest clinical evidence and future promise to assist in risk prediction.

Cystatin C

Plasma cystatin C, an accurate biomarker of kidney function, is also strongly associated with CVD mortality. In a meta-analysis of 10 general population cohorts with 64,010 patients with creatinine-based eGFR >90, 60–89, 45–59, 30–44, and 15–29, the risk of CVD mortality increased by 1.4-, 1.6-, 1.7-, 1.7-, and three-fold, respectively, in those reclassified to a lower eGFR category with cystatin C (Shlipak et al. 2013). Those reclassified to a higher eGFR category with cystatin C did not have increased risk of CVD mortality. Similar findings have been reported for CVD events more broadly (Peralta et al. 2011). This likely reflects the higher fidelity association of cystatin C with true renal function compared to creatinine, which has more confounding non-GFR determinants such as muscle mass, diet, and physical activity. Chronic inflammation, integral to the pathogenesis of CVD in CKD, is also positively associated with cystatin C and negatively associated with creatinine, which may also partially account for these findings (Schei et al. 2016).

Cardiac Troponin

Troponin levels are thought to be elevated in CKD due to both chronic myocardial injury and reduced renal clearance. Troponin is a well-established risk factor for CVD mortality in patients with end-stage renal disease (ESRD), and its routine measurement for risk prediction in this population is approved in the United States. In a meta-analysis of 5 studies of 1634 ESRD patients, elevated troponin T increased the risk of CVD mortality by 3.3-fold (Michos et al. 2014). A CRIC study of 3664 CKD patients had similar findings. Risk of CVD mortality increased by 1.9-, 3.6-, and 5.2-fold in those with high-sensitivity troponin T in quartiles 2–4, respectively (Wang et al. 2020). In the same study, a smaller cohort of 3314 CKD patients demonstrated that the risk of incident heart failure increased by 1.3-, 2.1-, and 2.4-fold in those with high-sensitivity troponin T in quartiles 2–4, respectively (Bansal et al. 2019b). These findings are supported by a meta-analysis of 4 cohorts with 2012 CKD patients, which demonstrated that the risk of major adverse cardiac events increased by 2.7-fold in those with elevated troponin T (Michos et al. 2014).

Natriuretic Peptides

N-terminal prohormone brain natriuretic peptide (NT-proBNP) increases with severity of CKD and is associated with CVD mortality in this population. In a CRIC

study of 3664 CKD patients, risk of CVD mortality increased by 2.4-, 3.5-, and 6.9-fold in those with NT-proBNP in quintiles 3–5, respectively (Wang et al. 2020). In the same study, a smaller cohort of 3314 CKD patients demonstrated that the risk of incident heart failure increased by 2.0-, 3.2-, 4.4-, and 7.6-fold in those with NT-proBNP in quintiles 2–5, respectively (Bansal et al. 2019b). A meta-analysis of 8 cohorts with 5634 CKD stage 5 patients similarly demonstrated that the risk of CVD mortality increased at a higher threshold of NT-proBNP >6000 pg/mL (Harrison et al. 2020). Similar results were found for brain natriuretic peptide.

Soluble Urokinase Plasminogen Activator Receptor

Soluble urokinase plasminogen activator receptor (suPAR) is an immune-derived signaling molecule that independently mediates both CKD and CVD and is emerging as a possible key link between the two. While most biomarkers in this section correlate with and even predict progression of CKD, suPAR is the first biomarker shown to predict incident renal dysfunction in those without CKD. This was first demonstrated in a cohort of 2292 patients who underwent cardiac catheterization and later replicated in other diverse cohorts (Hayek et al. 2015). Risk of incident renal dysfunction increased by 2.0- and 3.1-fold in those with suPAR in quartiles 3 and 4, respectively. Higher suPAR levels also increase risk of CVD events and mortality in diverse populations including those with CKD. In a cohort of 486 CKD patients, risk of CVD events increased by 2.7- and 3.4-fold in those with suPAR in tertiles 2 and 3, respectively (Meijers et al. 2015). Similar results including increased risk of CVD mortality, stroke, and sudden cardiac death have been shown in ESRD patients (Drechsler et al. 2017; Torino et al. 2018). Mounting evidence supports suPAR as a potential therapeutic target with trials currently ongoing to determine whether modifying suPAR levels will impact the risk of kidney injury.

Uric Acid

Serum uric acid has been shown to predict incident CKD in diverse populations. In a study of 1109 type 2 diabetic patients with eGFR >60 and normal urine albumin, risk of incident renal dysfunction (eGFR <60) increased by 1.5-, 1.4-, 2-, and 2.6-fold in those with serum uric acid in quintiles 2–5, respectively (De Cosmo et al. 2015). Serum uric acid is also independently associated with increased CVD mortality in CKD patients. In a meta-analysis of 11 cohorts with 27,081 CKD patients, the risk of CVD mortality increased by 12% for every 1 mg/dL increase in serum uric acid (Luo et al. 2019). These results are supported with similar findings for coronary artery disease, heart failure, and stroke (Kim et al. 2010; Huang et al. 2014).

Other Biomarkers

Several other biomarkers are independently associated with both progression of CKD and increased CVD mortality including fibroblast growth factor 23, growth

differentiation factor 15, and asymmetric dimethylarginine (Fliser et al. 2007; Nair et al. 2017; Eiselt et al. 2014). In a cohort of 1128 CKD patients, the risk of CVD mortality increased by 1.6-fold in those with fibroblast growth factor 23 in quartile 4 (Ix et al. 2012). Meta-analyses of multiple CKD cohorts have also found that high levels of fibroblast growth factor 23 increased the risk of CVD events including myocardial infarction, stroke, heart failure, and peripheral arterial disease (Marthi et al. 2018). In a CRIC study of CKD patients, the risk of CVD mortality increased by 2.1- and 3.8-fold for those with growth differentiation factor 15 in quartiles 3 and 4, respectively (Wang et al. 2020). In the same study, the risk of incident heart failure increased by 1.5-, 2.1-, and 2.4-fold in those with growth differentiation factor-15 in quintiles 3–5, respectively (Bansal et al. 2019b). In a cohort of 820 patients with CKD stages 3 and 4, the risk of CVD mortality increased by 25% for every 1 standard deviation increase in asymmetric dimethylarginine (Young et al. 2009).

Serum neutrophil gelatinase-associated lipocalin is associated with progression of CKD and increased risk of CVD events (Bolignano et al. 2009). In a cohort of 252 CKD patients without a history of CVD, the risk of CVD events increased by 4% for every 10 ng/mL increase in serum neutrophil gelatinase-associated lipocalin (Hasegawa et al. 2016).

Serum fibrinogen levels increase with severity of CKD and are associated with increased risk of CVD events but not CVD mortality. In two cohorts with 1678 CKD patients, risk of acute myocardial infarction and stroke increased by 10% and 8%, respectively, for every 50 mg/dL increase in fibrinogen (Weiner et al. 2008). However, in a general population cohort of 9184 patients, there was no association between fibrinogen and CVD mortality in those with CKD (Stack et al. 2014).

The role of several urinary biomarkers in the development of CVD in CKD patients was investigated in a CRIC study. Risk of heart failure increased by 21%, 22%, and 20% for every 1 standard deviation increase in kidney injury molecule-1, urine neutrophil gelatinase-associated lipocalin, and *N*-acetyl-β-d-glucosaminidase, respectively (Park et al. 2017). Risk of atherosclerotic CVD events increased by 21% for every 1 standard deviation increase in kidney injury molecule-1.

The utility of many other biomarkers in stratifying the risk of CVD in CKD patients is under investigation. The importance of risk stratification ultimately lies in establishing clinically useful downstream strategies to prevent the incidence and progression of CKD and CVD.

Models for Cardiovascular Disease Risk Prediction

Risk assessments made using tools such as the Pooled Cohort Equations depend on population studies, which have unfortunately demonstrated significant weaknesses when used to assess patients with CKD. Predicted risk falls significantly short of observed risk, model discrimination is poor, and the underestimation is nonuniform, which has stymied attempts at effectively recalibrating these tools (Fig. 14.6) (Weiner et al. 2007). Intuitively, the simplest method of improving risk prediction of CVD events would be to incorporate measures of CKD, such as eGFR and ACR,

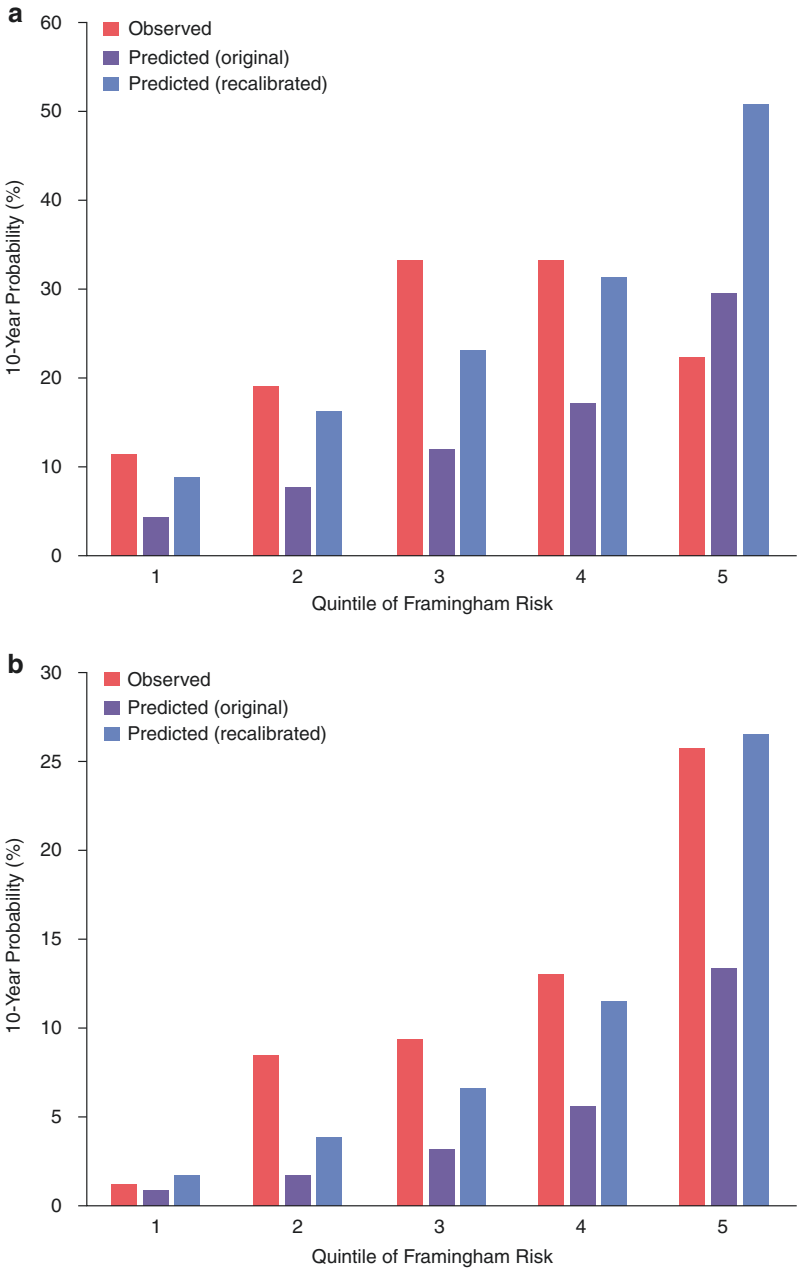

Fig. 14.6 Risk prediction of coronary events in CKD using the Framingham model
Observed and predicted 10-year risk of coronary events in (**a**) men and (**b**) women with CKD stratified by the quintile of risk predicted by the Framingham model. In men, the model was poorly calibrated ($p < 0.001$), underpredicting and overpredicting coronary events in quintiles 1–4 and 5, respectively. In women, the model was poorly calibrated ($p < 0.001$), underpredicting coronary events in all quintiles. Model recalibration did not improve prediction in men ($p < 0.001$) but did in women ($p = 0.06$) (Weiner et al. 2007)
Abbreviations: CKD chronic kidney disease

into the equations. However, initial studies to this effect were conflicting likely due to variability in study population, inclusion of albuminuria, CVD outcomes, and statistical approaches. In 2015, the CKD Prognosis Consortium conducted a comprehensive and rigorous meta-analysis of 24 cohorts with 637,315 patients without a history of CVD (Matsushita et al. 2015). The C-statistics for CVD outcomes based on traditional risk factors were 0.729–0.838. Inclusion of eGFR and ACR, or both, led to significant improvements in risk discrimination with increases in C-statistic from 0.005 to 0.030 for all CVD outcomes but most notably CVD mortality and heart failure. ACR outperformed and eGFR was at least as good as most traditional risk factors.

Despite this evidence, national and international guidelines have not provided consistent or precise recommendations on how to account for CKD in CVD risk prediction. The 2018 American Heart Association and American College of Cardiology cholesterol guidelines classified eGFR <60 but not albuminuria as a risk enhancer for CVD (Grundy et al. 2019). Further, these guidelines did not provide a quantitative method to account for the added risk in their endorsed Pooled Cohort Equations. The 2019 European Society of Cardiology dyslipidemia guidelines classified eGFR 30–59 as equivalent to a 10-year CVD mortality of 5–10% and eGFR <30 or albuminuria in diabetics as equivalent to a 10-year CVD mortality of ≥10% (Mach et al. 2020). This approach excludes other risk factors, albuminuria in nondiabetics, and does not provide a quantitative method to account for CKD in their endorsed Systematic Coronary Risk Evaluation algorithm.

A major barrier to incorporating CKD into CVD risk prediction is the inability to incorporate eGFR or albuminuria into the existing Pooled Cohort Equations and Systematic Coronary Risk Evaluation tools because these were derived from population studies that did not measure those parameters. To overcome this, the CKD Prognosis Consortium recalibrated both risk equations by using a "CKD patch" that was derived from their external dataset of 35 general population, high-risk, and CKD cohorts with 4.1 million patients (Matsushita et al. 2020). This CKD patch was then validated against a separate external dataset of 37 cohorts with 4.9 million patients. The CKD patch significantly improved risk prediction for both atherosclerotic CVD with the Pooled Cohort Equations (Δ C-statistic: 0.010, categorical net reclassification improvement: 0.056) and CVD mortality with the Systematic Coronary Risk Evaluation (Δ C-statistic: 0.027, categorical net reclassification improvement: 0.080). Although small, these improvements reflect a 5- to ten-fold improvement compared to the addition of C-reactive protein or fibrinogen to these same models. These modified risk calculators can be found online at http://ckdpcrisk.org/

Pathophysiology

Cardiac Disease

Cardiomyopathy with progressive left ventricular failure in CKD patients is driven by three major processes: pressure overload, volume overload, and nonhemodynamic alterations in the cardiac myocardium.

Pressure Overload

Pressure overload describes myocardial contraction against excessive afterload. In CKD, excessive afterload is primarily due to hypertension and arterial stiffness. Hypertension causes CKD through arteriosclerosis and progressive glomerular damage termed "nephrosclerosis," but this process also cyclically worsens hypertension by reducing blood flow to downstream peritubular capillaries (Ku et al. 2019). This leads to renin hypersecretion and increased levels of angiotensin II, which, in turn, causes vasoconstriction, sodium retention, extracellular volume expansion, and increased sympathetic outflow, all of which promote hypertension. Endothelial dysfunction, impaired nitrous oxide production, oxidative stress, and elevated levels of endothelin have also been implicated in this process. Arterial stiffness, particularly in the aorta, increases in CKD through vascular injury, which is described in more detail in section "Vascular Disease". Increased aortic stiffness results in loss of its "cushioning effect" and causes a decrease in diastolic and an increase in systolic blood pressure (Zanoli et al. 2019). These changes decrease coronary perfusion and increase afterload, respectively. Pressure overload in CKD results in concentric hypertrophy to reduce wall stress and preserve left ventricular function.

Volume Overload

Mechanical cardiac stress in CKD is also caused by volume overload. Hypervolemia is common in the early stages of CKD even in the absence of overt clinical signs and symptoms (Hung et al. 2014; Hung et al. 2015). This is driven by sodium retention from both reduced glomerular filtrations of sodium as renal function declines and tubular reabsorption of sodium to help maintain GFR. These processes are mediated by increased activity of the renin–angiotensin–aldosterone system (RAAS) and neural sympathetic outflow. Anemia commonly occurs in CKD due to a combination of hemodilution from hypervolemia, relative deficiency of erythropoietin, uremic inhibition of erythropoiesis, disordered iron homeostasis, and decreased erythrocyte survival (Babitt and Lin 2012). Anemia decreases blood viscosity, which, in turn, increases venous return (Metivier et al. 2000). Both intravascular hypervolemia and anemia increase cardiac preload, which causes eccentric hypertrophy and left ventricular dilation.

Nonhemodynamic Factors

Cardiac hypertrophy in CKD also occurs through multiple nonhemodynamic mechanisms (Wang and Shapiro 2019). Stimulation of RAAS and sympathetic outflow in CKD directly contribute to cardiac hypertrophy and fibrosis through mechanisms involving mitogen-activated protein kinases and generation of reactive oxygen species. Upregulation of cytokine transforming growth factor beta occurs independently in both CKD and with cardiac pressure overload and appears to mediate cardiac hypertrophy and fibrosis. CKD mineral and bone disorder involves increased parathyroid hormone, increased serum phosphate, increased fibroblast growth factor 23, decreased vitamin D, and decreased soluble Klotho. Each of these changes through a variety of dependent and independent mechanisms increases cardiac hypertrophy and fibrosis. Insulin resistance and hyperinsulinemia are early features of CKD, which increase cardiac hypertrophy through several mechanisms including phosphorylation of angiotensin II and vascular endothelial growth factor. Uremic toxins increase inflammation and oxidative stress in the myocardium and have been associated with increased cardiac hypertrophy, fibrosis, and apoptosis. Finally, endogenous cardiotonic steroids are increased in CKD and may cause cardiac hypertrophy and fibrosis through activation of a sodium–potassium adenosine triphosphatase signaling pathway and production of reactive oxygen species.

Uremic Cardiomyopathy

Each of these distinct processes – pressure overload, volume overload, and nonhemodynamic cardiac remodeling – combines to cause left ventricular hypertrophy histologically characterized in CKD by profound myocardial fibrosis. Echocardiographic evidence of left ventricular hypertrophy is evident in 40% of those with advanced CKD and in up to 80% of those with ESRD (Levin et al. 1996; Parfrey et al. 1996). Myocardial fibrosis has been observed to afflict up to 90% of CKD and ESRD patients without obstructive coronary lesions in postmortem studies (Mall et al. 1990). Interstitial fibrosis, particularly around intramyocardial arteries, in concert with dysfunctional calcium reuptake into the sarcoplasmic reticulum impairs passive relaxation and ultimately progresses into diastolic heart failure (Kennedy et al. 2003). Diastolic dysfunction is evident in over two-thirds of those with CKD stages 2–4 and in up to 85% of those with ESRD (Park et al. 2012; Farshid et al. 2013). This clinical phenotype of cardiac disease in CKD is often termed “uremic cardiomyopathy.” Overt systolic dysfunction does not typically arise until severe hemodynamic disturbances or myocardial ischemia begin to occur. Reduced ejection fraction is observed in only 8% of predialysis CKD patients without an association with eGFR (Park et al. 2012; Mark et al. 2006).

Vascular Disease

The arterial phenotype in CKD reflects multimodal vascular disease from functional impairment and structural injury. Functional impairment occurs through endothelial dysfunction and early vascular cell wall senescence. Structural injury occurs through increased atherosclerotic plaque formation, vascular calcification, increased intima-media thickness, and loss of elastin. Like the nonhemodynamic mechanisms of myocardial injury, these changes are mediated through a complex interplay between inflammation, oxidative stress, and uremia.

Atherosclerosis

Atheromatous plaques are observed in 70% of CKD patients, and the risk of formation increases by 1.3-, 1.7-, and 3.7-fold in CKD stage 3, CKD stage 4–5, and ESRD, respectively (Betriu et al. 2014). This is partly due to significant quantitative and qualitative changes in the lipid profile. Quantitative changes including elevated triglycerides, elevated total cholesterol, elevated very low density lipoprotein, elevated lipoprotein A, and reduced high-density lipoprotein have been associated with increased risk of atherosclerosis (Valdivielso et al. 2019). Low-density lipoprotein is notably less predictive of CVD risk among CKD patients than in the general population. This suggests that qualitative changes in the lipid profile account for a significant portion of the risk. Qualitative changes include reduced low-density lipoprotein size, increased triglyceride to cholesterol ratio, and multiple pathogenic modifications of lipoproteins including glycation, oxidation, and carbamylation. These changes are the effects of reduced renal clearance and increased inflammation and oxidative stress from CKD but, in turn, also cyclically cause inflammation and oxidative stress. In this way, changes in lipid profile in CKD not only promote atheromatous plaque formation but also multimodal vascular injury.

Calcification

Vascular calcification in CKD is associated with atheromatous plaques in large arteries but often occurs without plaques in smaller arteries rich in vascular smooth muscle cells (Zanoli et al. 2019; Valdivielso et al. 2019). It is driven by an accumulation of unstable phosphate and calcium ions that form mineral deposits and promote abnormal differentiation of vascular smooth muscle cells to osteoblast- and chondroblast-like cells. The former process reflects CKD mineral and bone disorder, which is characterized by disordered hormone regulation of phosphate by intestinal absorption, renal reabsorption, and bone metabolism attenuated by reduced renal clearance. Disordered mineral metabolism occurs in the early stages of CKD even in the absence of elevated serum phosphate. This is characterized by deficiency in Klotho receptor, suppressed by albuminuria and inflammation, which in turn

upregulates its ligand fibroblast growth factor 23, which has an integral role in vascular calcification. In later stages of CKD, elevated serum phosphate also promotes phenotype switching of vascular smooth muscle cells into osteoblast- and chondroblast-like cells that begin expressing bone-forming genes. Calcium phosphate crystals, in addition to other uremic toxins, also increase synthesis of proinflammatory cytokines like tumor necrosis factor and interleukin-6, which further promotes vascular calcification. Tumor necrosis factor interferes with endothelial nitric oxide synthase, which leads to formation of reactive oxygen species, which in turn promotes phenotypic switching of vascular smooth muscle cells. Inflammation also mediates vascular infiltration by white blood cells, such as CD14+ and CD16+ monocytes, and uremic toxins, such as endothelin-1 and advanced glycation end products, which also promote phenotypic switching of vascular smooth muscle cells.

Other Vascular Injuries

Vascular smooth muscle cell proliferation, hypertrophy, and reduced apoptosis also contribute to increasing intima-media thickness and reducing vessel caliber in CKD. This is mediated through inflammation, oxidative stress, and uremic toxins such as uric acid, modified lipoproteins, and indoxyl sulfate (Zanoli et al. 2019; Valdivielso et al. 2019). The function of endothelial cells, which mediate the cross talk between intravascular and vascular cells, is also impaired by these factors. For example, shear stress from blood flow normally stimulates endothelial synthesis of nitric oxide, which causes smooth muscle relaxation. However, this process is disrupted by inhibition of endothelial nitric oxide synthase by inflammation and uremic toxins including uric acid, advanced glycation end products, and asymmetric dimethylarginine. Endothelial damage results in the release of microvesicles and specific microRNAs, which can cause further vascular injury (Neuen et al. 2019). Finally, there is increasing evidence that uremia in CKD results in early vascular cell wall senescence characterized by accumulation of oxidative damage and loss of both physiological function and regenerative capability. Early evidence suggests that CKD mineral and bone disorder, carbamylated low-density lipoprotein, indoxyl sulfate, and CD14+ CD16+ monocytes may be involved in this process (Valdivielso et al. 2019).

Management

Overview

Despite extensive study and purported understanding of the pathophysiology underlying CVD in CKD, there are no effective therapies that target the underlying processes. Age-standardized rates of CKD mortality have continued to increase, and

advancements in prevention and treatment have lagged far behind other critical non-communicable diseases (GBD Chronic Kidney Disease Collaboration 2020). Despite its increasing global prevalence of nearly 10% and mortality now accounting for nearly 5% of deaths worldwide, its recognition as a problem by public health authorities and the general population is lacking. CKD is recognized as a health-care priority in only 36% of countries, and there is a national strategy in place to combat CKD in only 17% of countries. Awareness and adoption of CKD guidelines by primary care physicians and specialists is below average in almost half of the countries worldwide, which is accentuated by less than 10% of patients being aware of their disease. No goals have been set by the World Health Organization to limit the global CKD epidemic. The lack of awareness and progress in treating CKD is reflected by its significantly lower research funding, with nephrology having the lowest number of published clinical trials among all medicine subspecialties (Yaseen et al. 2019). There have been few significant drug developments in nephrology since the 1980s. Even the recent discovery of improvement in renal outcomes in diabetics with sodium–glucose cotransporter-2 (SGLT-2) inhibitors has come from secondary analyses of cardiovascular trials. These challenges have led to a clinical focus on traditional cardiovascular risk factor control rather than treatment of underlying CKD to mitigate the increased risk of CVD in patients with CKD (Table 14.2).

Lifestyle Interventions

Each of the lifestyle interventions discussed below is recommended by most CKD guidelines based on interventional trials in the general population that demonstrate improved cardiac and renal outcomes. The limited scale and duration of studies in CKD patients frequently prevents evaluation of relevant clinical outcomes, namely, CVD events but will be the focus of this section. Reducing sodium intake reduces risk of CVD in CKD. In the CRIC study, risk of CVD events and CKD progression was 36% and 54% higher for those in the highest quartile of sodium excretion (Mills et al. 2016; He et al. 2016). A Cochrane review of eight randomized controlled trials (RCTs) found that dietary sodium reduction reduced proteinuria and blood pressure (McMahon et al. 2015). RAAS inhibition combined with dietary sodium reduction reduces risk of both renal and CVD events greater than RAAS inhibition alone (Lambers Heerspink et al. 2012). A Cochrane review found that a very low protein diet may also reduce progression of advanced CKD to ESRD by decreasing intraglomerular pressure (Hahn et al. 2018). A systematic review of 41 RCTs found that exercise training improved functional capacity, quality of life, and systolic blood pressure in CKD patients (Heiwe and Jacobson 2014). Physical activity improved

Table 14.2 Lifestyle and pharmacological interventions to reduce risk of CVD in CKD

Interventions	Description
Lifestyle	
Dietary sodium restriction	Reduces proteinuria and blood pressure (McMahon et al. 2015) and potentiates RAAS inhibition (Lambers Heerspink et al. 2012)
Dietary protein restriction	Reduces progression to advanced CKD (Hahn et al. 2018)
Physical activity	Reduces blood pressure (Heiwe and Jacobson 2014)
Weight loss	Reduces proteinuria and decline in eGFR (Bolignano and Zoccali 2013)
Smoking cessation	May reduce progression of CKD (Lee et al. 2020)
Pharmacological	
Blood pressure reduction	Likely reduces CVD events and mortality (Ettehad et al. 2016; Cheung et al. 2017). Conflicting evidence on CKD progression (Cheung et al. 2017; Lv et al. 2013)
RAAS inhibition	Reduces CKD progression (Xie et al. 2016; KDIGO 2020), CVD events (Xie et al. 2016), and possibly CVD mortality (Mann et al. 2001; Heart Outcomes Prevention Evaluation Study Investigators 2000) independent of blood pressure, particularly in those with diabetes and albuminuria
Glycemic control	Hemoglobin A1c <6.5–7% reduces myocardial infarction and CKD progression (KDIGO 2020; Ruospo et al. 2017). Metformin reduces heart failure hospitalization (Crowley et al. 2017). SGLT-2 inhibitors reduce CKD progression, CVD events, and CVD mortality or heart failure hospitalization (McGuire et al. 2021). Limited evidence for GLP-1 RAs in CKD
Lipid control	Statins with and without ezetimibe reduce CVD events and mortality in those not on dialysis (Herrington et al. 2016; Baigent et al. 2011; Major et al. 2015). Statins reduce proteinuria and decline in eGFR but not CKD progression (Su et al. 2016)
Antiplatelet therapy	Likely reduces CVD events in secondary prevention (Palmer et al. 2013) but increases bleeding and does not reduce CVD events or mortality in primary prevention (Major et al. 2016; Wolfe et al. 2021)
Hemoglobin control	Erythropoietin-stimulating agents targeting hemoglobin ≥12 g/dL increase stroke and do not affect CKD progression (Palmer et al. 2010). Evidence for iron is conflicting on CVD events (Agarwal et al. 2015; Macdougall et al. 2019) and limited on CKD progression
Phosphate reduction	Does not reduce CVD events or mortality (Ruospo et al. 2018). Limited evidence for effect on CKD progression
Vitamin D supplementation	Reduces CVD mortality in observational studies but not small RCTs (Lu et al. 2017). Limited evidence for effect on CKD progression
Uric acid reduction	Does not reduce CVD events, CVD mortality, or CKD progression in limited RCTs (Kimura et al. 2018; Doria et al. 2020)

Abbreviations: *CVD* cardiovascular disease, *RAAS* renin-angiotensin-aldosterone system, *eGFR* estimated glomerular filtration rate, *SGLT-2* sodium glucose transporter protein 2, *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *RCT* randomized controlled trial

eGFR in one trial, but these findings have been inconsistently replicated (Flesher et al. 2011). An observational study of CKD patients also found an association between increased duration of light activity and decreased all-cause mortality (Beddhu et al. 2015). A systematic review of 31 weight loss studies in obese CKD patients demonstrated significant improvements in proteinuria, albuminuria, and eGFR (Bolignano and Zoccali 2013). Finally, duration since smoking cessation proportionally reduces risk of CKD progression (Xia et al. 2017; Lee et al. 2020).

Blood Pressure Reduction

Recent evidence supports a blood pressure target of at least <130/80 mmHg for CKD patients. A meta-analysis of 6 RCTs with 4106 CKD patients demonstrated that a 10 mmHg reduction in systolic blood pressure reduced the risk of CVD events by 16% and all-cause mortality by 19% (Ettehad et al. 2016). The recent Systolic Blood Pressure Intervention Trial (SPRINT) RCT has randomized a prespecified subgroup of 2646 CKD patients with eGFR 20–59 and proteinuria <1 g/day to a target systolic blood pressure of <120 or < 140 mmHg (Cheung et al. 2017). Intensive systolic blood pressure reduction significantly reduced the risk of all-cause mortality by 28%, but the observed reductions in CVD mortality by 43% ($p = 0.06$) and CVD events by 19% ($p = 0.12$) only approached statistical significance. A post hoc analysis found no reduction in CVD events in those with eGFR <45, but this should only be considered hypothesis-generating, as the study was not powered to evaluate this smaller subgroup of 891 CKD patients (Obi et al. 2018). The intensive systolic blood pressure reduction group also had a 2.0-fold increased risk of a ≥ 30% decline in eGFR (Cheung et al. 2017). This appeared to have been an acute and self-limited hemodynamic change, as it was not appreciated past 6-month follow-up after which the annual decline in eGFR was similar to that attributed to normal aging. A meta-analysis of 11 RCTs demonstrated that intensive blood pressure control reduced the risk of renal failure by 27% in those with CKD and proteinuria (Lv et al. 2013). Low baseline diastolic blood pressure (<50 mmHg) in SPRINT was associated with increased risk of CVD events, but the effects of intensive systolic blood pressure reduction on mortality and CVD events did not vary by baseline diastolic blood pressure levels (Beddhu et al. 2018).

Renin–Angiotensin–Aldosterone System Inhibition

Inhibition of RAAS through angiotensin-converting enzyme inhibitors (ACEis) and angiotensin II receptor blockers (ARBs) improves cardiac and renal outcomes in CKD patients, particularly those with albuminuria and diabetes, independent of blood pressure control. A network meta-analysis of 119 RCTs with 64,768 CKD patients compared RAAS inhibitors to placebo and found that both ACEis and

ARBs reduced the risk of renal failure by 39% and 30%, respectively, and CVD events by 18% and 24%, respectively (Xie et al. 2016). ACEis reduced the risk of all-cause mortality by 28%, but neither ACEis nor ARBs reduced the risk of CVD mortality. The largest RAAS inhibitor RCT, the Heart Outcomes Prevention Evaluation (HOPE) study, conducted a prespecified subgroup analysis of 3394 patients with an eGFR <65 and demonstrated that ACEis reduced the risk of CVD mortality, myocardial infarction, stroke, and hospitalization for heart failure by 33%, 26%, 31%, and 18%, respectively (Mann et al. 2001). This analysis was only adjusted for center effect, but the relationship persisted in both nondiabetic and normotensive subgroups. An update to a Cochrane review of 49 RCTs demonstrated that RAAS inhibitors in patients with diabetic nephropathy reduced the risk of severe albuminuria by 55% and serum creatinine doubling by 32% (KDIGO 2020). These renal protective effects were independent of blood pressure, and full doses of ACEis additionally reduced all-cause mortality by 22% (Lewis et al. 2001; Brenner et al. 2001; Strippoli et al. 2006). A Micro-HOPE study subgroup of 1140 diabetic patients with microalbuminuria demonstrated that ACEis reduced the risk of composite CVD events – myocardial infarction, stroke, and CVD mortality – by 28.6% (Heart Outcomes Prevention Evaluation Study Investigators 2000). The cardiac and renal protective effects of RAAS inhibitors are potentiated by not only dietary sodium restriction but also diuretic therapy (Patel et al. 2007; Heerspink et al. 2010). A Cochrane review found insufficient evidence to support the use of RAAS inhibitors in early nondiabetic nephropathy (Sharma et al. 2011). Similarly, no robust studies have reported the effects of RAAS inhibitors in CKD patients with normal albuminuria.

Glycemic Control

Targeting lower hemoglobin A1c levels with glucose-lowering agents reduces the risks of microvascular and macrovascular complications of diabetes. Randomized controlled trials in CKD patients support targeting an individualized hemoglobin A1c of less than 6.5–8.0% due to better overall survival, CVD outcomes, and decreased progression of CKD. A systematic review and meta-analysis of RCTs compared higher (standard of care) hemoglobin A1c targets to targets of less than 7%, 6.5%, and 6%, respectively, in CKD patients with diabetes (KDIGO 2020; Ruospo et al. 2017). A target of <7.0% in 11 trials reduced the risk of myocardial infarction and moderate albuminuria. A target of <6.5% in six trials reduced the risk of moderate albuminuria and ESRD. A target of <6.0% in two trials increased all-cause mortality but decreased myocardial infarction and moderate albuminuria. A higher hemoglobin A1c target may be warranted in patients with advanced CKD stages 4–5 and ESRD who are at higher risk of hypoglycemia and in whom hemoglobin A1c values are less accurate and reliable (Freedman et al. 2010; Moen et al. 2009).

Metformin and SGLT-2 inhibitors should be first-line agents in most patients with diabetes and CKD with eGFR >30 due to their efficacy, low risk of hypoglycemia, and improvements in cardiac and renal outcomes. In the general population, metformin is well established as having superior or at least comparable efficacy compared to other oral agents in reducing hemoglobin A1c without hypoglycemia or weight gain (Maruthur et al. 2016). A meta-analysis of two RCTs in the general population demonstrated that metformin reduced the risk of CVD mortality by 30–40% compared to sulfonylurea. A meta-analysis of five observational studies in CKD patients demonstrated that metformin reduced the risk of all-cause mortality by 23% and heart failure hospitalization by 9% (Crowley et al. 2017). No RCTs have evaluated the effects of metformin on cardiac or renal outcomes in patients with both CKD and diabetes.

SGLT-2 inhibitors have modest efficacy in reducing hemoglobin A1c, reducing blood pressure, and promoting weight loss (Vasilakou et al. 2013). However, they have significant cardiac and renal protective effects independent of glucose lowering. A meta-analysis of three RCTs in diabetics demonstrated that SGLT-2 inhibitors reduced the risk of CVD events by 18% and heart failure hospitalization by 40% in the eGFR 30–59 subgroup (Zelniker et al. 2019). A meta-analysis of two RCTs in patients with heart failure with reduced ejection fraction <40% demonstrated that SGLT-2 inhibitors reduced the risk of composite outcome of heart failure hospitalization or CVD mortality by 23% in the eGFR 30–59 subgroup (Zannad et al. 2020). This finding was similar in those both with and without diabetes. The primary outcomes in these trials were cardiovascular, so the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial was conducted to examine primary renal outcomes in patients with both diabetes and albuminuric CKD. Canagliflozin reduced risk of primary composite outcome of ESRD, doubling of serum creatinine, or death from cardiac or renal causes by 30% as well as the secondary composite outcome of ESRD or renal death by 28% (Perkovic et al. 2019). A meta-analysis of this trial and five others in diabetics had similar findings (McGuire et al. 2021).

If glycemic targets are not reached with metformin and SGLT-2 inhibitors, a glucagon-like peptide-1 receptor agonist (GLP-1 RA) should be added as a third agent, as it has been shown to reduce CVD events, reduce albuminuria, and likely preserve eGFR. A meta-analysis of seven RCTs of diabetic patients with and without CKD demonstrated that GLP-1 RAs reduced the risk of all-cause mortality, CVD mortality, stroke, and heart failure hospitalization by 12%, 12%, 16%, and 9%, respectively (Kristensen et al. 2019). There was also a reduction in the risk of composite renal outcome of severe albuminuria, decline in eGFR, ESRD, or renal death by 17% driven primarily by reduction in albuminuria.

Lipid Control

Statin therapy has significant cardiac and renal protective effects in CKD patients not on dialysis. In a meta-analysis of 28 trials comparing statins to placebo in CKD

patients, every 1 mmol/L reduction in LDL achieved by statins reduced the risk of vascular death, vascular event, coronary event, and stroke by 12%, 21%, 24%, and 26%, respectively (Herrington et al. 2016). Even after controlling for smaller reductions in LDL achieved by those with advanced CKD, the magnitude of risk reduction decreased proportionally with decreasing eGFR ($p = 0.008$), and there was no risk reduction in those on dialysis. Although this suggests against initiating statins for those on dialysis, it may be reasonable to continue statins for those already taking them. In one trial including patients who transitioned to dialysis after randomization, the effects of statins on major vascular events were similar for both those on and not on dialysis (Baigent et al. 2011). The same trial demonstrated the efficacy of adding ezetimibe to a moderate-dose statin for CKD patients who cannot tolerate a high-dose statin. A combination of simvastatin and ezetimibe reduced the risk of major vascular event by 17%. Statins had similar cardiovascular benefits for primary prevention in another meta-analysis of six trials in early CKD patients with no history of CVD (Major et al. 2015). A meta-analysis of 57 statin trials in CKD patients found modest renal benefits with decreased risk of proteinuria and rate of eGFR decline but no decreased risk of kidney failure events. Accordingly, both American and European cardiology guidelines support initiation of statin therapy in patients with CKD and continuation, but not initiation, of these therapies in those on dialysis (Grundy et al. 2019; Mach et al. 2020).

Antiplatelet Therapy

The use of antiplatelets in CKD patients is not well studied. In a Cochrane review of 50 RCTs of CKD patients with and without a history of CVD, antiplatelets as a class reduced the risk of myocardial infarction by 13% but increased the risk of major and minor bleeding by 33% and 49%, respectively (Palmer et al. 2013). RCTs of low-dose aspirin in the general population have found significant benefits in secondary prevention of atherosclerotic CVD that supports its use for this indication in most CKD patients despite their increased risk of bleeding (Baigent et al. 2009). Low-dose aspirin use for primary prevention of CVD in CKD is increasingly controversial because recent trials have found reduced efficacy compared to older trials and concern for underreported bleeding events. In a meta-analysis of 13 trials in patients without a history of CVD, low-dose aspirin reduced risk of composite CVD outcomes by 11% and increased the risk of major bleeding by 43% (Zheng and Roddick 2019). The number needed to treat and harm were 210 and 241 patients, respectively. In a meta-analysis of 3 RCTs with 4468 CKD patients without a history of CVD, low-dose aspirin did not reduce the risk of any CVD event and increased the risk of major and minor bleeding by 2.0- and 2.7-fold, respectively (Major et al. 2016). Similar findings were demonstrated in a post hoc analysis of the ASPirin in Reducing Events in the Elderly (ASPREE) RCT with a subgroup of 4758 CKD patients (Wolfe et al. 2021). The Aspirin To Target Arterial Events in

Chronic Kidney Disease (ATTACK trial) RCT with 25,210 CKD patients without a history of CVD is currently ongoing to better elucidate the risks and benefits of low-dose aspirin for primary prevention in this population (Major and Burton 2021).

Other Therapies

Several CKD-specific, nontraditional risk factors – anemia, hyperphosphatemia, vitamin D deficiency, and hyperuricemia – are associated with CKD progression and CVD events, but interventions targeting these parameters in RCTs have not shown improvement in clinical outcomes. RCTs investigating treatment of anemia with erythropoietin-stimulating agents targeting a hemoglobin level of at least 12 g/dL have found increased risk of CVD events. In a meta-analysis of 27 RCTs of CKD patients, use of erythropoietin-stimulating agents for a higher hemoglobin target increased risk of stroke by 51% (Palmer et al. 2010). There was a nonsignificant trend toward increased risk of CVD events by 15% ($p = 0.08$) and ESRD by 8% ($p = 0.15$). These findings have led to a focus on iron repletion and a decreased hemoglobin threshold of at least <10 g/dL prior to initiating an erythropoietin-stimulating agent. Both oral and intravenous iron are effective in improving hemoglobin in CKD patients (Shepshelovich et al. 2016). Many benefits of intravenous iron including reduced risk of CVD mortality have been shown in patients with heart failure, many with concomitant CKD. One small RCT of CKD patients suggested that intravenous iron compared to oral iron increased the incidence of CVD events (Agarwal et al. 2015). However, a larger RCT comparing high- and low-dose intravenous iron strategies in CKD patients found reduced risk of composite CVD events in the former group, although this may have been driven by reduced need and use of erythropoietin-stimulating agents (Macdougall et al. 2019). In a Cochrane review of 104 RCTs, sevelamer was superior to calcium-based binders, but phosphate binders compared to placebo did not reduce the risk of CVD events or mortality (Ruospo et al. 2018). A recent RCT of CKD patients also found that phosphate binders did not reduce risk of surrogates for CVD including arterial stiffening and aortic calcification (Toussaint et al. 2020). Vitamin D analogues are primarily used in CKD patients to suppress parathyroid hormone and maintain serum calcium levels to increase bone mineral density and reduce risk of fractures. A meta-analysis of 10 observational studies in CKD patients demonstrated that vitamin D analogues decreased the risk of CVD mortality by 45% (Lu et al. 2017). These findings have not been replicated in smaller RCTs to date. Trials have had conflicting results for the clinical benefit of urate-lowering therapies in CKD patients. A meta-analysis of 28 RCTs of patients with hyperuricemia found that urate-lowering therapies did not reduce the risk of CVD events or kidney failure but did attenuate decline in eGFR (Chen et al. 2020). The largest RCTs in CKD patients have had similar findings (Kimura et al. 2018; Doria et al. 2020).

Conclusions

The prevalence of and mortality from CKD is increasing. Most deaths and disabilities in those with CKD are from CVD. CKD increases the risk of CVD mortality, myocardial infarction, peripheral arterial disease, stroke, heart failure, valvular heart disease, atrial fibrillation, and sudden cardiac death, even after controlling for traditional risk factors. Many nontraditional CVD risk factors in CKD, such as anemia and hyperphosphatemia, have been identified. The strongest risk factors for CVD events in CKD patients are a prior history of CVD and left ventricular hypertrophy. Biomarkers such as cystatin C, troponin, natriuretic peptides, suPAR, and uric acid may help predict risk of CVD in these patients. The current CVD risk assessment models endorsed by clinical guidelines have poor risk discrimination in CKD patients that could be readily improved by incorporating eGFR and ACR into the models. CKD causes CVD through a complex interplay between inflammation, oxidative stress, and uremia, which ultimately leads to left ventricular hypertrophy with diastolic dysfunction and multimodal vascular injury. Management of the increased risk of CVD in CKD is currently focused on traditional CVD risk factor control. Traditional risk factor control with some efficacy in improving clinical cardiac and renal outcomes in CKD includes intensive blood pressure reduction to at least <130/80 mmHg; RAAS inhibition with ACEis or ARBs, particularly in diabetics or in those with albuminuria; glycemic control to an individualized hemoglobin A1c goal of <6.5–8.0% using metformin, SGLT-2 inhibitors, and possibly GLP-1 RAs; statins with or without ezetimibe in nondialysis CKD; and aspirin for secondary prevention. Lifestyle interventions – dietary sodium and protein restriction, exercise, weight loss, and smoking cessation – may have some benefits but have not clearly improved clinical outcomes in RCTs. Nontraditional risk factor control with erythropoietin-stimulating agents, iron, vitamin D analogues, phosphate binders, and urate-lowering therapies has not clearly improved clinical outcomes in RCTs.

References

Agarwal R, Kusek JW, Pappas MK. A randomized trial of intravenous and oral iron in chronic kidney disease. Kidney Int. 2015;88(4):905–14.

Babitt JL, Lin HY. Mechanisms of anemia in CKD. J Am Soc Nephrol. 2012;23(10):1631–4.

Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet (London, England). 2009;373(9678):1849–60.

Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet (London, England). 2011;377(9784):2181–92.

Bansal N, Zelnick LR, Alonso A, Benjamin EJ, de Boer IH, Deo R, et al. eGFR and albuminuria in relation to risk of incident atrial fibrillation: a meta-analysis of the Jackson heart study,

the multi-ethnic study of atherosclerosis, and the cardiovascular health study. Clin J Am Soc Nephrol. 2017;12(9):1386–98.
Bansal N, Zelnick L, Bhat Z, Dobre M, He J, Lash J, et al. Burden and outcomes of heart failure hospitalizations in adults with chronic kidney disease. J Am Coll Cardiol. 2019a;73(21):2691–700.
Bansal N, Zelnick L, Go A, Anderson A, Christenson R, Deo R, et al. Cardiac biomarkers and risk of incident heart failure in chronic kidney disease: The CRIC (Chronic Renal Insufficiency Cohort) Study. J Am Heart Assoc. 2019b;8(21):e012336.
Beddhu S, Wei G, Marcus RL, Chonchol M, Greene T. Light-intensity physical activities and mortality in the United States general population and CKD subpopulation. Clin J Am Soc Nephrol. 2015;10(7):1145–53.
Beddhu S, Chertow GM, Cheung AK, Cushman WC, Rahman M, Greene T, et al. Influence of baseline diastolic blood pressure on effects of intensive compared with standard blood pressure control. Circulation. 2018;137(2):134–43.
Betriu A, Martinez-Alonso M, Arcidiacono MV, Cannata-Andia J, Pascual J, Valdivielso JM, et al. Prevalence of subclinical atheromatosis and associated risk factors in chronic kidney disease: the NEFRONA study. Nephrol Dial Transplant. 2014;29(7):1415–22.
Bolignano D, Zoccali C. Effects of weight loss on renal function in obese CKD patients: a systematic review. Nephrol Dial Transplant. 2013;28(Suppl 4):iv82–98.
Bolignano D, Lacquaniti A, Coppolino G, Donato V, Campo S, Fazio MR, et al. Neutrophil gelatinase-associated lipocalin (NGAL) and progression of chronic kidney disease. Clin J Am Soc Nephrol. 2009;4(2):337–44.
Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345(12):861–9.
Bright R. Cases and observations illustrative of renal disease accompanied with the secretion of albuminous urine. Guy's Hospital Report. 1836;10:338–40.
Chen Q, Wang Z, Zhou J, Chen Z, Li Y, Li S, et al. Effect of urate-lowering therapy on cardiovascular and kidney outcomes: a systematic review and meta-analysis. Clin J Am Soc Nephrol. 2020;15(11):1576–86.
Cheung AK, Rahman M, Reboussin DM, Craven TE, Greene T, Kimmel PL, et al. Effects of intensive BP control in CKD. J Am Soc Nephrol. 2017;28(9):2812–23.
Crowley MJ, Diamantidis CJ, McDuffie JR, Cameron CB, Stanifer JW, Mock CK, et al. Clinical outcomes of metformin use in populations with chronic kidney disease, congestive heart failure, or chronic liver disease: a systematic review. Ann Intern Med. 2017;166(3):191–200.
De Cosmo S, Viazzi F, Pacilli A, Giorda C, Ceriello A, Gentile S, et al. Serum uric acid and risk of CKD in type 2 diabetes. Clin J Am Soc Nephrol. 2015;10(11):1921–9.
Deo R, Khodneva YA, Shlipak MG, Soliman EZ, Judd SE, McClellan WM, et al. Albuminuria, kidney function, and sudden cardiac death: findings from the reasons for geographic and racial differences in stroke (REGARDS) study. Heart Rhythm. 2017;14(1):65–71.
Doria A, Galecki AT, Spino C, Pop-Busui R, Cherney DZ, Lingvay I, et al. Serum urate lowering with allopurinol and kidney function in type 1 diabetes. N Engl J Med. 2020;382(26):2493–503.
Drechsler C, Hayek SS, Wei C, Sever S, Genser B, Krane V, et al. Soluble Urokinase plasminogen activator receptor and outcomes in patients with diabetes on hemodialysis. Clin J Am Soc Nephrol. 2017;12(8):1265–73.
Eiselt J, Rajdl D, Racek J, Vostrý M, Rulcová K, Wirth J. Asymmetric dimethylarginine and progression of chronic kidney disease: a one-year follow-up study. Kidney Blood Press Res. 2014;39(1):50–7.
Eknoyan G, Lameire N, Eckardt K, Kasiske B, Wheeler D, Levin A, et al. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. 2013;3(1):5–14.
Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet (London, England). 2016;387(10022):957–67.

Evans M, Grams ME, Sang Y, Astor BC, Blankestijn PJ, Brunskill NJ, et al. Risk factors for prognosis in patients with severely decreased GFR. Kidney Int Rep. 2018;3(3):625–37.

Farshid A, Pathak R, Shadbolt B, Arnolda L, Talaulikar G. Diastolic function is a strong predictor of mortality in patients with chronic kidney disease. BMC Nephrol. 2013;14:280.

Flesher M, Woo P, Chiu A, Charlebois A, Warburton DE, Leslie B. Self-management and biomedical outcomes of a cooking, and exercise program for patients with chronic kidney disease. J Ren Nutr. 2011;21(2):188–95.

Fliser D, Kollerits B, Neyer U, Ankerst DP, Lhotta K, Lingenhel A, et al. Fibroblast growth factor 23 (FGF23) predicts progression of chronic kidney disease: the Mild to Moderate Kidney Disease (MMKD) Study. J Am Soc Nephrol. 2007;18(9):2600–8.

Freedman BI, Shihabi ZK, Andries L, Cardona CY, Peacock TP, Byers JR, et al. Relationship between assays of glycemia in diabetic subjects with advanced chronic kidney disease. Am J Nephrol. 2010;31(5):375–9.

GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet (London, England). 2020;395(10225):709–33.

Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the Management of Blood Cholesterol: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Circulation. 2019;139(25):e1082–e143.

Hahn D, Hodson EM, Fouque D. Low protein diets for non-diabetic adults with chronic kidney disease. Cochrane Database Syst Rev. 2018;10(10):Cd001892.

Harrison TG, Shukalek CB, Hemmelgarn BR, Zarnke KB, Ronksley PE, Iragorri N, et al. Association of NT-proBNP and BNP with future clinical outcomes in patients with ESKD: a systematic review and meta-analysis. Am J Kidney Dis. 2020;76(2):233–47.

Hasegawa M, Ishii J, Kitagawa F, Takahashi H, Sugiyama K, Tada M, et al. Plasma neutrophil gelatinase-associated Lipocalin as a predictor of cardiovascular events in patients with chronic kidney disease. Biomed Res Int. 2016;2016:8761475.

Hayek SS, Sever S, Ko YA, Trachtman H, Awad M, Wadhwani S, et al. Soluble urokinase receptor and chronic kidney disease. N Engl J Med. 2015;373(20):1916–25.

He J, Mills KT, Appel LJ, Yang W, Chen J, Lee BT, et al. Urinary sodium and potassium excretion and CKD progression. J Am Soc Nephrol. 2016;27(4):1202–12.

Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet (London, England). 2000;355(9200):253–9.

Heerspink HJ, Ninomiya T, Perkovic V, Woodward M, Zoungas S, Cass A, et al. Effects of a fixed combination of perindopril and indapamide in patients with type 2 diabetes and chronic kidney disease. Eur Heart J. 2010;31(23):2888–96.

Heiwe S, Jacobson SH. Exercise training in adults with CKD: a systematic review and meta-analysis. Am j Kidney Dis. 2014;64(3):383–93.

Herrington WG, Emberson J, Mihaylova B, Blackwell L, Reith C, Solbu MD, et al. Impact of renal function on the effects of LDL cholesterol lowering with statin-based regimens: a meta-analysis of individual participant data from 28 randomised trials. Lancet Diab Endocrinol. 2016;4(10):829–39.

Huang H, Huang B, Li Y, Huang Y, Li J, Yao H, et al. Uric acid and risk of heart failure: a systematic review and meta-analysis. Eur J Heart Fail. 2014;16(1):15–24.

Hung SC, Kuo KL, Peng CH, Wu CH, Lien YC, Wang YC, et al. Volume overload correlates with cardiovascular risk factors in patients with chronic kidney disease. Kidney Int. 2014;85(3):703–9.

Hung SC, Lai YS, Kuo KL, Tarng DC. Volume overload and adverse outcomes in chronic kidney disease: clinical observational and animal studies. J Am Heart Assoc. 2015;4(5):e001918.

Iimori S, Naito S, Noda Y, Nishida H, Kihira H, Yui N, et al. Anaemia management and mortality risk in newly visiting patients with chronic kidney disease in Japan: The CKD-ROUTE study. Nephrology (Carlton, Vic). 2015;20(9):601–8.

Ix JH, Katz R, Kestenbaum BR, de Boer IH, Chonchol M, Mukamal KJ, et al. Fibroblast growth factor-23 and death, heart failure, and cardiovascular events in community-living individuals: CHS (Cardiovascular Health Study). J Am Coll Cardiol. 2012;60(3):200–7.

KDIGO. 2020 clinical practice guideline for diabetes Management in Chronic Kidney Disease. Kidney Int. 2020;98(4s):S1–s115.

Kelly DM, Rothwell PM. Does chronic kidney disease predict stroke risk independent of blood pressure?: a systematic review and meta-regression. Stroke. 2019;50(11):3085–92.

Kennedy D, Omran E, Periyasamy SM, Nadoor J, Priyadarshi A, Willey JC, et al. Effect of chronic renal failure on cardiac contractile function, calcium cycling, and gene expression of proteins important for calcium homeostasis in the rat. J Am Soc Nephrol. 2003;14(1):90–7.

Kim SY, Guevara JP, Kim KM, Choi HK, Heitjan DF, Albert DA. Hyperuricemia and coronary heart disease: a systematic review and meta-analysis. Arthritis Care Res. 2010;62(2):170–80.

Kimura K, Hosoya T, Uchida S, Inaba M, Makino H, Maruyama S, et al. Febuxostat therapy for patients with stage 3 CKD and asymptomatic hyperuricemia: a randomized trial. Am J Kidney Dis. 2018;72(6):798–810.

Kristensen SL, Rørth R, Jhund PS, Docherty KF, Sattar N, Preiss D, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Diab Endocrinol. 2019;7(10):776–85.

Ku E, Lee BJ, Wei J, Weir MR. Hypertension in CKD: Core curriculum 2019. Am J Kidney Dis. 2019;74(1):120–31.

Lambers Heerspink HJ, Holtkamp FA, Parving HH, Navis GJ, Lewis JB, Ritz E, et al. Moderation of dietary sodium potentiates the renal and cardiovascular protective effects of angiotensin receptor blockers. Kidney Int. 2012;82(3):330–7.

Lee S, Kang S, Joo YS, Lee C, Nam KH, Yun HR, et al. Smoking, smoking cessation, and progression of chronic kidney disease: results from KNOW-CKD study. Nicotine Tob Res. 2020.

Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–12.

Levin A, Singer J, Thompson CR, Ross H, Lewis M. Prevalent left ventricular hypertrophy in the predialysis population: identifying opportunities for intervention. Am J Kidney Dis. 1996;27(3):347–54.

Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001;345(12):851–60.

Lu RJ, Zhu SM, Tang FL, Zhu XS, Fan ZD, Wang GL, et al. Effects of vitamin D or its analogues on the mortality of patients with chronic kidney disease: an updated systematic review and meta-analysis. Eur J Clin Nutr. 2017;71(6):683–93.

Luo Q, Xia X, Li B, Lin Z, Yu X, Huang F. Serum uric acid and cardiovascular mortality in chronic kidney disease: a meta-analysis. BMC Nephrol. 2019;20(1):18.

Lv J, Ehteshami P, Sarnak MJ, Tighiouart H, Jun M, Ninomiya T, et al. Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis. CMAJ. 2013;185(11):949–57.

Macdougall IC, White C, Anker SD, Bhandari S, Farrington K, Kalra PA, et al. Intravenous iron in patients undergoing maintenance hemodialysis. N Engl J Med. 2019;380(5):447–58.

Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111–88.

Major RW, Burton JO. "To take or not to take an aspirin?" The age-old question of cardiovascular disease primary prevention for people with chronic kidney disease. Kidney Int. 2021;99(2):308–10.

Major RW, Cheung CK, Gray LJ, Brunskill NJ. Statins and cardiovascular primary prevention in CKD: a meta-analysis. Clin J Am Soc Nephrol. 2015;10(5):732–9.
Major RW, Oozeerally I, Dawson S, Riddleston H, Gray LJ, Brunskill NJ. Aspirin and cardiovascular primary prevention in non-endstage chronic kidney disease: a meta-analysis. Atherosclerosis. 2016;251:177–82.
Major RW, Cheng MRI, Grant RA, Shantikumar S, Xu G, Oozeerally I, et al. Cardiovascular disease risk factors in chronic kidney disease: a systematic review and meta-analysis. PLoS One. 2018;13(3):e0192895.
Mall G, Huther W, Schneider J, Lundin P, Ritz E. Diffuse intermyocardiocytic fibrosis in uraemic patients. Nephrol Dial Transplant. 1990;5(1):39–44.
Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. Ann Intern Med. 2001;134(8):629–36.
Mark PB, Johnston N, Groenning BA, Foster JE, Blyth KG, Martin TN, et al. Redefinition of uremic cardiomyopathy by contrast-enhanced cardiac magnetic resonance imaging. Kidney Int. 2006;69(10):1839–45.
Marthi A, Donovan K, Haynes R, Wheeler DC, Baigent C, Rooney CM, et al. Fibroblast growth Factor-23 and risks of cardiovascular and noncardiovascular diseases: a meta-analysis. J Am Soc Nephrol. 2018;29(7):2015–27.
Martínez-Castelao A, Górriz JL, Portolés JM, De Alvaro F, Cases A, Luño J, et al. Baseline characteristics of patients with chronic kidney disease stage 3 and stage 4 in Spain: the MERENA observational cohort study. BMC Nephrol. 2011;12:53.
Maruthur NM, Tseng E, Hutfless S, Wilson LM, Suarez-Cuervo C, Berger Z, et al. Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med. 2016;164(11):740–51.
Masson P, Webster AC, Hong M, Turner R, Lindley RI, Craig JC. Chronic kidney disease and the risk of stroke: a systematic review and meta-analysis. Nephrol Dial Transplant. 2015;30(7):1162–9.
Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet (London, England). 2010;375(9731):2073–81.
Matsushita K, Mahmoodi BK, Woodward M, Emberson JR, Jafar TH, Jee SH, et al. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. JAMA. 2012;307(18):1941–51.
Matsushita K, Coresh J, Sang Y, Chalmers J, Fox C, Guallar E, et al. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. Lancet Diabetes Endocrinol. 2015;3(7):514–25.
Matsushita K, Ballew SH, Coresh J, Arima H, Ärnlöv J, Cirillo M, et al. Measures of chronic kidney disease and risk of incident peripheral artery disease: a collaborative meta-analysis of individual participant data. Lancet Diabetes Endocrinol. 2017;5(9):718–28.
Matsushita K, Jassal SK, Sang Y, Ballew SH, Grams ME, Surapaneni A, et al. Incorporating kidney disease measures into cardiovascular risk prediction: development and validation in 9 million adults from 72 datasets. EClin Med. 2020;27:100552.
McGuire DK, Shih WJ, Cosentino F, Charbonnel B, Cherney DZI, Dagogo-Jack S, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. JAMA Cardiol. 2021;6(2):148–58.
McMahon EJ, Campbell KL, Bauer JD, Mudge DW. Altered dietary salt intake for people with chronic kidney disease. Cochrane Database Syst Rev. 2015;(2):Cd010070.
Meijers B, Poesen R, Claes K, Dietrich R, Bammens B, Sprangers B, et al. Soluble urokinase receptor is a biomarker of cardiovascular disease in chronic kidney disease. Kidney Int. 2015;87(1):210–6.
Metivier F, Marchais SJ, Guerin AP, Pannier B, London GM. Pathophysiology of anaemia: focus on the heart and blood vessels. Nephrol Dial Transplant. 2000;15(Suppl 3):14–8.

Michos ED, Wilson LM, Yeh HC, Berger Z, Suarez-Cuervo C, Stacy SR, et al. Prognostic value of cardiac troponin in patients with chronic kidney disease without suspected acute coronary syndrome: a systematic review and meta-analysis. Ann Intern Med. 2014;161(7):491–501.

Mills KT, Chen J, Yang W, Appel LJ, Kusek JW, Alper A, et al. Sodium excretion and the risk of cardiovascular disease in patients with chronic kidney disease. JAMA. 2016;315(20):2200–10.

Moen MF, Zhan M, Hsu VD, Walker LD, Einhorn LM, Seliger SL, et al. Frequency of hypoglycemia and its significance in chronic kidney disease. Clin J Am Soc Nephrol. 2009;4(6):1121–7.

Nair V, Robinson-Cohen C, Smith MR, Bellovich KA, Bhat ZY, Bobadilla M, et al. Growth differentiation factor-15 and risk of CKD progression. J Am Soc Nephrol. 2017;28(7):2233–40.

Neuen BL, Young T, Heerspink HJL, Neal B, Perkovic V, Billot L, et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. Lancet Diab Endocrinol. 2019;7(11):845–54.

Obi Y, Kalantar-Zadeh K, Shintani A, Kovesdy CP, Hamano T. Estimated glomerular filtration rate and the risk-benefit profile of intensive blood pressure control amongst nondiabetic patients: a post hoc analysis of a randomized clinical trial. J Intern Med. 2018;283(3):314–27.

Palmer SC, Navaneethan SD, Craig JC, Johnson DW, Tonelli M, Garg AX, et al. Meta-analysis: erythropoiesis-stimulating agents in patients with chronic kidney disease. Ann Intern Med. 2010;153(1):23–33.

Palmer SC, Di Micco L, Razavian M, Craig JC, Perkovic V, Pellegrini F, et al. Antiplatelet agents for chronic kidney disease. Cochrane Database Syst Rev. 2013;(2):Cd008834.

Parfrey PS, Foley RN, Harnett JD, Kent GM, Murray DC, Barre PE. Outcome and risk factors for left ventricular disorders in chronic uraemia. Nephrol Dial Transplant. 1996;11(7):1277–85.

Park M, Hsu CY, Li Y, Mishra RK, Keane M, Rosas SE, et al. Associations between kidney function and subclinical cardiac abnormalities in CKD. J Am Soc Nephrol. 2012;23(10):1725–34.

Park M, Hsu CY, Go AS, Feldman HI, Xie D, Zhang X, et al. Urine kidney injury biomarkers and risks of cardiovascular disease events and all-cause death: the CRIC study. Clin J Am Soc Nephrol. 2017;12(5):761–71.

Patel A, MacMahon S, Chalmers J, Neal B, Woodward M, Billot L, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet (London, England). 2007;370(9590):829–40.

Peralta CA, Katz R, Sarnak MJ, Ix J, Fried LF, De Boer I, et al. Cystatin C identifies chronic kidney disease patients at higher risk for complications. J Am Soc Nephrol. 2011;22(1):147–55.

Perkovic V, Verdon C, Ninomiya T, Barzi F, Cass A, Patel A, et al. The relationship between proteinuria and coronary risk: a systematic review and meta-analysis. PLoS Med. 2008;5(10):e207.

Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019;380(24):2295–306.

Ritchie J, Rainone F, Green D, Alderson H, Chiu D, Middleton R, et al. Extreme elevations in blood pressure and all-cause mortality in a referred CKD population: results from the CRISIS study. Int J Hypertens. 2013;2013:597906.

Ruospo M, Saglimbene VM, Palmer SC, De Cosmo S, Pacilli A, Lamacchia O, et al. Glucose targets for preventing diabetic kidney disease and its progression. The Cochrane database of systematic reviews. 2017;6(6):Cd010137.

Ruospo M, Palmer SC, Natale P, Craig JC, Vecchio M, Elder GJ, et al. Phosphate binders for preventing and treating chronic kidney disease-mineral and bone disorder (CKD-MBD). The Cochrane database of systematic reviews. 2018;8(8):Cd006023.

Samad Z, Sivak JA, Phelan M, Schulte PJ, Patel U, Velazquez EJ. Prevalence and Outcomes of Left-Sided Valvular Heart Disease Associated With Chronic Kidney Disease. J Am Heart Assoc. 2017;6(10):e006044.

Saran R, Robinson B, Abbott KC, Agodoa LYC, Bragg-Gresham J, Balkrishnan R, et al. US renal data system 2018 annual data report: epidemiology of kidney disease in the United States. Am J Kidney Dis. 2019;73(3 Suppl 1):A7–a8.

Schei J, Stefansson VT, Mathisen UD, Eriksen BO, Solbu MD, Jenssen TG, et al. Residual associations of inflammatory markers with eGFR after accounting for measured GFR in a community-based cohort without CKD. Clin J Am Soc Nephrol. 2016;11(2):280–6.

Shah R, Matthews GJ, Shah RY, McLaughlin C, Chen J, Wolman M, et al. Serum Fractalkine (CX3CL1) and cardiovascular outcomes and diabetes: findings from the chronic renal insufficiency cohort (CRIC) study. Am J Kidney Dis. 2015;66(2):266–73.

Sharma P, Blackburn RC, Parke CL, McCullough K, Marks A, Black C. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for adults with early (stage 1 to 3) non-diabetic chronic kidney disease. Cochrane Database Syst Rev. 2011;(10):Cd007751.

Shepshelovich D, Rozen-Zvi B, Avni T, Gafter U, Gafter-Gvili A. Intravenous versus Oral iron supplementation for the treatment of anemia in CKD: an updated systematic review and meta-analysis. Am J Kidney Dis. 2016;68(5):677–90.

Shlipak MG, Matsushita K, Ärnlöv J, Inker LA, Katz R, Polkinghorne KR, et al. Cystatin C versus creatinine in determining risk based on kidney function. N Engl J Med. 2013;369(10):932–43.

Stack AG, Donigiewicz U, Abdalla AA, Weiland A, Casserly LF, Cronin CJ, et al. Plasma fibrinogen associates independently with total and cardiovascular mortality among subjects with normal and reduced kidney function in the general population. QJM. 2014;107(9):701–13.

Strippoli GF, Bonifati C, Craig M, Navaneethan SD, Craig JC. Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. Cochrane Database Syst Rev. 2006;2006(4):Cd006257.

Su X, Zhang L, Lv J, Wang J, Hou W, Xie X, et al. Effect of statins on kidney disease outcomes: a systematic review and meta-analysis. Am J Kidney Dis. 2016;67(6):881–92.

Suzuki T, Agarwal SK, Deo R, Sotoodehnia N, Grams ME, Selvin E, et al. Kidney function and sudden cardiac death in the community: the atherosclerosis risk in communities (ARIC) study. Am Heart J. 2016;180:46–53.

Thompson S, James M, Wiebe N, Hemmelgarn B, Manns B, Klarenbach S, et al. Cause of death in patients with reduced kidney function. J Am Soc Nephrol. 2015;26(10):2504–11.

Torino C, Pizzini P, Cutrupi S, Postorino M, Tripepi G, Mallamaci F, et al. Soluble Urokinase plasminogen activator receptor (suPAR) and all-cause and cardiovascular mortality in diverse hemodialysis patients. Kidney Int Rep. 2018;3(5):1100–9.

Toussaint ND, Pedagogos E, Lioufas NM, Elder GJ, Pascoe EM, Badve SV, et al. A randomized trial on the effect of phosphate reduction on vascular end points in CKD (IMPROVE-CKD). J Am Soc Nephrol. 2020;31(11):2653–66.

Turin TC, Ahmed SB, Tonelli M, Manns B, Ravani P, James M, et al. Kidney function, albuminuria and life expectancy. Can J Kidney Health Dis. 2014;1:33.

Valdivielso JM, Rodríguez-Puyol D, Pascual J, Barrios C, Bermúdez-López M, Sánchez-Niño MD, et al. Atherosclerosis in chronic kidney disease: more, less, or just different? Arterioscler Thromb Vasc Biol. 2019;39(10):1938–66.

van der Velde M, Matsushita K, Coresh J, Astor BC, Woodward M, Levey A, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. Kidney Int. 2011;79(12):1341–52.

Vashistha V, Lee M, Wu YL, Kaur S, Ovbiagele B. Low glomerular filtration rate and risk of myocardial infarction: a systematic review and meta-analysis. Int J Cardiol. 2016;223:401–9.

Vasilakou D, Karagiannis T, Athanasiadou E, Mainou M, Liakos A, Bekiari E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med. 2013;159(4):262–74.

Vavilis G, Bäck M, Occhino G, Trevisan M, Bellocco R, Evans M, et al. Kidney dysfunction and the risk of developing aortic stenosis. J Am Coll Cardiol. 2019;73(3):305–14.

Wang X, Shapiro JI. Evolving concepts in the pathogenesis of uraemic cardiomyopathy. Nat Rev Nephrol. 2019;15(3):159–75.

Wang K, Zelnick LR, Anderson A, Cohen J, Dobre M, Deo R, et al. Cardiac biomarkers and risk of mortality in CKD (the CRIC study). Kidney Int Rep. 2020;5(11):2002–12.

Wanner C, Amann K, Shoji T. The heart and vascular system in dialysis. Lancet (London, England). 2016;388(10041):276–84.
Webster AC, Nagler EV, Morton RL, Masson P. Chronic Kidney Disease. Lancet (London, England). 2017;389(10075):1238–52.
Weiner DE, Tighiouart H, Elsayed EF, Griffith JL, Salem DN, Levey AS, et al. The Framingham predictive instrument in chronic kidney disease. J Am Coll Cardiol. 2007;50(3):217–24.
Weiner DE, Tighiouart H, Elsayed EF, Griffith JL, Salem DN, Levey AS, et al. The relationship between nontraditional risk factors and outcomes in individuals with stage 3 to 4 CKD. Am J Kidney Dis. 2008;51(2):212–23.
Wen CP, Cheng TY, Tsai MK, Chang YC, Chan HT, Tsai SP, et al. All-cause mortality attributable to chronic kidney disease: a prospective cohort study based on 462 293 adults in Taiwan. Lancet (London, England). 2008;371(9631):2173–82.
Wolfe R, Wetmore JB, Woods RL, McNeil JJ, Gallagher H, Roderick P, et al. Subgroup analysis of the ASPirin in reducing events in the elderly randomized clinical trial suggests aspirin did not improve outcomes in older adults with chronic kidney disease. Kidney Int. 2021;99(2):466–74.
Xia J, Wang L, Ma Z, Zhong L, Wang Y, Gao Y, et al. Cigarette smoking and chronic kidney disease in the general population: a systematic review and meta-analysis of prospective cohort studies. Nephrol Dial Transplant. 2017;32(3):475–87.
Xie X, Liu Y, Perkovic V, Li X, Ninomiya T, Hou W, et al. Renin-angiotensin system inhibitors and kidney and cardiovascular outcomes in patients with CKD: a Bayesian network meta-analysis of randomized clinical trials. Am J Kidney Dis. 2016;67(5):728–41.
Yaseen M, Hassan W, Awad R, Ashqar B, Neyra J, Heister T, et al. Impact of recent clinical trials on nephrology practice: are we in a stagnant era? Kidney Dis (Basel, Switzerland). 2019;5(2):69–80.
Young JM, Terrin N, Wang X, Greene T, Beck GJ, Kusek JW, et al. Asymmetric dimethylarginine and mortality in stages 3 to 4 chronic kidney disease. Clin J Am Soc Nephrol. 2009;4(6):1115–20.
Yuan J, Zou XR, Han SP, Cheng H, Wang L, Wang JW, et al. Prevalence and risk factors for cardiovascular disease among chronic kidney disease patients: results from the Chinese cohort study of chronic kidney disease (C-STRIDE). BMC Nephrol. 2017;18(1):23.
Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. Lancet (London, England). 2020;396(10254):819–29.
Zanoli L, Lentini P, Briet M, Castellino P, House AA, London GM, et al. Arterial stiffness in the heart disease of CKD. J Am Soc Nephrol. 2019;30(6):918–28.
Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet (London, England). 2019;393(10166):31–9.
Zeng WT, Sun XT, Tang K, Mei WY, Liu LJ, Xu Q, et al. Risk of thromboembolic events in atrial fibrillation with chronic kidney disease. Stroke. 2015;46(1):157–63.
Zheng SL, Roddick AJ. Association of aspirin use for primary prevention with cardiovascular events and bleeding events: a systematic review and meta-analysis. JAMA. 2019;321(3):277–87.

Chapter 15
Peripheral Arterial Disease and the Ankle–Brachial Index

Peter P. Toth

Introduction

Peripheral arterial disease (PAD) is widely prevalent throughout the world and represents the development of atherosclerotic disease in the lower extremities (Song et al. 2019). The prevalence of PAD increases as a function of age in both men and women, and Black men and women and Native American women appear to be disproportionately affected (Fig. 15.1a, b) (Allison et al. 2007; Virani et al. 2020). In the San Diego Population Study, Blacks have a higher prevalence of PAD compared to non-Hispanic Whites (odds ratio 2.30, $p < -0.024$), and this difference is not accounted for because of higher rates of hypertension, diabetes mellitus, or increased body mass index (Criqui et al. 2005). Based on the Third National Health and Nutrition Examination Survey (NHANES III), in 2004, it was estimated that approximately five million Americans (4.3% of the US population) over the age of 40 years had PAD (Selvin and Erlinger 2004). The Global Burden of Disease Study 2017 reported a worldwide prevalence of PAD of 118.1 million and a global incidence of 10.8 million cases (James et al. 2018). Approximately two-thirds of all cases of PAD are asymptomatic, 78.6 million are asymptomatic vs 39.5 million who are symptomatic with claudication; hence, PAD is likely significantly underdiagnosed and undertreated (James et al. 2018). In another analysis, the global prevalence estimate for PAD in 2015 was 236.6 million aged 25 years and older, with the Western Pacific Region having the highest prevalence (74.1 million) and the Eastern Mediterranean Region having the lowest prevalence (14.7 million) (Song et al. 2019).

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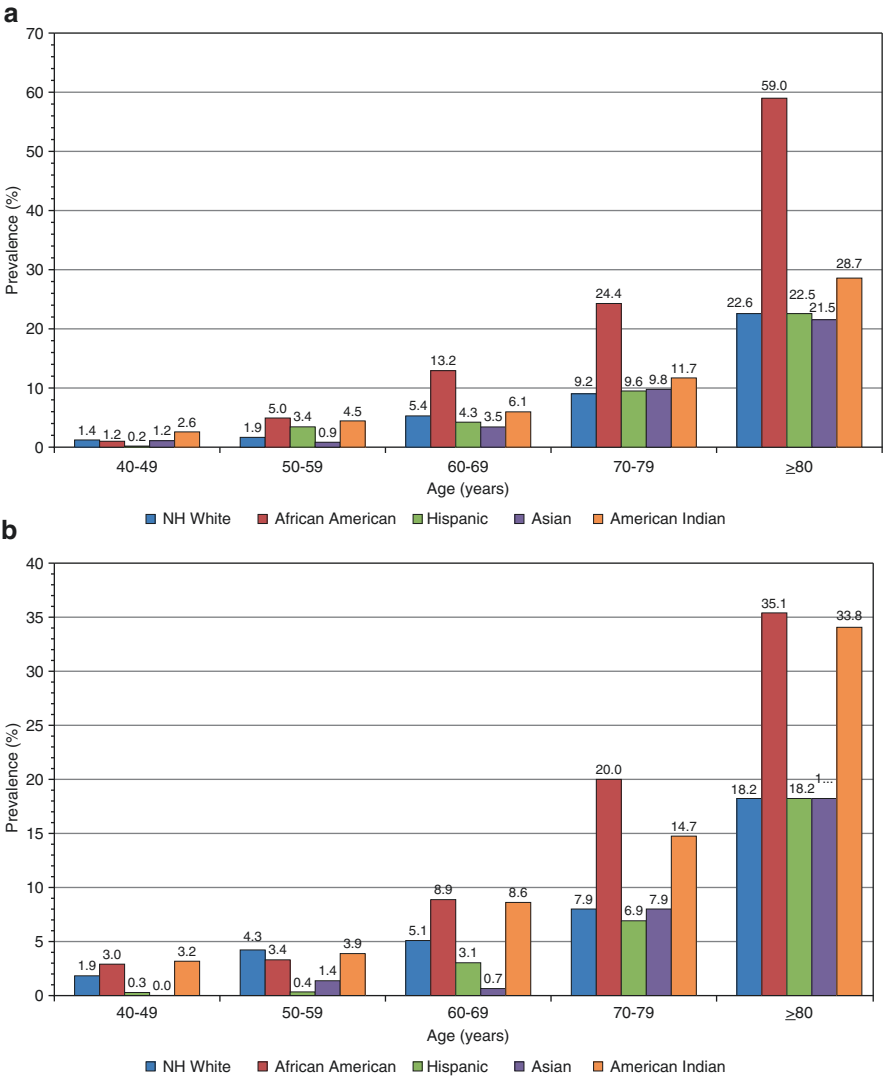

Fig. 15.1 (**a**, **b**) Estimates of peripheral arterial disease in men (**a**) and women (**b**) by age and ethnicity in the United States in 2000. (Reproduced with permission from Virani et al. (2020))

Peripheral Arterial Disease and Cardiovascular Events

Based on the Heart and Soul Study, PAD is associated with a 70% increased risk of cardiovascular events (adjusted hazard ratio (HR) 1.7, 95% confidence interval (CI), 1.0–2.9, $p = 0.04$) and an 80% increased risk of mortality (adjusted HR 1.8, 95% CI, 1.2–2.7, $p = 0.006$) compared to persons without PAD (Grenon et al. 2013). In the Fremantle Diabetes Study, PAD was associated with a 67% increase in risk for

cardiac mortality among diabetic patients (Norman et al. 2006). In the Multi-Ethnic Study of Atherosclerosis, over a median follow-up of 8.5 years, PAD was associated with 1.5-fold increase in risk for atrial fibrillation and a 1.7-fold increase in risk for incident stroke (O'Neal et al. 2014). PAD also increases risk for lower extremity revascularization as well as lower extremity amputation and associated disabilities. Lower extremity amputation due to critical limb ischemia in diabetic patients is associated with a 5-year mortality rate that is higher than many malignancies (Barnes et al. 2020). Early identification of PAD and the initiation of appropriate pharmacological and lifestyle modifications help reduce the progression of disease, risk for acute cardiovascular events, rate of functional decline, and need for surgical interventions. In patients with established PAD, adherence to therapy with aspirin, a statin, and an angiotensin-converting enzyme inhibitor coupled with smoking cessation over 3 years of follow-up is associated with a 36% ($p = 0.009$) reduction in risk for major acute coronary events (nonfatal myocardial infarction, stroke, or mortality) and a 44% ($p = 0.003$) lower risk of major acute limb events (major amputation, thrombolysis, or surgical bypass) compared to persons with PAD receiving less than four of these interventions (Armstrong et al. 2014) (Fig. 15.2).

Intermittent Claudication

Only a minority of patients with PAD experience intermittent claudication. In the Edinburgh Artery Study, only 15% of participants with PAD experienced claudication (Fowkes et al. 1991). Among patients experiencing claudication (that can manifest as muscle pain, cramping, or fatigue precipitated by activity-induced myocyte ischemia), symptoms can develop in a variety of locations depending upon the specific arteries afflicted with atherosclerotic disease. They include the following (Dhaliwal and Mukherjee 2007):

- Buttock and hip – aortoiliac artery disease
- Impotence – bilateral aortoiliac artery disease
- Thigh – common femoral or aortoiliac artery disease
- Upper two-thirds of the calf – superficial femoral artery disease
- Lower one-third of the calf – popliteal artery disease
- Foot claudication – tibial or peroneal artery disease

Among claudicants, symptoms typically subside within 10 minutes of initiation of rest. As shown in the Walking and Leg Circulation Study (WLCS), many patients remain asymptomatic because they reduce their level of activity in order to avoid the development of ischemia-related symptoms (McDermott et al. 2002). They can become progressively more sedentary to avoid symptoms, which paradoxically can hasten progression of PAD. Persons with persistently asymptomatic PAD (hazard ratio (HR) 2.94, 95% confidence interval (CI), 1.39–6.19, $p = 0.005$) and those with leg pain during both exertion and rest (HR 2.89, 95% CI, 1.47–5.68, $p = 0.002$) have greater loss of ambulatory capacity (walking time in minutes) than persons with

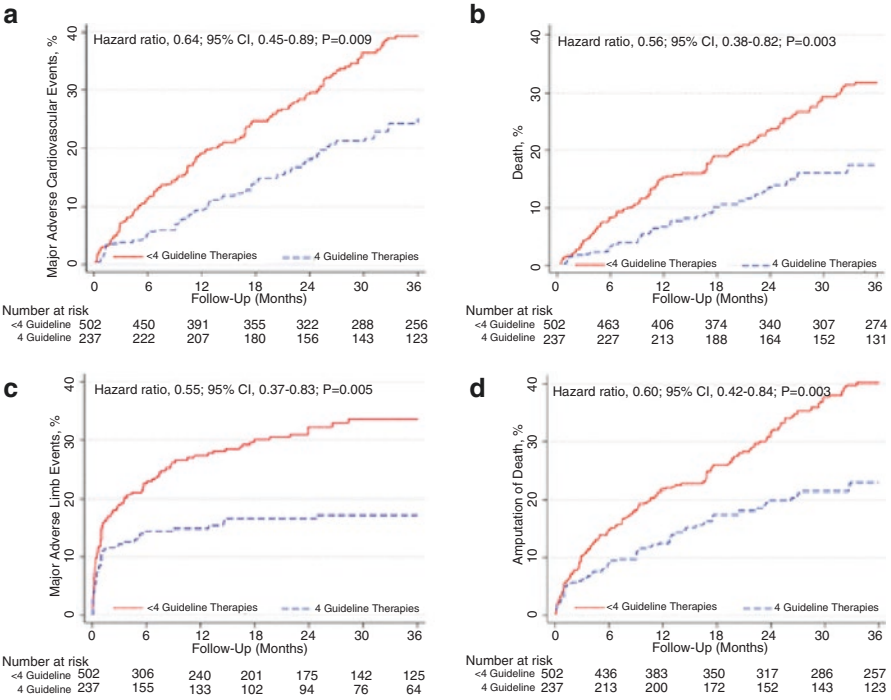

Fig. 15.2 Major adverse cardiovascular events and limb outcomes among patients adhering to four guideline-recommended therapies. Cumulative hazard curves to 3 years post procedure showing the proportion free of (**a**) MACE (MI, stroke, or death; $p = 0.009$), (**b**) death ($p = 0.003$), (**c**) MALE (bypass graft surgery, thrombolysis, or major amputation; $p = 0.005$), and (**d**) amputation or death ($p = 0.003$). All curves are after propensity weighting. CI confidence interval, MACE major adverse cardiovascular event, MALE major adverse limb event, MI myocardial infarction. (Reproduced from Armstrong et al. (2014)) (This is an open-access article under the terms of the Creative Commons Attribution-Non-Commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes)

intermittent claudication (McDermott et al. 2010). When compared to participants with intermittent claudication, persons with asymptomatic PAD have a higher calf muscle percentage fat (16.1 vs 9.5%), lower 6-minute walking length (966 vs 1129 ft), smaller calf muscle area (4935 vs 5592 mm^2), slower 4-minute usual-paced walking speed (0.94 vs 0.84 meters/sec), lower stair climbing score, and lower physical functioning score ($p < 0.001$ for all comparisons). Functional decline in patients with PAD is highly predictive of risk for cardiovascular events. In an analysis from WLCS II, participants in the tertile with the greatest 6-min walk decline had the highest subsequent mobility loss (hazard ratio (HR) 3.50, $p = 0.002$), all-cause mortality (HR 2.16, $p = 0.004$), and cardiovascular mortality (HR 2.45, $p = 0.031$), compared with those in the lowest tertile for 6-min walk decline (McDermott et al. 2011b).

Effects of PAD on Muscle and Bone

PAD is associated with a variety of histological and biochemical forms of injury. Among persons with PAD, as skeletal myocytes develop ischemia in response to inadequate oxygen delivery and are then exposed to higher oxygen tensions at rest, there is progressive ischemia–reperfusion injury secondary to the production of reactive oxygen species (e.g., superoxide anion, peroxide, peroxynitrite by nicotinamide adenine dinucleotide hydrogen (NADH) oxidase, xanthine oxidase, and nitric oxide synthase) that incur oxidative damage to skeletal muscle, interfere with mitochondrial electron transport and oxidative phosphorylation, potentiate inflammation, promote endothelial dysfunction, and precipitate myocyte apoptosis and necrosis (Wu et al. 2018; Gillani et al. 2012; Weiss et al. 2013). With progression of PAD, there is concomitant worsening mitochondriopathy with reduced capacity for adenosine triphosphate (ATP) biosynthesis, which exacerbates ischemic symptoms and leads to ultrastructural changes in muscle architecture (Makris et al. 2007; Ryan et al. 2018). PAD is also associated with accelerated hip bone loss and increased fracture risk. When comparing men (>65 years of age) with and without PAD during 4.6 years of follow-up, the mean annualized rate of bone loss at the hip was −0.66% and −0.34% for those with and without PAD, respectively. In addition, incident nonspinal fractures were experienced by 12% and 7.9% of men with and without PAD, respectively (Collins et al. 2009).

In the setting of critical limb ischemia, there is impaired mobilization of progenitor cells from the bone marrow, which is believed to adversely impact the capacity for neovascularization in the lower extremities despite ongoing severe ischemia. There are multiple pathogenic changes in the bone marrow of patients with critical limb ischemia, including reductions in both microvascular density and pan-neuronal and sympathetic innervation, highlighting the devastating effects of more advanced PAD on lower extremity function and physiology (Teraa et al. 2014). Additional changes associated with PAD pathophysiology are summarized in Table 15.1 (Hiatt et al. 2015). Patients with more advanced limb ischemia distal to an obstructive atherosclerotic lesion can present with the so-called “6 P’s,” which include pain, pallor, paresthesia (representing nerve ischemia), paralysis, pulselessness, and poikilothermia. Atypical symptoms (paresthesias, low back pain, bone pain) can arise from the presence of such comorbidities as peripheral neuropathy as well as spinal and joint degenerative disease.

Risk Factors for Peripheral Arterial Disease

The most important risk factors for PAD include cigarette smoking, dyslipidemia, hypertension, advanced age, diabetes mellitus, chronic kidney disease, obesity, sedentary lifestyle, a family history of premature atherosclerotic disease onset, and heightened systemic inflammation (Song et al. 2019; Selvin and Erlinger 2004; Shammas 2007; Joosten et al. 2012; Kravos and Bubnič-Sotošek 2009). Based on

Table 15.1 Mechanisms of exercise impairment in peripheral arterial disease (PAD)

Healthy physiology	PAD pathophysiology
Arterial flow	Normal at rest, inadequate increment with exercise to meet metabolic demand
Endothelial and microvasculature dysfunction	Impaired endothelium-dependent vasodilation on exercise challenge
Inflammation	Increase in the plasma levels of numerous inflammatory mediators; inflammation-impaired actions of progenitor/satellite cell differentiation and responses and growth factors
Reactive oxygen species and oxidative/reductive stress	During ischemia, skeletal muscle mitochondria release free radicals, including superoxide and other reactive oxygen species that are derived from the oxidation–reduction cascade
Muscle structural abnormalities	Muscle apoptosis and atrophy; fiber-type switching; altered myosin heavy chain expression; and fiber denervation
Muscle metabolic abnormalities	Altered oxygen coupling and mitochondrial respiration: In patients with PAD, prolongation of the kinetic rates of oxygen consumption and tissue hemoglobin desaturation has been described at the onset of exercise

Reproduced with permission from Hiatt et al. (2015)

participants in the Framingham Offspring Study, the odds ratios and 95% CIs for significant risk factor associations with PAD based on multivariable analyses include the following: each 10 years of age, 2.6 (2.0, 3.4); hypertension, 2.2 (1.4, 3.5); smoking, 2.0 (1.1, 3.4); 10 pack-years of smoking, 1.3 (1.2, 1.4); 50 mg/dL of fibrinogen, 1.2 (1.1, 1.4); 5 mg/dL of high-density lipoprotein cholesterol (HDL-C), 0.9 (0.8, 1.0); and coronary disease, 2.6 (1.6, 4.1) (Murabito et al. 2002). Among patients with PAD, smoking, lipoprotein(a) (Lp(a)), elevated high-sensitivity C-reactive protein (hsCRP), and the total cholesterol to HDL-C ratio (TC/HDL-C) correlate significantly with progression of large vessel disease, whereas diabetes was found to be the only risk factor that correlates with progression of small vessel disease (Aboyans et al. 2006). Among women, TC/HDL-C, HDL-C, hsCRP, and soluble intercellular adhesion molecule-1 (sICAM-1) levels correlate significantly with incident PAD over a median follow-up of 12.3 years (Pradhan et al. 2008) (Fig. 15.3).

Inflammation is a primary driver of atherosclerosis throughout the arterial vasculature (Libby 2002; Libby et al. 2009; Brevetti et al. 2010). As serum levels of the inflammatory mediators interleukin-6, s-ICAM-1, and soluble vascular cell adhesion molecule-1 rise, performance on the 6-minute walk test deteriorates (McDermott Mary and Lloyd-Jones 2009) (Fig. 15.4). In the European Prospective Investigation into Cancer and Nutrition in Norfolk cohort, a 2.7-fold increase in Lp(a) was associated with a hazard ratio of 1.37 for the development of PAD (Gurdasani et al. 2012). Lipoprotein-associated phospholipase A_2 ($LpPLA_2$) is a proinflammatory enzyme that hydrolyzes oxidized phospholipids and potentiates atherogenesis. In the Cardiovascular Health Study, for every standard deviation rise in the serum mass of LpPLA2, risk for developing incident PAD increased with a hazard ratio (HR) of

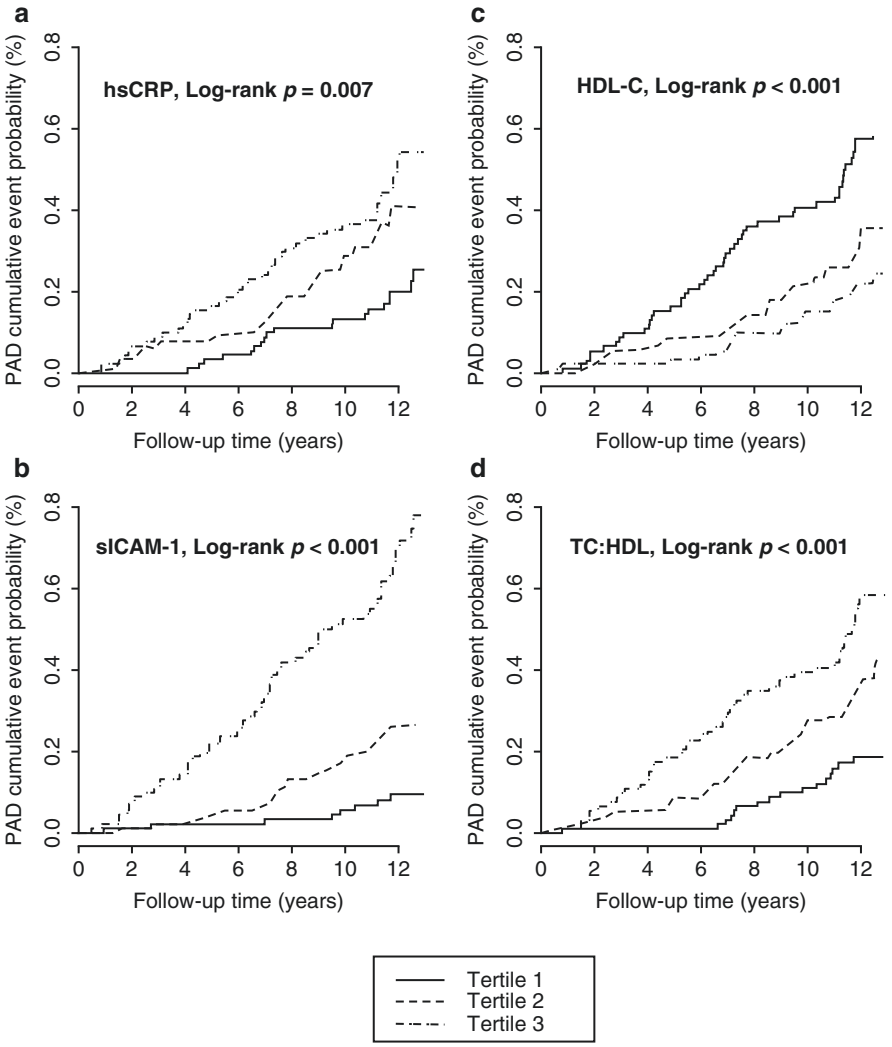

Fig. 15.3 PAD cumulative incidence curves according to tertile of hsCRP (**a**), sICAM-1 (**b**), HDL-C (**c**), and TC/HDL-C (**d**). (Reproduced with permission from Pradhan et al. (2008))

1.28 (95% CI, 1.13–1.45) (Garg et al. 2016). Insulin resistance correlates with lower serum levels of adiponectin. In the Health Professionals Follow-Up Study, as serum levels of adiponectin decrease, risk for PAD continuously increases (Joosten et al. 2013). Whole-microRNA (miRNA) transcriptome profiling has shown that PAD is characterized by a miRNA signature comprising 12 miRNAs, which can be used as biomarkers to diagnose PAD (Stather et al. 2013).

Based on an analysis of NHANES III, the prevalence of PAD is significantly higher in persons with low income and lower levels of education as assessed by the

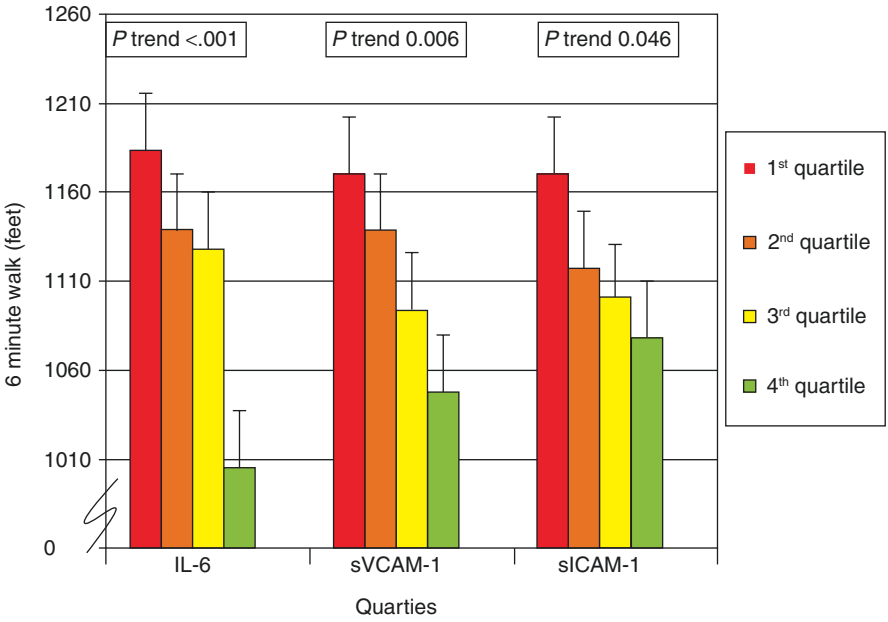

Fig. 15.4 Adjusted associations of circulating biomarker levels with 6-min walk performance among men and women with peripheral arterial disease. The mean 6-min walk distance is shown across quartiles of each biomarker level. Standard error bars are depicted for each biomarker quartile. (Reproduced with permission from McDermott and Lloyd-Jones (2009))

poverty–income ratio, which incorporates self-reported income relative to the poverty line and attained level of education. When comparing persons in the highest to the lowest levels of the poverty–income ratio, persons in the lowest level had a significantly higher prevalence of PAD (odds ratio 2.69, 95% CI, 1.80–4.03, $p < 0.0001$) (Pande and Creager 2014). In the WLCS II cohort, compared to men, women were more likely to: (1) become less able to walk continuously for 6 minutes (HR 2.30, $p = 0.004$); (2) experience new-onset mobility disability (HR 1.79, $p = 0.030$); and (3) experience more rapid declines in walking velocity ($p = 0.022$) and distance attained in a 6-minute walk ($p = 0.041$) over 4 years of follow-up (McDermott Mary et al. 2011). There are sex-related differences in risk for either proximal or distal disease among 8930 men and women (average age 67.5 years) with PAD (Chen et al. 2013). Distal disease correlates highly with male sex, age, diabetes, heart failure, and critical limb ischemia. Proximal disease, on the other hand, is highly associated with female sex, smoking, hypertension, hyperlipidemia, coronary artery disease, cerebrovascular disease, chronic obstructive pulmonary disease, and critical limb ischemia. The development of distal disease is a grave prognostic sign and dramatically impacts life expectancy (Chen et al. 2013) (Fig. 15.5).

Patients with the following features are at increased risk for PAD: (1) 65 years or older; (2) 50–64 years of age plus risk factors for atherosclerosis (hypertension, diabetes mellitus, hyperlipidemia, history of smoking) or family history of

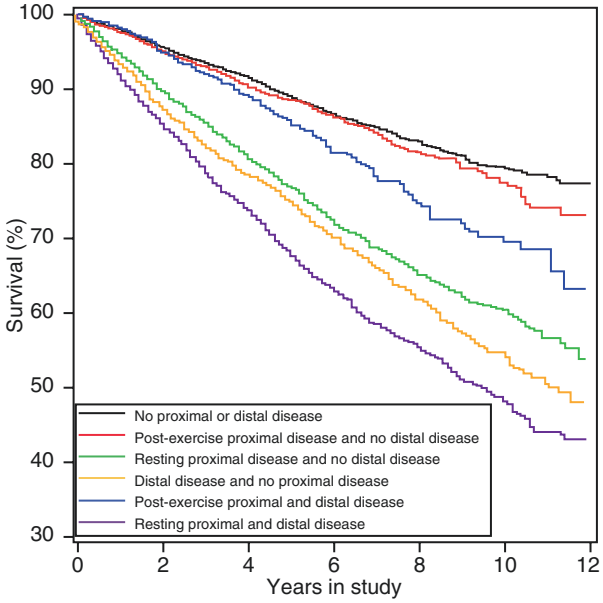

Fig. 15.5 Kaplan–Meier survival curves for survival free of death over 12 years of follow-up by proximal and distal disease status. (Reproduced with permission from Chen et al. (2013)) (This is an open-access article under the terms of the Creative Commons Attribution-Non-Commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes)

peripheral artery disease; (3) younger than 50 years plus diabetes and one additional risk factor for atherosclerosis; and (4) individuals with known atherosclerotic disease in another vascular bed (abdominal aorta, carotid, coronary, mesenteric, renal, or subclavian arteries) (Gerhard-Herman et al. 2017). PAD is suggested by a variety of components of the medical history or physical examination findings, such as reduced lower extremity pulses, decreased ambulatory capacity, intermittent claudication, pain at rest from a high-grade obstructive lesion, lower extremity gangrene, vascular bruit (e.g., femoral bruit), a nonhealing wound, dependent rubor, and pallor when lifting the leg (Gerhard-Herman et al. 2017). PAD can have both large vessel and microvascular components and both correlate with increased risk for lower extremity amputation (Behroozian and Beckman 2020). When both macro- and microvascular diseases are present, there is synergistic amplification of risk for amputation.

According to the 2016 American Heart Association (AHA)/American College of Cardiology (ACC) Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease, patients at increased risk for PAD should undergo: (1) a comprehensive medical history and review of symptoms to assess for exertional leg symptoms, including claudication or other walking impairment, ischemic rest pain, and nonhealing wounds, and (2) vascular examination, including palpation of lower extremity pulses (i.e., femoral, popliteal, dorsalis pedis, and posterior tibial),

auscultation of femoral bruits, and inspection of the legs and feet. If there is evidence of PAD, the patient should undergo noninvasive blood pressure measurement in both arms at least once during the initial assessment in order to evaluate for subclavian artery obstruction and subclavian steal syndrome (Grenon et al. 2013; Gerhard-Herman et al. 2017). In addition, these patients should undergo ankle–brachial index measurement.

The Ankle–Brachial Index

The resting ankle–brachial index (ABI) is a cost-effective first-line diagnostic test to ascertain whether a patient has PAD (Gerhard-Herman et al. 2017) (Fig. 15.6). The ABI is a noninvasive test performed by measuring systolic blood pressure in the arms at the level of the brachial artery and in the ankles at the level of the posterior tibialis and dorsalis pedis arteries with the patient in the supine position using a continuous-wave Doppler device. The ABI of each leg is derived by dividing the

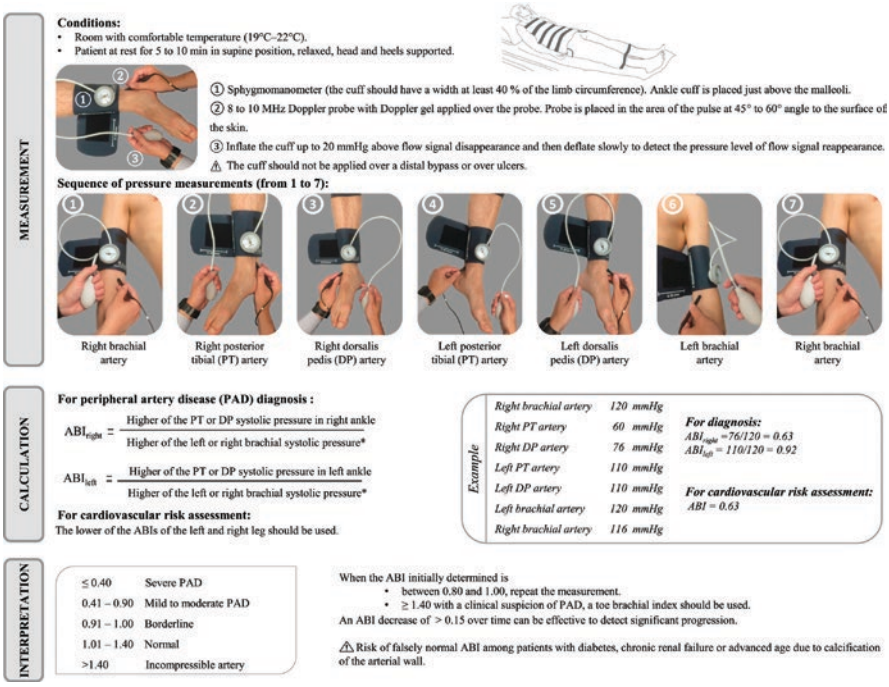

Fig. 15.6 Performing an ankle–brachial index measurement according to the American Heart Association standards. (Reproduced with permission from Chaudru et al. (2016))

highest value of the dorsalis pedis pressure or posterior tibial pressure by the highest value of the right or left brachial pressure (Fig. 15.6). If blood flow is normal in the lower extremities, then blood pressure in the dorsalis pedis and anterior tibialis arteries should be equal to or higher than that observed in the brachial artery with an ABI of 1.0 or more (WOCN Clinical Practice Wound Subcommittee, 2005 2012). Despite their acceptable sensitivity and specificity, ABIs in general are underutilized and incorrectly performed (Davies et al. 2014).

The interpretation of ABIs is summarized in Table 15.2. A normal ABI exceeds 1.0 because ankle pressures exceed brachial pressures in the absence of atherosclerotic disease. This occurs because of arteriole-induced retrograde wave reflection, leading to pressure amplification (Aboyans et al. 2012). This is further amplified by increased arterial impedance as the pressure wave enters progressively smaller conduit luminal diameters. An ABI of 1.0–1.40 is considered normal with no evidence for clinically significant atherosclerotic disease in the lower extremities. If the ABI > 1.40, this is frequently a manifestation of medial calcinosis with loss of arterial compliance and distensibility, observed in patients with diabetes or end-stage renal disease. Patients with such high ABIs have poorly compressible peripheral or noncompressible arteries. An ABI of 0.95 has a specificity and sensitivity of approximately 86% and 91%, respectively, for PAD that is ≥50% obstructive (Guo et al. 2008). As the ABI steadily falls below the 0.9 threshold, the underlying PAD becomes progressively more severe. An ABI <0.5 portends increased risk for critical limb ischemia and lower extremity amputation due to the presence of severe obstructive atherosclerotic disease. Based on an analysis of eight different studies, the specificity and accuracy of ABI <0.9 for detecting a ≥ 50% obstructive lesion vary somewhat but are acceptable at 83.3–99.0% and 72.1–89.2%, respectively (Dachun et al. 2010).

With respect to ABI measurements, the 2016 AHA/ACC Guidelines for Peripheral Arterial Disease recommend the following (COR, class of recommendation):

1. In patients with history or physical examination findings suggestive of PAD, the resting ABI, with or without segmental pressures and waveforms, is recommended to establish the diagnosis (COR I).
2. Resting ABI results should be reported as abnormal (ABI <0.9), borderline (ABI 0.91–0.99), normal (ABI 1.00–1.40), or noncompressible (ABI ≥1.40) (COR I) (see Table 15.2).

Table 15.2 Ranges of ankle–brachial indices and their interpretation

Ankle–brachial index	Meaning
>1.40	Incompressible vessels
1.0–1.4	Normal
0.91–0.99	Borderline
0.70–0.90	Mildly abnormal
0.40–0.69	Moderately abnormal
<0.40	Severely abnormal

3. In patients at increased risk for PAD but without history or physical examination findings suggestive of PAD, the measurement of the resting ABI is reasonable (COR IIa).
4. In patients not at increased risk for PAD and without history or physical examination findings suggestive of PAD, the ABI is not recommended (COR III; no benefit).

Correlation of ABI Measurements with Cardiovascular Outcomes

The ABI has considerable prognostic value beyond its role in diagnosing patients with PAD. In the WLCS III cohort, participants underwent ABI measurements as well as magnetic resonance imaging of their superficial femoral arteries in order to visualize and quantify atherosclerotic plaque (McDermott et al. 2011a). As ABIs decreased, the mean plaque area increased (Fig. 15.7) and luminal patency decreased. In the Strong Heart Study of Native Americans, both high and low ABIs correlated with excess risk for all-cause and cardiovascular mortality (Resnick et al. 2004) (Fig. 15.8). The Chronic Renal Insufficiency Cohort Study evaluated the

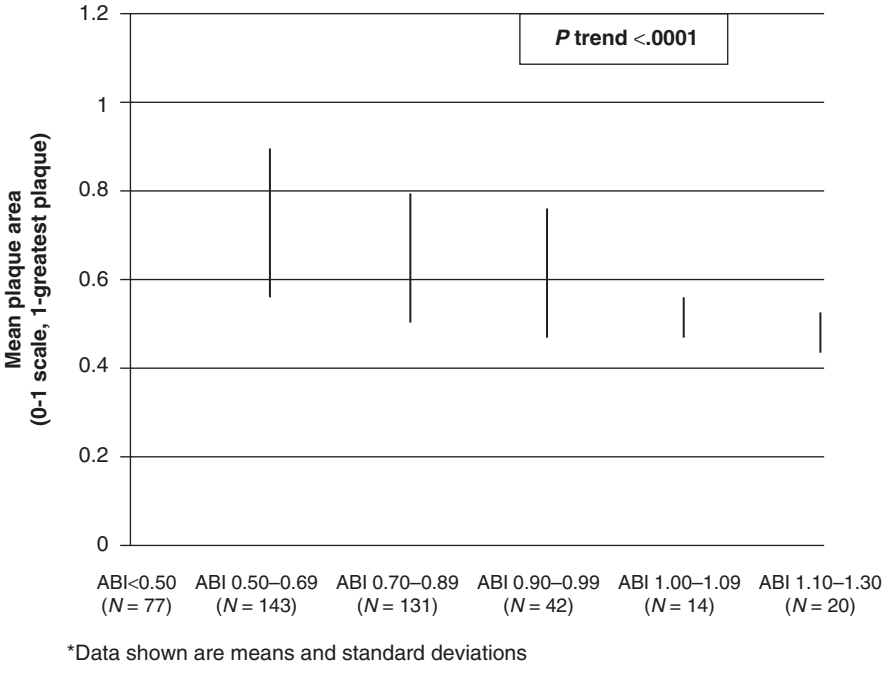

Fig. 15.7 Unadjusted mean plaque area across ABI categories. Mean plaque area has been normalized for artery size by dividing the average wall area by the median outer wall area normalized for artery size. (Reproduced with permission from McDermott et al. (2011a))

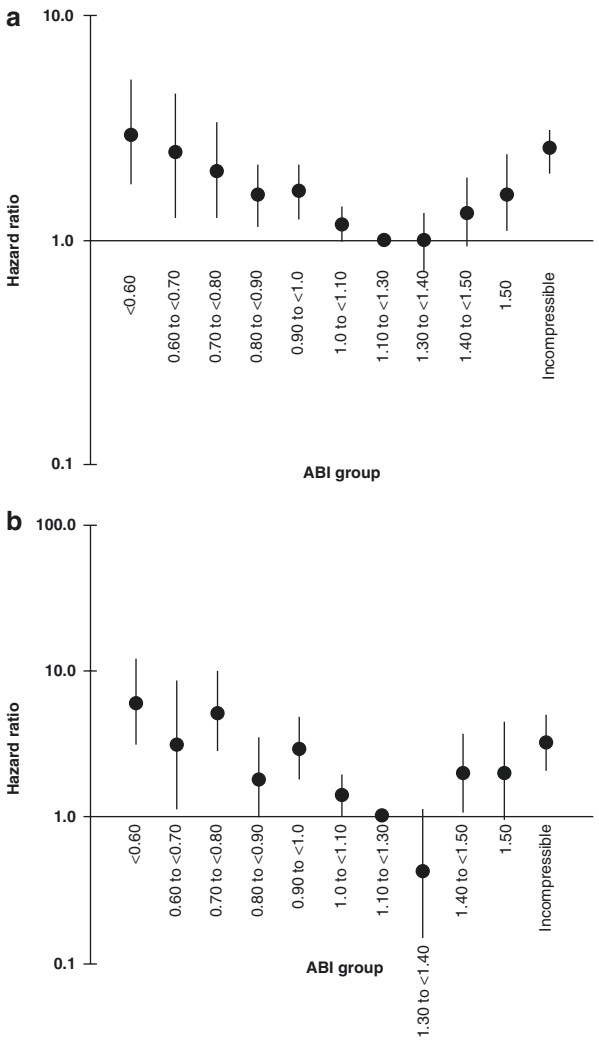

Fig. 15.8 (**a**) Adjusted hazard ratios for all-cause mortality by baseline ABI. (**b**) Adjusted hazard ratios for CVD mortality by baseline ABI. (Reproduced with permission from Resnick et al. (2004))

relationships between ABIs and risk for PAD, myocardial infarction, heart failure, cardiovascular disease, and all-cause mortality among 3939 patients with chronic kidney disease. As ABIs decreased, the incidence of each of these endpoints increased significantly over 8 years of follow-up (p-value for trend <0.001 for all) (Chen et al. 2016) (Fig. 15.9). A decrease in ABIs is consistent with progression/worsening of PAD. Among patients with established PAD, a reduction in ABI of 0.15 or more resulted in increased risk of both all-cause and cardiovascular mortality after 3 years (relative risk 2.4 and 2.8, respectively) (Criqui et al. 2008). Clearly, ABI measurement is not only an accurate, inexpensive, and noninvasive means by which to diagnose PAD, but it also is a method to identify patients at high risk for acute cardiovascular and limb-related events. It is an extremely valuable and

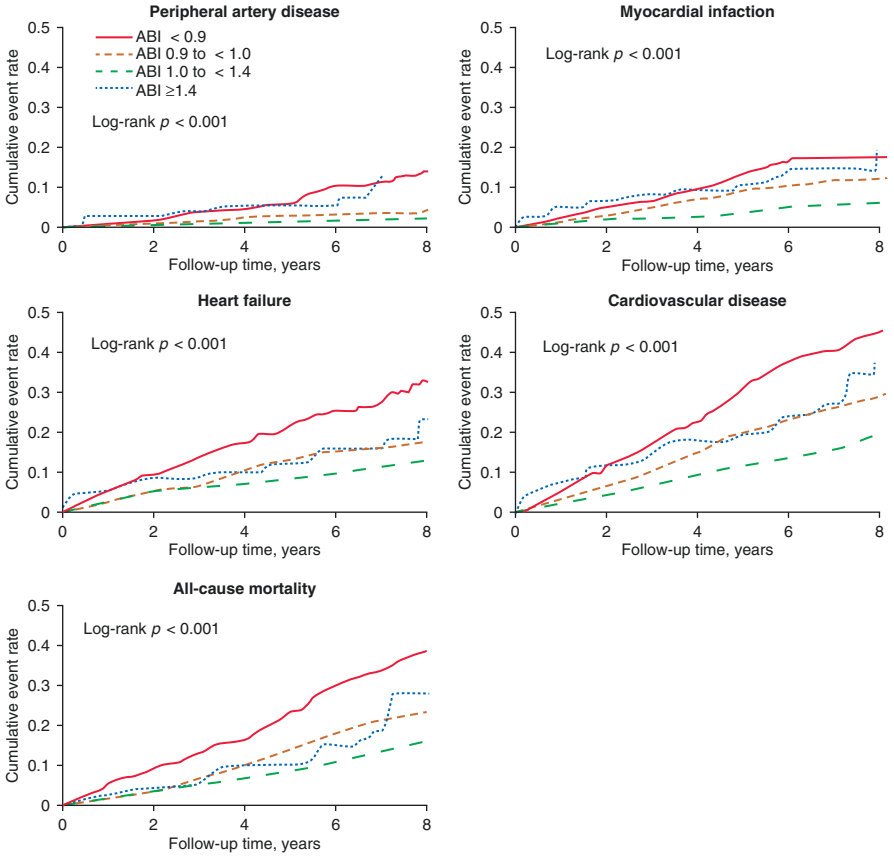

Fig. 15.9 Kaplan–Meier estimates of cumulative incidence of peripheral artery disease, myocardial infarction, heart failure, composite cardiovascular disease, and all-cause mortality. ABI ankle–brachial index. (Reproduced with permission from Chen et al. (2016)) (This is an open-access article under the terms of the Creative Commons Attribution-Non-Commercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial, and no modifications or adaptations are made)

validated diagnostic and prognostic tool. However, although it has high sensitivity for detecting PAD, its specificity is relatively low when looking for associations with other endpoints (Doobay and Anand 2005). This is illustrated in Table 15.3. One way to view this characteristic of ABI measurements is that a low ABI rules in high-risk status, but a normal ABI does not necessarily rule it out because a high-risk patient could have multivessel coronary disease, but the lower extremities may be clear of disease or have an early disease onset such that the lower extremity systolic pressure is not affected. Despite this, it has considerable value as a risk prediction tool for cardiovascular events.

Table 15.3 Summary of population-based studies that quantified the sensitivity and specificity of ABI measurement for cardiovascular events and mortality

Sensitivity of low ABI (95% CI)	Specificity of low ABI (95% CI)	Positive likelihood ratio (95% CI)	
CHD	16.5 (12.8–20.2)	92.7 (92.1–93.3)	2.53 (1.45–4.40)
Stroke	16.0 (12.9–19.1)	92.2 (91.9–92.5)	2.45 (1.76–3.41)
All-cause mortality	31.2 (27.8–34.6)	88.9 (88.2–89.6)	3.97 (3.17–4.96)
Cardiovascular mortality	41.0 (33.8–48.2)	87.9 (87.2–88.6)	5.61 (3.45–9.13)

Reproduced with permission from Doobay and Anand (2005)

References

Aboyans V, Criqui MH, Denenberg JO, Knoke JD, Ridker PM, Fronek A. Risk factors for progression of peripheral arterial disease in large and small vessels. Circulation. 2006;113:2623–9.

Aboyans V, Criqui MH, Abraham P, et al. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. Circulation. 2012;126:2890–909.

Allison MA, Ho E, Denenberg JO, et al. Ethnic-specific prevalence of peripheral arterial disease in the United States. Am J Prev Med. 2007;32:328–33.

Armstrong EJ, Chen DC, Westin GG, et al. Adherence to guideline recommended therapy is associated with decreased major adverse cardiovascular events and major adverse limb events among patients with peripheral arterial disease. J Am Heart Assoc. 2014;3:e000697.

Barnes JA, Eid MA, Creager MA, Goodney PP. Epidemiology and risk of amputation in patients with diabetes mellitus and peripheral artery disease. Arterioscler Thromb Vasc Biol. 2020;40:1808–17.

Behroozian A, Beckman JA. Microvascular disease increases amputation in patients with peripheral artery disease. Arterioscler Thromb Vasc Biol. 2020;40:534–40.

Brevetti G, Giugliano G, Brevetti L, Hiatt WR. Inflammation in peripheral artery disease. Circulation. 2010;122:1862–75.

Chaudru S, de Müllenheim PY, Le Faucheur A, Kaladji A, Jaquinandi V, Mahé G. Training to perform ankle-brachial index: systematic review and perspectives to improve teaching and learning. Eur J Vasc Endovasc Surg. 2016;51:240–7.

Chen Q, Smith CY, Bailey KR, Wennberg PW, Kullo IJ. Disease location is associated with survival in patients with peripheral arterial disease. J Am Heart Assoc. 2013;2:e000304.

Chen J, Mohler ER 3rd, Garimella PS, et al. Ankle Brachial Index and Subsequent Cardiovascular Disease Risk in Patients With Chronic Kidney Disease. J Am Heart Assoc. 2016;5(6):e003339.

Collins TC, Ewing SK, Diem SJ, et al. Peripheral arterial disease is associated with higher rates of hip bone loss and increased fracture risk in older men. Circulation. 2009;119:2305–12.

Criqui MH, Vargas V, Denenberg JO, et al. Ethnicity and peripheral arterial disease: the San Diego population study. Circulation. 2005;112:2703–7.

Criqui MH, Ninomiya JK, Wingard DL, Ji M, Fronek A. Progression of peripheral arterial disease predicts cardiovascular disease morbidity and mortality. J Am Coll Cardiol. 2008;52:1736–42.

Dachun X, Jue L, Liling Z, et al. Sensitivity and specificity of the ankle—brachial index to diagnose peripheral artery disease: a structured review. Vasc Med. 2010;15:361–9.

Davies JH, Kenkre J, Williams EM. Current utility of the ankle-brachial index (ABI) in general practice: implications for its use in cardiovascular disease screening. BMC Fam Pract. 2014;15:69.

Dhaliwal G, Mukherjee D. Peripheral arterial disease: epidemiology, natural history, diagnosis and treatment. Int J Angiol. 2007;16:36–44.

Doobay AV, Anand SS. Sensitivity and specificity of the ankle–brachial index to predict future cardiovascular outcomes. Arterioscler Thromb Vasc Biol. 2005;25:1463–9.

Fowkes FG, Housley E, Cawood EH, Macintyre CC, Ruckley CV, Prescott RJ. Edinburgh Artery Study: prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. Int J Epidemiol. 1991;20:384–92.

Garg PK, Arnold AM, Hinckley Stukovsky KD, et al. Lipoprotein-associated phospholipase A2 and incident peripheral arterial disease in older adults: the cardiovascular health study. Arterioscler Thromb Vasc Biol. 2016;36:750–6.

Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Circulation. 2017;135:e686–725.

Gillani S, Cao J, Suzuki T, Hak DJ. The effect of ischemia reperfusion injury on skeletal muscle. Injury. 2012;43:670–5.

Grenon SM, Vittinghoff E, Owens CD, Conte MS, Whooley M, Cohen BE. Peripheral artery disease and risk of cardiovascular events in patients with coronary artery disease: insights from the heart and soul study. Vasc Med. 2013;18:176–84.

Guo X, Li J, Pang W, et al. Sensitivity and specificity of ankle-brachial index for detecting angiographic stenosis of peripheral arteries. Circ J. 2008;72:605–10.

Gurdasani D, Sjouke B, Tsimikas S, et al. Lipoprotein(a) and risk of coronary, cerebrovascular, and peripheral artery disease. Arterioscler Thromb Vasc Biol. 2012;32:3058–65.

Hiatt WR, Armstrong EJ, Larson CJ, Brass EP. Pathogenesis of the limb manifestations and exercise limitations in peripheral artery disease. Circ Res. 2015;116:1527–39.

James SL, Abate D, Abate KH, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the global burden of disease study 2017. Lancet. 2018;392:1789–858.

Joosten MM, Pai JK, Bertoia ML, et al. Associations between conventional cardiovascular risk factors and risk of peripheral artery disease in men. JAMA. 2012;308:1660–7.

Joosten MM, Joshipura KJ, Pai JK, et al. Total adiponectin and risk of symptomatic lower extremity peripheral artery disease in men. Arterioscler Thromb Vasc Biol. 2013;33:1092–7.

Kravos A, Bubnič-Sotošek K. Ankle–brachial index screening for peripheral artery disease in asymptomatic patients between 50 and 70 years of age. J Int Med Res. 2009;37:1611–9.

Libby P. Inflammation in atherosclerosis. Nature. 2002;420:868–74.

Libby P, Ridker PM, Hansson GK. Inflammation in atherosclerosis: from pathophysiology to practice. J Am Coll Cardiol. 2009;54:2129–38.

Makris KI, Nella AA, Zhu Z, et al. Mitochondriopathy of peripheral arterial disease. Vascular. 2007;15:336–43.

McDermott Mary M, Lloyd-Jones DM. The role of biomarkers and genetics in peripheral arterial disease. J Am Coll Cardiol. 2009;54:1228–37.

McDermott Mary M, Ferrucci L, Liu K, et al. Women with peripheral arterial disease experience faster functional decline than men with peripheral arterial disease. J Am Coll Cardiol. 2011;57:707–14.

McDermott MM, Greenland P, Liu K, et al. The ankle brachial index is associated with leg function and physical activity: the walking and leg circulation study. Ann Intern Med. 2002;136:873–83.

McDermott MM, Ferrucci L, Liu K, et al. Leg symptom categories and rates of mobility decline in peripheral arterial disease. J Am Geriatr Soc. 2010;58:1256–62.

McDermott MM, Liu K, Carr J, et al. Superficial femoral artery plaque, the ankle-brachial index, and leg symptoms in peripheral arterial disease: the walking and leg circulation study (WALCS) III. Circ Cardiovasc Imaging. 2011a;4:246–52.

McDermott MM, Liu K, Ferrucci L, et al. Decline in functional performance predicts later increased mobility loss and mortality in peripheral arterial disease. J Am Coll Cardiol. 2011b;57:962–70.

Murabito JM, Evans JC, Nieto K, Larson MG, Levy D, Wilson PW. Prevalence and clinical correlates of peripheral arterial disease in the Framingham Offspring Study. Am Heart J. 2002;143:961–5.

Norman PE, Davis WA, Bruce DG, Davis TME. Peripheral arterial disease and risk of cardiac death in type 2 diabetes. The Fremantle Diabetes Study. Diabetes Care. 2006;29:575–80.

O'Neal WT, Efird JT, Nazarian S, Alonso A, Heckbert SR, Soliman EZ. Peripheral arterial disease and risk of atrial fibrillation and stroke: the multi–ethnic study of atherosclerosis. J Am Heart Assoc. 2014;3:e001270.

Pande RL, Creager MA. Socioeconomic inequality and peripheral artery disease prevalence in US adults. Circ Cardiovasc Qual Outcomes. 2014;7:532–9.

Pradhan AD, Shrivastava S, Cook NR, Rifai N, Creager MA, Ridker PM. Symptomatic peripheral arterial disease in women: nontraditional biomarkers of elevated risk. Circulation. 2008;117:823–31.

Resnick HE, Lindsay RS, McDermott MM, et al. Relationship of high and low ankle brachial index to all-cause and cardiovascular disease mortality: the Strong Heart Study. Circulation. 2004;109:733–9.

Ryan TE, Yamaguchi DJ, Schmidt CA et al. Extensive skeletal muscle cell mitochondriopathy distinguishes critical limb ischemia patients from claudicants. JCI Insight. 2018;3(21):e123235.

Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States. Circulation. 2004;110:738–43.

Shammas NW. Epidemiology, classification, and modifiable risk factors of peripheral arterial disease. Vasc Health Risk Manag. 2007;3:229–34.

Song P, Rudan D, Zhu Y, et al. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis. Lancet Glob Health. 2019;7:e1020–30.

Stather PW, Sylvius N, Wild JB, Choke E, Sayers RD, Bown MJ. Differential microRNA expression profiles in peripheral arterial disease. Circ Cardiovasc Genet. 2013;6:490–7.

Teraa M, Fledderus JO, Rozbeh RI, Leguit RJ, Verhaar MC. Bone marrow microvascular and neuropathic alterations in patients with critical limb ischemia. Circ Res. 2014;114:311–4.

Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke statistics update: a report from the American Heart Association. Circulation. 2020;141:e139–596.

Weiss DJ, Casale GP, Koutakis P, et al. Oxidative damage and myofiber degeneration in the gastrocnemius of patients with peripheral arterial disease. J Transl Med. 2013;11:230.

WOCN Clinical Practice Wound Subcommittee, 2005. Ankle Brachial Index: quick reference guide for clinicians. J Wound Ostomy Continence Nurs. 2012;39:S21–9.

Wu MY, Yiang GT, Liao WT, et al. Current mechanistic concepts in ischemia and reperfusion injury. Cell Physiol Biochem. 2018;46:1650–67.

Part IV
Novel Risk Factors

Chapter 16
Lipoprotein(a)

Anne Langsted and Børge G. Nordestgaard

Introduction

Cardiovascular disease is still the leading cause of death worldwide with an estimated nine million deaths per year. Several modifiable risk factors have been identified. In the past couple of decades, low-density lipoprotein (LDL) cholesterol has been identified as a causal risk factor for atherosclerotic cardiovascular disease. This lipoprotein has been extensively studied, and several effective and safe therapies have been found to lower LDL cholesterol, leading to reduced atherosclerotic cardiovascular disease as well as cardiovascular and all-cause mortality. However, after lowering LDL cholesterol, residual cardiovascular risk remains and the task in more recent years has been to identify "new" causal risk factors.

Lipoprotein(a) is a genetically determined lipoprotein that consists of an LDL-like particle with apolipoprotein(a) bound to it. Lipoprotein(a) has been studied for many years, but controversies regarding its role in cardiovascular disease have existed, and it is only in the last decade that this lipoprotein has been established as an additional causal risk factor. This chapter will focus on the discovery of lipoprotein(a) as a causal risk factor for cardiovascular disease.

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Historical Interest

Lipoprotein(a) was first described by Kåre Berg, a Norwegian professor in medical genetics, and his first paper on lipoprotein(a) was published in 1963 (Berg 1963). Lipoprotein(a) was originally thought to be a qualitative autosomal genetic marker present in only 1/3 of the population; however, in was later found to be present in all individuals with highly variable concentrations. In the following two decades, not much attention was given to this lipoprotein. The *LPA* gene was sequenced in 1987 (McLean et al. 1987), a gene coding for the apolipoprotein(a) part of lipoprotein(a), and, following this, several papers were published (Nordestgaard and Langsted 2016). In the first retrospective studies examining lipoprotein(a) in patients with cardiovascular disease, levels were higher in those with atherosclerotic cardiovascular disease compared to those without the disease. Following this, prospective studies further found an increased risk of myocardial infarction in individuals with elevated lipoprotein(a) levels. However, not all retrospective and prospective studies found that elevated lipoprotein(a) was associated with increased risk of cardiovascular disease, and this could be due to lack of standardization of the lipoprotein(a) measurement.

In 2009, several important studies were published on lipoprotein(a). First, in the Copenhagen General Population Study, a large prospective study of the general population, a Mendelian randomization study using genetic instruments found lipoprotein(a) to be causally associated with the risk of myocardial infarction (Kamstrup et al. 2009). Second, the Emerging Risk Factors Collaboration published a large meta-analysis showing that high lipoprotein(a) levels were independently associated with high risk of coronary heart disease (Emerging Risk Factors et al. 2009). Third, a large gene study identified two variants in the *LPA* locus to be strongly associated with lipoprotein(a) levels and highly associated with risk of coronary heart disease (Clarke et al. 2009). These three studies including both observational and genetic evidence lay the ground for the following research, resulting in lipoprotein(a) being widely accepted as a causal, genetic risk factor for cardiovascular disease.

Shortly, following these publications, the interest in this lipoprotein became apparent in guidelines and consensus statements. The first was a consensus statement on lipoprotein(a) from the European Atherosclerosis Society published in 2010 recommending to measure lipoprotein(a) in individuals at elevated risk of cardiovascular disease (Nordestgaard et al. 2010).

In 2013, a genome-wide association study with aortic valve calcification was published and found that carriers of a single-nucleotide polymorphism (SNP) in the *LPA* locus were associated with aortic valve calcification (Thanassoulis et al. 2013), and later it was shown in observational and Mendelian randomization studies that high plasma levels of lipoprotein(a) were causally associated with aortic valve stenosis.

Measurement

Lipoprotein(a) is a complex lipoprotein consisting of a lipoprotein particle similar to LDL with a triglyceride and cholesteryl ester core and phospholipids and cholesterol on the surface, and, further, a single molecule of apolipoprotein B (Fig. 16.1). A disulfide bond attaches apolipoprotein B to apolipoprotein(a) that resembles plasminogen and can vary greatly in size. Apolipoprotein(a) consists of several structures called kringles, originating from the *PLG* gene, coding for plasminogen. In plasminogen, there are five different kringles (kringles I–V). In lipoprotein(a), kringles I–III are not present, kringle V exists in a single copy, whereas kringle IV has several copies and can be divided into 10 types, most of which are present in a single copy. However, the kringle IV type 2 (KIV2) present in lipoprotein(a) can vary in number from 2 to more than 40 copies; the number of repeats is inversely associated with the plasma levels of lipoprotein(a), as the largest copy numbers often are degraded within liver cells before secretion. Lipoprotein(a) concentrations can be reported as lipoprotein(a) total mass (mg/dL), particle number (nmol/L), or lipoprotein(a) cholesterol mass (mg/dL or mmol/L).

Sizable fluctuations are observed in the median/mean levels of lipoprotein(a) among different studies, and apart from the genetic differences such as race or sex, many of these fluctuations can probably be ascribed to the use of different assays in laboratories. In the first studies, it was the standard to report lipoprotein(a) levels as total mass and most assays were based on an antigen–antibody complex using an immunoassay; however, an increasing number of assays now report in particle number. A problem in measuring lipoprotein(a) is the variable size of KIV2 in apolipoprotein(a), and when assays use polyclonal antibodies directed at apolipoprotein(a), results can thereby vary in signal due to the size. Optimally,

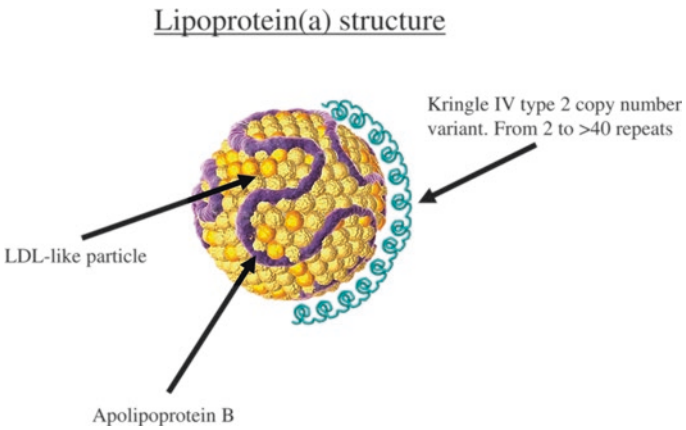

Fig. 16.1 Structure of lipoprotein(a). Lipoprotein(a) consists of an LDL-like particle with one apolipoprotein(a) covalently bound to apolipoprotein B via a disulfide bridge. Apolipoprotein(a) contains an inactive protease region similar to plasminogen and a variable number of kringle-shaped protein structures called kringle IV types 1–10 where type 2 (KIV2) varies from 2 to >40 number of repeats

monoclonal antibodies directed at one particular binding site at apolipoprotein(a) outside of KIV2 are preferred; however, these are expensive to develop and use. Instead, an alternative is to use polyclonal antibodies that are latex-enhanced and also to use several calibrators at different levels of plasma lipoprotein(a) and thus different numbers of KIV2 to indirectly adjust for the variability in the size of the particle. Most commonly, an assay will have a joint gold standard reference material most often reported as particle number, in order to compare between different assays. The size heterogeneity of lipoprotein(a) causes problems with the reference method for these assays. Furthermore, lipoprotein(a) has been shown to be altered when frozen at −80 °C for several years, at least for some assays.

Plasma levels of lipoprotein(a) are mainly genetically determined, and up to 80–90% of the variation can be ascribed to the *LPA* gene coding for apolipoprotein(a). One important *LPA* variant is the KIV2 copy number variant, where every segment is 5.6 kb long. It can, e.g., be measured by real-time polymerase chain reaction (PCR) determining the total number of copies on both alleles; alternatively, labor-intensive isoelectric focusing of plasma can exactly determine which two alleles of KIV2 are expressed. Furthermore, a number of single-nucleotide polymorphisms (SNPs), associated with both plasma lipoprotein(a) levels and the KIV2 variant, are found.

Population Distribution

Levels of lipoprotein(a) vary greatly in the general population, and the distribution is highly skewed with a tail toward the right reaching values as high as >400 mg/dL (Fig. 16.2). In addition, levels differ among ethnicities/race, and compared to Whites, Blacks have up to four times higher median and mean lipoprotein(a) levels as shown in large population studies and clinical trials. Some studies have also found that Asians and Hispanics have higher levels than Whites but lower levels than Blacks. The distribution of plasma lipoprotein(a) levels varies among ethnicities, where Whites, Asians, and Hispanics have the right-skewed distribution, whereas Blacks have a more symmetrical distribution. Also, the variation in the number of repeats in apolipoprotein(a) is greatly varied among ethnicities and the KIV2 copy number variant allele frequency explains from 17% of plasma lipoprotein(a) levels in Blacks (Sudanese), through 27% in Whites (Danes), and up to 77% in Asians (Malays). Importantly, when measuring the KIV2 number of repeats, repeats on both alleles are often combined, and it is therefore not possible to distinguish whether there are differences between the two alleles of an individual, and thus these measurements cannot reflect the dominant allele. In both Whites and Blacks, the variants found in the *LPA* gene are major determinants of lipoprotein(a) levels, and the low number of KIV2 repeats associated with high lipoprotein(a) levels is much more dominant in Whites than in Blacks. Two SNPs (rs10455872 and rs3798220) in the *LPA* gene discovered in 2009 (Clarke et al. 2009) explain 25% and 8% of the variation in total plasma lipoprotein(a) levels. Further, many other

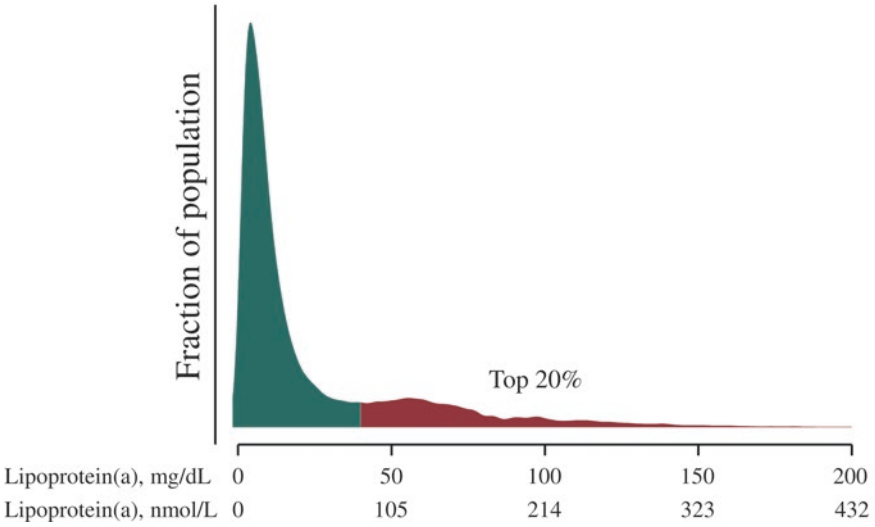

Fig. 16.2 Distribution of plasma lipoprotein(a) in the general population of Whites. Plasma concentrations of lipoprotein(a) in 70,000 individuals from the Copenhagen General Population Study. The top 20% represents individuals at increased cardiovascular risk and corresponds to a lipoprotein(a) level of 42 mg/dL (88 nmol/L) or higher. Conversion from mg/dL to nmol/L was done by the following equation based on 13,900 individuals with measurements in both mg/dL and nmol/L: lipoprotein(a) in nmol/L = 2.18*(lipoprotein(a) in mg/dL)–3.83

SNPs in or close to the *LPA* gene have been found to be less important determinants of plasma lipoprotein(a) levels. Lipoprotein(a) is highly genetically determined, and this makes this lipoprotein very suitable for analyses of causality by, for example, Mendelian randomization analyses.

Influencing Factors

Most lipoproteins are highly affected by physiological and lifestyle factors; however, plasma lipoprotein(a) levels being mainly genetically determined remain quiet stable from childhood to old age. That said, some factors do have a minimal effect.

Not many studies have examined the effect of age on lipoprotein(a) levels; however, some have found no association and others have found increasing lipoprotein(a) levels with increasing age (Enkhmaa et al. 2016). In 70,000 individuals in the Copenhagen General Population Study, the median levels of lipoprotein(a) increased slightly from 8.4 mg/dL at age 20 years to 10.3 mg/dL at age 85 years (Fig. 16.3). Some studies have also found that the mean lipoprotein(a) levels were higher in women than in men and this was most significant in individuals with established coronary artery disease. However, these higher levels seen in women could be due

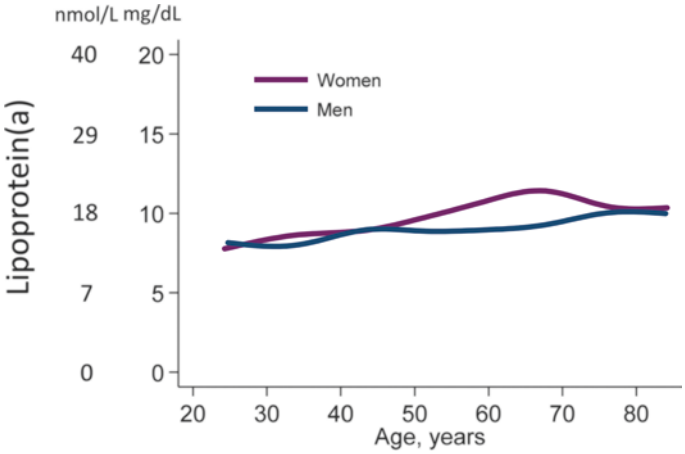

Fig. 16.3 Levels of lipoprotein(a) according to age and sex based on 70,000 individuals from the Copenhagen General Population Study of White Danish descent. Conversion from mg/dL to nmol/L was done by the following equation based on 13,900 individuals with measurements in both mg/dL and nmol/L: lipoprotein(a) in nmol/L = 2.18*(lipoprotein(a) in mg/dL)–3.83

to an increase in levels during menopause. In the Copenhagen General Population Study, levels were higher in women from 50 to 80 years but similar at age < 50 and > 80 years (Fig. 16.3). Several smaller studies have shown different minor effects on lipoprotein(a) levels with different types of diets in subpopulations; some have found increases in lipoprotein(a) levels with protein-rich diets, while others have not, and some have found increases in lipoprotein(a) levels with low-fat high-carbohydrate diets; however, in a large study on the general population, the association of habitual food intake with lipoprotein(a) levels was modest and nonsignificant. Lipoprotein(a) has been shown to be modestly higher with higher levels of C-reactive protein (CRP); however, findings from observational studies do not clarify whether elevated lipoprotein(a) levels lead to low-grade inflammation/elevated CRP levels or whether low-grade inflammation leads to increased levels of lipoprotein(a). In a genetic Mendelian randomization analysis, it seems that there is no causal association between high lipoprotein(a) levels and low-grade inflammation.

Kidney disease is one disease that markedly influences lipoprotein(a) levels (Kronenberg and Utermann 2013). Higher levels are observed in individuals suffering from nephrotic syndrome, end-stage renal disease, or receiving dialysis. Higher lipoprotein(a) plasma levels are observed with lower glomerular filtration rate, and levels start to increase in chronic kidney patients even before the glomerular filtration rate is affected.

The liver synthesizes apolipoprotein(a), and the rate of synthesis is the main determinant of lipoprotein(a) levels. Diseases affecting the liver can thereby potentially influence lipoprotein(a) levels, and low levels of lipoprotein(a) have been observed in individuals with hepatocellular damage in a dose-dependent manner; therefore, compared to healthy individuals, patients with hepatitis and liver cirrhosis have lower lipoprotein(a) levels.

Myocardial Infarction

Up until today, a large amount of evidence exists from both epidemiological and genetic studies to show that high lipoprotein(a) levels are observationally and causally associated with increased risk of myocardial infarction. The first case–control studies found that individuals with myocardial infarction had higher levels of lipoprotein(a) after the event, compared to individuals without an event, and, later, several case–control studies found similar results. In a meta-analysis from 2000, 17 out of 19 prospective studies found higher risk of coronary heart disease, when comparing top versus bottom tertile of lipoprotein(a) (Danesh et al. 2000). The risk ratio when combining all 19 prospective studies was 1.7 (95% confidence interval, 1.4–1.9). The same meta-analysis also found increased risk when combining nine studies including individuals with already established cardiovascular disease. An explanation to why not all studies individually find an association between high lipoprotein(a) levels and increased risk of cardiovascular disease could be because of difficulties in measurement of lipoprotein(a), mainly due to the varying isoform size of apolipoprotein(a). Furthermore, many studies did not examine risk at extremely high levels, where the most significant risk is present. In 2009, the Emerging Risk Factors Collaboration included 36 prospective studies in analyses and found a 1.5-fold higher risk of myocardial infarction and coronary death for individuals with lipoprotein(a) levels >100 mg/dL compared to those with levels <4 mg/dL (Emerging Risk Factors et al. 2009). Also, in the Copenhagen General Population Study, there was a 2.4-fold increased risk of myocardial infarction for individuals with lipoprotein(a) levels >100 mg/dL compared to those with levels <5 mg/dL (Nordestgaard and Langsted 2016). The first genetic evidence linking lipoprotein(a) to the risk of cardiovascular disease was published several years ago by the group of Gerd Utermann; in addition, very large studies on this topic were published in 2009. One large study used a gene chip including 48,742 single-nucleotide polymorphisms (SNPs) in 2100 genes to test for associations in subjects with coronary disease and control subjects. In this study, they found two variants in the *LPA* gene that were highly associated with both increased levels of lipoprotein(a) and an increased risk of coronary disease (Clarke et al. 2009). A second study from 2009 using three cohorts from the Danish population found that increasing levels of lipoprotein(a) were associated with increased risk of myocardial infarction and that decreasing number of KIV2 repeats associated with elevated levels of lipoprotein(a) were also associated with increased risk of myocardial infarction (Kamstrup et al. 2009). For risk of myocardial infarction in 108,000 individuals from the Copenhagen General Population Study, a doubling in lipoprotein(a) levels resulted in a hazard ratio of 1.09 (95% confidence interval, 1.07–1.12) for plasma lipoprotein(a), and from instrumental variable analyses, a causal risk ratio of 1.15 (1.11–1.20) for *LPA* KIV2 and 1.10 (1.06–1.13) for *LPA* rs10455872 (Fig. 16.4). In the same population, myocardial infarction events per 10,000 person-years were 39 in individuals with lipoprotein(a) levels of 0–9 mg/dL (0–16 nmol/L) and 64 in individuals with levels ≥94 mg/dL (≥200 nmol/L) (Fig. 16.5). Findings are consistent with a causal association of elevated lipoprotein(a) levels with increased risk of myocardial infarction.

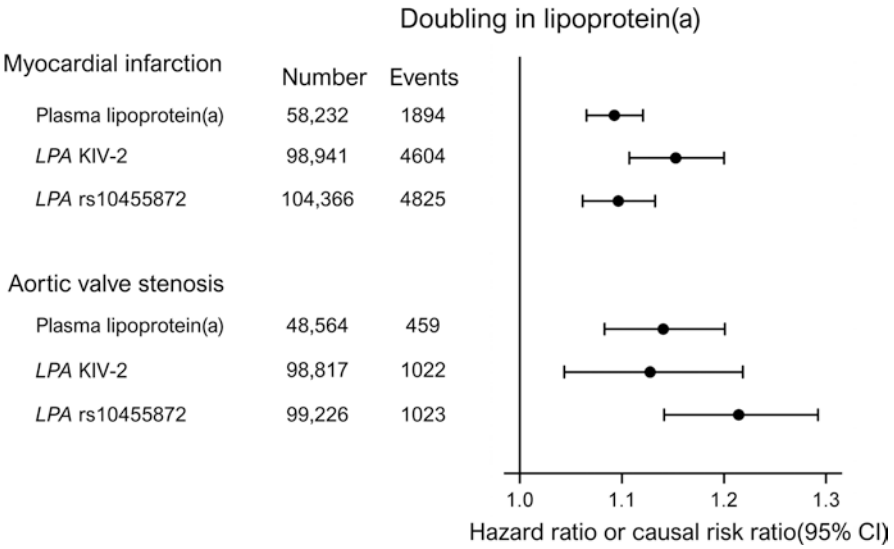

Fig. 16.4 Risk of myocardial infarction and aortic valve stenosis for a doubling in lipoprotein(a) levels based on 108,000 individuals from the Copenhagen General Population Study of White Danish descent. Observational analyses of plasma lipoprotein(a) levels were done by Cox proportional hazard regression models and were adjusted for age and sex. Genetic analyses for causal risk ratios for *LPA* KIV2 and *LPA* rs10455872 were done by instrumental variable analyses also adjusted for age and sex

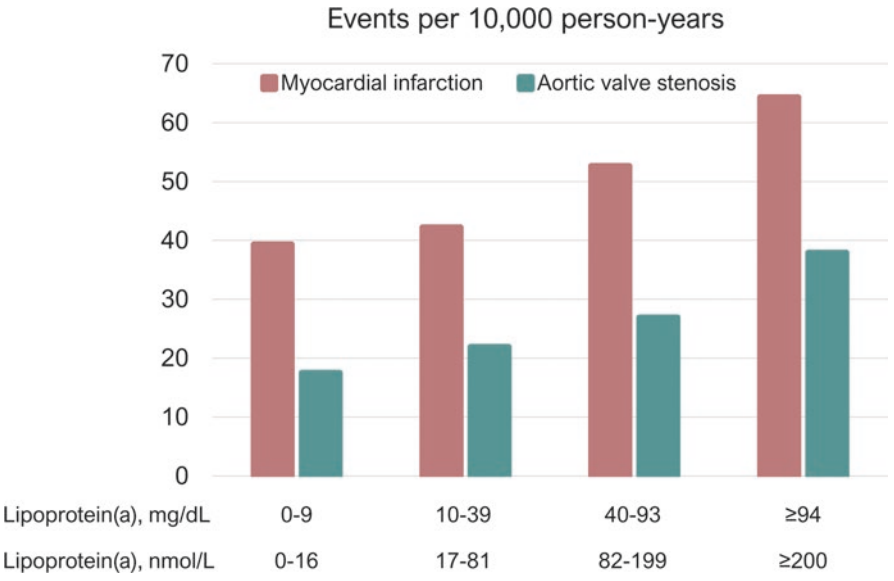

Fig. 16.5 Myocardial infarction and aortic valve stenosis events per 10,000 person-years based on 108,000 individuals from the Copenhagen General Population Study of White Danish descent. Events per 10,000 person-years in groups of plasma lipoprotein(a): 0–9 mg/dL (0–16 nmol/L), 10–39 mg/dL (17–81 nmol/L), 40–93 mg/dL (82–199 nmol/L), and ≥ 94 mg/dL (≥200 nmol/L)

Many studies have followed these landmark studies examining the risk of myocardial infarction, both observationally and from genetics, and the vast majority of these studies find a clear association between high levels of lipoprotein(a) and increased risk of myocardial infarction.

Aortic Valve Stenosis

High lipoprotein(a) levels are also a risk factor for aortic valve stenosis. The first study on lipoprotein(a) and risk of aortic valve stenosis was published in 1995 and found that in a Japanese population, increasing age and elevated lipoprotein(a) were the main determinants for risk of aortic valve stenosis. Another study found that in the older US population, age, male sex, and lipoprotein(a) levels were significantly higher in individuals with aortic valve stenosis compared to healthy controls. Genetic evidence was obtained in 2013 from a genome-wide association study examining the presence of aortic valve calcification by computed tomography (CT) scanning; one SNP in the *LPA* gene (the same as was found for myocardial infarction (Clarke et al. 2009)) reached significance for the presence of aortic valve calcification (Thanassoulis et al. 2013). This finding was further replicated in White European, African American, and Hispanic-American cohorts. Another study from the Copenhagen General Population Study published in 2014 combined the two SNPs found in the paper from 2009 (Clarke et al. 2009) and the KIV2 number of repeats and found that plasma lipoprotein(a) as well as genetically elevated lipoprotein(a) levels resulted in an increased risk of aortic valve stenosis (Kamstrup et al. 2014). For risk of aortic valve stenosis in 108,000 individuals from the Copenhagen General Population Study, a doubling in lipoprotein(a) levels resulted in a hazard ratio of 1.14 (95% CI, 1.08–1.20) for plasma lipoprotein(a), and from instrumental variable analyses, a causal risk ratio of 1.13 (1.04–1.22) for *LPA* KIV2 and 1.21 (1.14–1.29) for *LPA* rs10455872 (Fig. 16.4). In the same population, aortic valve stenosis events per 10,000 person-years were 18 in individuals with lipoprotein(a) levels 0–9 mg/dL (0–16 nmol/L) and 38 in individuals with levels ≥94 mg/dL (≥200 nmol/L) (Fig. 16.5). Taken together, these studies and others have confirmed that high lipoprotein(a) levels are one of the most important causal risk factors for aortic valve stenosis, and risk estimates for identical lipoprotein(a) levels are found to be slightly higher than those for myocardial infarction.

Venous Thromboembolism

One of the proposed pathophysiological pathways of lipoprotein(a) is through interference with normal fibrinolysis and thereby indirectly increased thrombosis. Therefore, and because of lipoprotein(a)‘s causal association with myocardial infarction, it seems logical that lipoprotein(a) could be causally associated with the

risk of deep venous thrombosis and pulmonary embolism. However, it has only been shown that extremely high lipoprotein(a) levels are associated with a modest risk of venous thromboembolism. In an observational prospective study, top versus bottom tertile of lipoprotein(a) was not associated with increased risk, whereas the top 5% was associated with increased risk of venous thromboembolism. In a meta-analysis of case–control studies, three studies found high lipoprotein(a) levels to be associated with increased risk, whereas three studies found no association. Several large genetic studies including the two abovementioned SNPs and KIV2 number of repeats found no association of *LPA* risk scores with risk of thromboembolism. There might be a minor observational increased risk of venous thromboembolism at extremely high levels of lipoprotein(a); however, the risk does not seem to be causal as genetic studies have found no association.

Diabetes Mellitus

The association of lipoprotein(a) levels with risk of type 2 diabetes was first examined in 2010 in the Women's Health Study, which showed that low levels of lipoprotein(a) were associated with an increased risk of diabetes (Mora et al. 2010), and this finding was replicated in the Copenhagen City Heart Study. Following this finding, genetic studies were performed to examine whether this surprising association was causal. In a large Mendelian randomization study, it was found that high KIV2 number of repeats, associated with low levels of plasma lipoprotein(a), was associated with an increased risk of diabetes; however, for the other genetic instrument, this study found no association (Kamstrup and Nordestgaard 2013). In a large Icelandic case–control study, it was found that both low plasma lipoprotein(a) levels and genetically low lipoprotein(a) based on SNPs and two loss-of-function mutations were associated with an increased risk of diabetes, indicating that this association could be causal (Gudbjartsson et al. 2019). There has been concern that when lowering lipoprotein(a) for prevention of cardiovascular risk, a harmful effect could be an increase in the risk of diabetes. However, the risk of diabetes at low lipoprotein(a) levels is only observed at extremely low levels, and, therefore, for now it seems safe to lower levels from high to median population levels for cardiovascular protection without increasing the risk of diabetes. That said, evidence from large phase 3 randomized trials will provide the final answer.

Heart Failure

Heart failure can be caused by previous myocardial infarction events or the presences of aortic valve stenosis, and the role of lipoprotein(a) in heart failure has been examined accordingly. Combining the Copenhagen General Population Study and the Copenhagen City Heart Study, high levels of lipoprotein(a) were

both observationally and genetically associated with high risk of incident heart failure. Furthermore, mediation analyses, excluding individuals with previous myocardial infarction or aortic valve stenosis, found that 63% of heart failure risk from lipoprotein(a) was mediated through myocardial infarction and aortic valve stenosis combined. Also, in the Atherosclerosis Risk in Communities (ARIC) study, individuals in the highest quintile of lipoprotein(a) had a higher risk of hospitalization due to heart failure compared to those in the lowest quintile. When excluding individuals with previous myocardial infarction, results attenuated and became nonsignificant.

Ischemic Stroke

The association of lipoprotein(a) with risk of ischemic stroke has been examined in several studies, and results are somewhat conflicting. Two large prospective studies, the Prospective Epidemiological Study of Myocardial Infarction (PRIME) from France and Northern Ireland and the European Prospective Investigation into Cancer (EPIC)-Norfolk from the UK, found no association with high plasma lipoprotein(a) levels and risk of ischemic stroke. On the contrary, the ARIC study, a prospective study on Black and White adults in the United States, supports an observational association between high plasma lipoprotein(a) levels and high risk of ischemic stroke, and, also, a large meta-analyses from the Emerging Risk Factors Collaboration combining 24 studies found an association (Emerging Risk Factors et al. 2009). For genetic associations, the Heart Protection Study from the UK found no association between the two most common lipoprotein(a)-increasing SNPs and risk of ischemic stroke. On the contrary, results from the Copenhagen General Population Study from Denmark indicated both an observational and a causal role for lipoprotein(a) in the risk of ischemic stroke, as both high plasma lipoprotein(a) levels and *LPA* risk genotypes significantly increased the risk in individuals in the general population (Langsted et al. 2019). Also, a large study including participants from the UK Biobank found that genetically lowered lipoprotein(a) resulted in an 13% lower risk of stroke (Emdin et al. 2016).

Risk estimates for high lipoprotein(a) levels or genetic variants for risk of ischemic stroke are smaller than those found for myocardial infarction and aortic valve stenosis, where individuals with high lipoprotein(a) levels have up to three- to fourfold higher risk than individuals with low levels.

Mortality

As high lipoprotein(a) levels are a well-established risk factor for myocardial infarction and aortic valve stenosis, the potential of reducing lipoprotein(a) levels might result in reducing mortality as well. In a meta-analysis including 24 studies, the

Emerging Risk Factors Collaboration found that high lipoprotein(a) levels were observationally associated with increased risk of cardiovascular mortality (Emerging Risk Factors et al. 2009), and several other studies have also reported this association. However, other studies found no association of high plasma lipoprotein(a) levels with the risk of either cardiovascular or all-cause mortality. A study from the Copenhagen General Population Study found an increased risk of cardiovascular and all-cause mortality, both from high plasma lipoprotein(a) levels and via KIV2 genetically elevated lipoprotein(a); however, no association was found for the abovementioned SNP strongly associated with high lipoprotein(a) levels (Langsted et al. 2018). Both the SNP and KIV2 are associated with levels of plasma lipoprotein(a) and with the risk of myocardial infarction and aortic valve stenosis; however, it might seem that different mechanisms affect morbidity and mortality.

Familial Hypercholesterolemia

Familial hypercholesterolemia (FH) is a common autosomal genetic disease where individuals have extremely high levels of LDL cholesterol and thereby are at an extremely high risk of cardiovascular events. The risk of myocardial infarction in individuals with FH is roughly 50% for men by the age of 50 and 30% for women by the age of 60 if LDL cholesterol levels are left untreated. Most commonly, a mutation in the LDL receptor results in deficient removal of LDL cholesterol from the blood; however, other mutations have also been identified. If an individual is homozygous for the mutations, atherosclerosis develops from early childhood and myocardial infarction events occur even before the age of 20. Studies have shown that individuals with heterozygous and homozygous FH have high levels of lipoprotein(a) compared to healthy controls. However, while LDL cholesterol levels are high due to less removal by the defective LDL receptor, lipoprotein(a) has been shown not to be removed by the LDL receptor and therefore the mechanism must be different.

When measuring LDL cholesterol by standard hospital assays, lipoprotein(a) cholesterol will be included in this measurement. In the Copenhagen General Population Study, it was found that 25% of all individuals diagnosed with clinical FH are diagnosed because of high lipoprotein(a) levels (Langsted et al. 2016). Further, the study found that individuals with FH who are already at very high risk of cardiovascular disease because of high LDL cholesterol levels have an even higher risk of myocardial infarction if they also have high lipoprotein(a) levels (Fig. 16.6). The European Atherosclerosis Society consensus panel recommends screening of all FH patients for high lipoprotein(a) in order to identify those at the highest risk of cardiovascular disease (Nordestgaard et al. 2010); a similar recommendation comes from the US National Lipid Association.

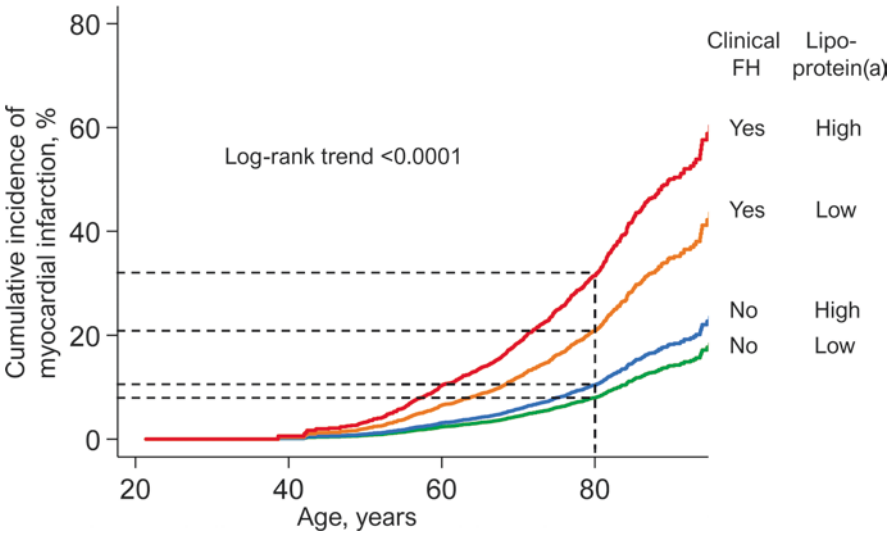

Fig. 16.6 Cumulative incidences of myocardial infarction by age and as a function of clinical familial hypercholesterolemia and lipoprotein(a) concentrations based on 46,200 White individuals from the Copenhagen General Population Study with lipoprotein(a) measurements. Diagnosis of clinical familial hypercholesterolemia was based on the Dutch Lipid Clinic Network criteria, and the definition included participants with possible, probable, or definite familial hypercholesterolemia. The cumulative incidences by age 80 years are shown by dashed lines. (Adapted from Langsted et al. (2016); with permission from Elsevier)

Mechanism of Action

Even though the evidence supporting lipoprotein(a) as a causal risk factor for cardiovascular disease is overwhelming and robust, the exact (patho-)physiological mechanisms behind these findings have not yet been established. Before the causal association of high lipoprotein(a) with high risk of cardiovascular disease was established, it was proposed by Brown and Goldstein that lipoprotein(a) might play a part in wound healing as a survival function (Brown and Goldstein 1987). The repeated copies of KIV2 present in the apolipoprotein(a) part of lipoprotein(a) are similar to those of kringles found in plasminogen. In plasminogen, KIV is the active part and exhibits fibrinolytic activity of plasmin to facilitate removal of already formed blood clots in the circulation; however, in lipoprotein(a), KIV is not proteolytically active and therefore theoretically could prevent plasminogen/plasmin from carrying out its normal fibrinolytic function via competitive inhibition. Plasminogen plays a key role in the fibrinolysis cascade, and it circulates as a closed, activation-resistant conformation. When it binds to fibrin clots, or to cell surfaces, plasminogen converts to an open form that can transform into active plasmin with help from different enzymes, including tissue plasminogen activator. At sites of injury, and on cell surfaces in general, fibrin clots display receptors with affinity to both

plasminogen and apolipoprotein(a), and studies have shown that lipoprotein(a) inhibits conversion of plasminogen to plasmin on endothelial cell surfaces. Lipoprotein(a) has also been suggested to play a role in clot biology at other points, such as overproduction of plasminogen activator inhibitor-1 (PAI-1) induced by oxidized lipoprotein(a), promotion of tissue factor expression in monocytes, and binding and inhibition of tissue factor pathway inhibitor. In vitro and animal studies have shown competitive inhibition of plasmin activation and function by lipoprotein(a); however, in vivo, this competitive inhibition may not be active, perhaps because of the large amount of plasminogen compared to lipoprotein(a) in the human circulation.

This proposed mechanism that lipoprotein(a) plays a role in wound healing by binding to fibrin by the kringles and inhibiting fibrinolysis would imply that high levels of lipoprotein(a) would be associated with low risk of bleeding. This has, however, not been convincingly shown, but one study found that high lipoprotein(a) levels were associated with observational and genetic low risk of bleedings in the brain and airways (Langsted et al. 2017).

As a pathophysiological pathway, this proposed plasminogen-associated mechanism could also lead to thrombosis and thereby other related diseases. It could be that lipoprotein(a) is attached to fibrin and thereby transported to vulnerable plaques and adding to cholesterol at these sites, resulting in narrowing of atherosclerotic stenoses. Further, it might be transported to sites of turbulent blood flow, leading to acceleration of aortic valve stenosis.

Another possible pathophysiological mechanism is that since lipoprotein(a) partly consists of an LDL-like particle containing cholesterol, it could promote atherosclerosis via the same pathways as established for LDL cholesterol. It might be that lipoprotein(a) has higher affinity toward binding in the extracellular intima and thereby to a greater extent than LDL cholesterol gets trapped in the arterial wall. The apolipoprotein(a) and apolipoprotein B100 parts of lipoprotein(a) might interact and bind to proteins and proteoglycans found in the atherosclerotic lesions. Contradicting this is the fact that in most individuals even at high lipoprotein(a) levels, the amount of cholesterol present in LDL particles largely exceeds that of cholesterol present in lipoprotein(a).

In 108,000 individuals from the Copenhagen General Population Study comparing the risk of myocardial infarction per 1 mmol/l (39 mg/dl) increase in cholesterol in LDL, remnant, and lipoprotein(a), there was a higher risk for lipoprotein(a) cholesterol compared to that of LDL cholesterol or remnant cholesterol (Fig. 16.7). This supports that lipoprotein(a) might have pathophysiological properties beyond that of its cholesterol content.

Finally, lipoprotein(a) has been shown to carry oxidized phospholipids, which might play an important role in inflammation and consequently atherosclerosis. The oxidized phospholipids are primarily found on apolipoprotein B100 and are positively correlated with the plasma levels of lipoprotein(a).

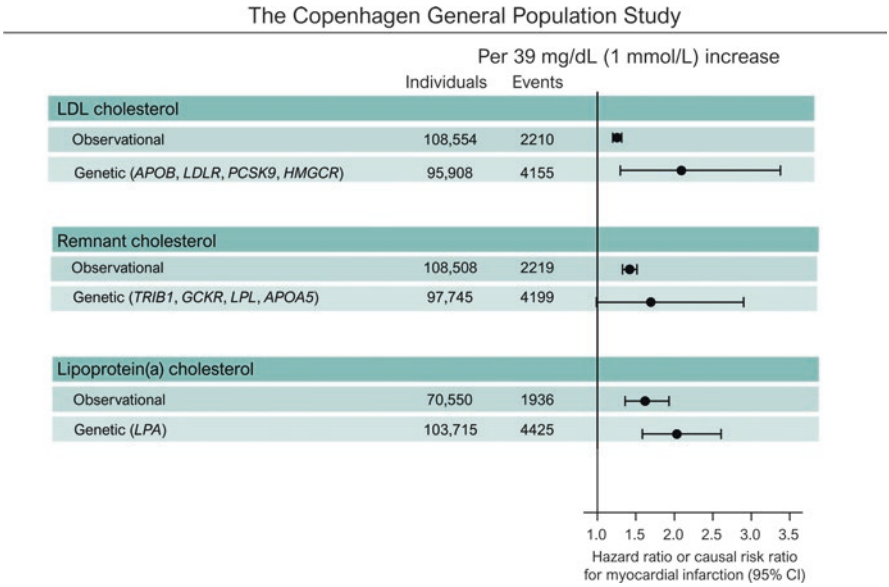

Fig. 16.7 Comparison of the risk of myocardial infarction with increasing levels of LDL cholesterol, remnant cholesterol, or lipoprotein(a) cholesterol according to observational and genetic study data in 108,000 individuals in the Copenhagen General Population Study. CI confidence interval. (Adapted from Nordestgaard et al. (2018))

Current Treatment Options

During the past decades, lipoprotein(a) has been firmly established as a causal risk factor for cardiovascular disease, and the need to find therapies to lower lipoprotein(a) becomes increasingly essential. The first step is to find a therapy that lowers lipoprotein(a) in an effective and safe manner, and the next step is to show that lowering of lipoprotein(a) in fact lowers the risk of cardiovascular disease; however, to date, this has not been shown. Several potential therapies have been suggested, and a few will hopefully turn out to be effective and safe (Table 16.1).

Statins effectively and safely lower LDL cholesterol and thereby also lower the risk of cardiovascular disease mainly by upregulating the expression of the LDL receptor. As lipoprotein(a) partly consists of an LDL particle, it is suggested that lipoprotein(a) could be removed by the LDL receptor. However, post hoc analyses of major randomized trials using statins have found no effect on lowering of lipoprotein(a), and the LDL receptor does not seem to be a major contributor to the removal of lipoprotein(a).

Niacin has been shown to lower lipoprotein(a) by up to 20%. Niacin has a positive effect on atherogenic lipids and the proposed mechanism is by reducing transcription of apolipoprotein(a) or by reducing secretion of apolipoprotein B. Two

Table 16.1 Potential lipoprotein(a)-lowering therapies and their mechanisms and problems

Therapy	Effect on Lp(a)	Mechanism/problem
Statins	0% to +7%	No effect
Niacin	−25%	Side effects
CETP inhibitor	0% to −50%	Attenuation of apoB lipidation
PCSK9 inhibitor	−25%	Decreased Lp(a) formation?
Apheresis	−35%	Removal of apoB-containing lipoproteins
Apo(a) antisense	−90%	Decreased hepatic apo(a) synthesis

large randomized controlled niacin trials in statin-treated patients found no reduction of cardiovascular event rates despite lowering of lipoprotein(a). Moreover, importantly, both studies found increased serious adverse events such as bleeding, infections, and gastrointestinal problems. Niacin is no longer available in the European market; however, it is still available in the United States.

Cholesteryl ester transfer protein (CETP) inhibitors were originally developed to raise HDL cholesterol levels; however, as low HDL cholesterol levels were found not to be causal for cardiovascular disease, other areas of therapy have been suggested, and among these is the lowering of lipoprotein(a). CETP inhibitors may lower lipoprotein(a) by up to ≈30%, but CETP inhibitors also lower LDL cholesterol to some extent.

Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors are monoclonal antibodies that lead to increased availability of the LDL receptor and have shown to lower LDL cholesterol by roughly 60% when applied on top of statins. PCSK9 inhibitors also lower lipoprotein(a) levels by around 25%; however, in individuals with high lipoprotein(a) levels, the effect is lower. Since lipoprotein(a) is not cleared via the LDL receptor, the mechanism must be different and it is proposed that this could be due to the impact on the rate of apolipoprotein B synthesis. PCSK9 inhibitors do not seem to be able to lower lipoprotein(a) enough to achieve a cardiovascular benefit; however, they may be a useful supplement in individuals with familial hypercholesterolemia with progressive cardiovascular disease and high lipoprotein(a) levels.

Lipoprotein apheresis is a very effective method to remove apoB-containing lipoproteins including lipoprotein(a) and has been shown to reduce lipoprotein(a) levels by up to 70% right after apheresis, with mean reductions of 35 % over the entire period from one apheresis to the next . Furthermore, smaller uncontrolled studies have found that the rate of major adverse coronary events was reduced in individuals with elevated lipoprotein(a) levels receiving apheresis every other week; however, other risk factors such as LDL cholesterol were also reduced. Apheresis is not only very effective but also very expensive and time-consuming, and, further, individuals receiving therapy every other week experience spikes of high lipoprotein(a) levels in-between sessions, which is possibly a risk factor for cardiovascular disease.

Future Treatment Options

A very promising lipoprotein(a)-lowering therapy is the antisense oligonucleotide binding to hepatic *LPA* mRNA, thereby reducing production of apolipoprotein(a). The first studies were conducted in gene-modulated mice since lipoprotein(a) is only present in humans, apes, old-world monkeys, and hedgehogs. Later, it was tested in monkeys and both studies found a substantial lowering of lipoprotein(a).

The first human study was a phase 1 randomized double-blind placebo-controlled single-dose/multi-dose trial. There was a dose-dependent reduction in lipoprotein(a), and the largest reduction was seen in the multi-dose arm lowering lipoprotein(a) by 79%. No serious adverse events were observed in this study. In a phase 2 study, individuals with elevated levels of lipoprotein(a) were assigned dose-ranging of the study drug and lipoprotein(a) levels were lowered by 72%; again, no serious adverse events were recorded. After this, the study drug was modified to induce quick and specific uptake by the liver where apolipoprotein(a) is produced and again lipoprotein(a) was safely lowered by 85% in the highest-dose group with no effect on the liver parameters. Recently, a phase 2 study of this modified drug has shown up to 80% reductions in lipoprotein(a) levels with no safety concerns regarding liver function or bleeding risk (Viney et al. 2016). Overall, the newest modified antisense oligonucleotide seems promising in the treatment of high lipoprotein(a) levels. However, no study on reduction in cardiovascular disease events has yet been conducted, but currently a phase 3 study named Lp(a)HORIZON is being conducted with cardiovascular disease as outcome, and results will hopefully show that this drug lowers not only lipoprotein(a) but also the risk of cardiovascular disease.

At the moment, treatment options for high lipoprotein(a) levels are limited and the focus must be on lowering other modifiable risk factors for cardiovascular disease. For individuals at high risk and with high lipoprotein(a) levels, aggressive therapy to lower LDL cholesterol must be applied; lowering of blood pressure and lifestyle changes must be recommended. In individuals with very high lipoprotein(a) levels, LDL cholesterol cannot be treated to very low levels because lipoprotein(a) cholesterol is comeasured in LDL cholesterol.

Conclusions

Lipoprotein(a) has been the focus of cardiovascular research since its discovery in 1963, with the most interest in the last decade. High levels of lipoprotein(a) have now been causally associated with increased risk of atherosclerotic stenosis (angina pectoris and claudication), myocardial infarction, aortic valve stenosis, heart

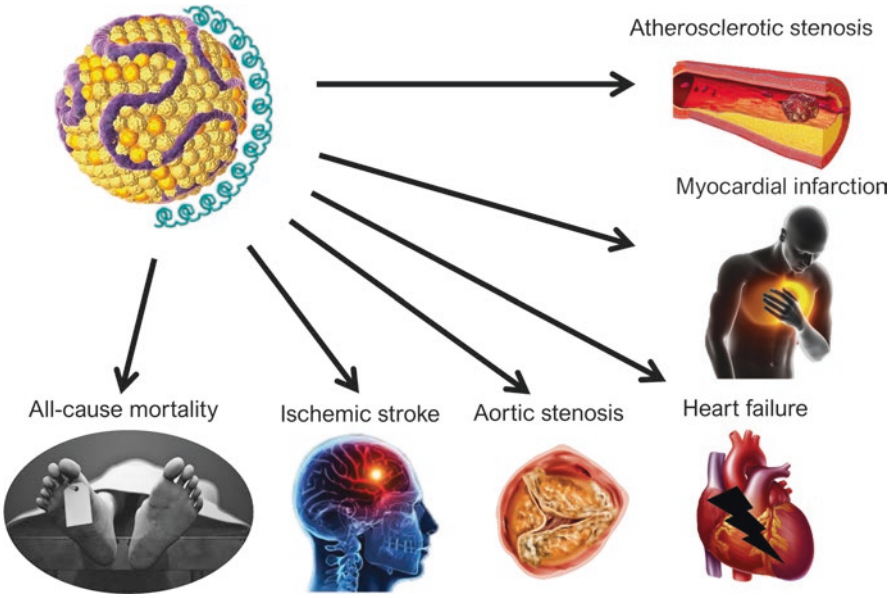

Fig. 16.8 High lipoprotein(a) levels and risk of cardiovascular disease. Lipoprotein(a) is observationally and causally associated with the risk of atherosclerotic stenosis, myocardial infarction, aortic valve stenosis, ischemic stroke, and all-cause mortality

failure, ischemic stroke, and cardiovascular and all-cause mortality (Fig. 16.8). Studies have found observational associations, and, further, Mendelian randomization studies have found that these associations are causal through human genetics. Currently, lipoprotein(a) is not a major focus at the general clinic, mainly because no sufficient treatment option is available to lower lipoprotein(a) levels; however, several major guidelines now recommend measuring lipoprotein(a) (Table 16.2). It is recommended to measure lipoprotein(a) in individuals at high risk such as in individuals with familial hypercholesterolemia, with a family history of premature cardiovascular disease, or with high LDL cholesterol despite aggressive treatment. Importantly, the latest European guidelines on cardiovascular disease prevention recommend that plasma lipoprotein(a) should be measured once in all individuals, as this is a genetic condition just like familial hypercholesterolemia. Currently, a phase 3 trial assessing the impact of lipoprotein(a) lowering on cardiovascular risk in high-risk patients is recruiting, and, hopefully, this will show that lowering of lipoprotein(a) by 80% also lowers the risk of cardiovascular disease – if this is documented, then the focus of elevated lipoprotein(a) risk will most likely be more general.

Table 16.2 Societies recommending screening for elevated lipoprotein(a) in guidelines

Society	Country	Year of published guideline
EAS	EU+	2010
ESC/EAS	EU+	2016
CCS	Canada	2016
AACE/ACE	US	2017
NICE	UK	2017
AHA/ACC[a]	US	2018
NLA	US	2019
ESC/EAS[b]	EU+	2019

[a]Elevated lipoprotein(a) is a risk-enhancing factor
[b]Plasma lipoprotein(a) should be measured once in all individuals

References

Berg K. A new serum type system in man--the LP system. Acta Pathol Microbiol Scand. 1963;59:369–82.

Brown MS, Goldstein JL. Plasma lipoproteins: teaching old dogmas new tricks. Nature. 1987;330(6144):113–4.

Clarke R, Peden JF, Hopewell JC, Kyriakou T, Goel A, Heath SC, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. N Engl J Med. 2009;361(26):2518–28.

Danesh J, Collins R, Peto R. Lipoprotein(a) and coronary heart disease. Meta-analysis of prospective studies. Circulation. 2000;102(10):1082–5.

Emdin CA, Khera AV, Natarajan P, Klarin D, Won HH, Peloso GM, et al. Phenotypic characterization of genetically lowered human lipoprotein(a) levels. J Am Coll Cardiol. 2016;68(25):2761–72.

Emerging Risk Factors C, Erqou S, Kaptoge S, Perry PL, Di Angelantonio E, Thompson A, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. JAMA. 2009;302(4):412–23.

Enkhmaa B, Anuurad E, Berglund L. Lipoprotein (a): impact by ethnicity and environmental and medical conditions. J Lipid Res. 2016;57(7):1111–25.

Gudbjartsson DF, Thorgeirsson G, Sulem P, Helgadottir A, Gylfason A, Saemundsdottir J, et al. Lipoprotein(a) concentration and risks of cardiovascular disease and diabetes. J Am Coll Cardiol. 2019;74(24):2982–94.

Kamstrup PR, Nordestgaard BG. Lipoprotein(a) concentrations, isoform size, and risk of type 2 diabetes: a Mendelian randomisation study. Lancet Diabetes Endocrinol. 2013;1(3):220–7.

Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. JAMA. 2009;301(22):2331–9.

Kamstrup PR, Tybjaerg-Hansen A, Nordestgaard BG. Elevated lipoprotein(a) and risk of aortic valve stenosis in the general population. J Am Coll Cardiol. 2014;63(5):470–7.

Kronenberg F, Utermann G. Lipoprotein(a): resurrected by genetics. J Intern Med. 2013;273(1):6–30.

Langsted A, Kamstrup PR, Benn M, Tybjaerg-Hansen A, Nordestgaard BG. High lipoprotein(a) as a possible cause of clinical familial hypercholesterolaemia: a prospective cohort study. Lancet Diabetes Endocrinol. 2016;4(7):577–87.

Langsted A, Kamstrup PR, Nordestgaard BG. High lipoprotein(a) and low risk of major bleeding in brain and airways in the general population: a Mendelian randomization study. Clin Chem. 2017;63(11):1714–23.

Langsted A, Kamstrup PR, Nordestgaard BG. High lipoprotein(a) and high risk of mortality. Eur Heart J. 2018.

Langsted A, Nordestgaard BG, Kamstrup PR. Elevated lipoprotein(a) and risk of ischemic stroke. J Am Coll Cardiol. 2019;74(1):54–66.

McLean JW, Tomlinson JE, Kuang WJ, Eaton DL, Chen EY, Fless GM, et al. cDNA sequence of human apolipoprotein(a) is homologous to plasminogen. Nature. 1987;330(6144):132–7.

Mora S, Kamstrup PR, Rifai N, Nordestgaard BG, Buring JE, Ridker PM. Lipoprotein(a) and risk of type 2 diabetes. Clin Chem. 2010;56(8):1252–60.

Nordestgaard BG, Langsted A. Lipoprotein (a) as a cause of cardiovascular disease: insights from epidemiology, genetics, and biology. J Lipid Res. 2016;57(11):1953–75.

Nordestgaard BG, Chapman MJ, Ray K, Boren J, Andreotti F, Watts GF, et al. Lipoprotein(a) as a cardiovascular risk factor: current status. Eur Heart J. 2010;31(23):2844–53.

Nordestgaard BG, Nicholls SJ, Langsted A, et al. Advances in lipid-lowering therapy through gene-silencing technologies. Nat Rev Cardiol. 2018;15:261–72.

Thanassoulis G, Campbell CY, Owens DS, Smith JG, Smith AV, Peloso GM, et al. Genetic associations with valvular calcification and aortic stenosis. N Engl J Med. 2013;368(6):503–12.

Viney NJ, van Capelleveen JC, Geary RS, Xia S, Tami JA, Yu RZ, et al. Antisense oligonucleotides targeting apolipoprotein(a) in people with raised lipoprotein(a): two randomised, double-blind, placebo-controlled, dose-ranging trials. Lancet. 2016;388(10057):2239–53.

Chapter 17
High-Sensitivity C-Reactive Protein

David I. Feldman, Roger S. Blumenthal, and Ty J. Gluckman

Introduction

The Role of Inflammation in Atherogenesis

Atherosclerosis, or the accumulation of lipids and fibrous elements in large arteries, underlies the development of atherosclerotic cardiovascular disease (ASCVD), including coronary heart disease (CHD) and stroke. While once believed to be a process driven predominantly by lipids such as low-density lipoprotein cholesterol (LDL-C), our understanding of the pathobiology of this condition has evolved to one that also recognizes the importance of growth factors, proliferation of smooth muscle cells, and inflammation.

Early in atherogenesis, the deposition of lipids and recruitment of inflammatory cells, such as T lymphocytes and macrophages, leads to the development of an early atheroma consisting of a thick fibrous cap surrounding a lipid-rich core. Progression of atherogenesis depends, in part, on plasma concentrations of cholesterol as well as

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mediators of inflammation such as high-sensitivity C-reactive protein (hsCRP), interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α).

With adequate control of these mediators, a stabilized plaque develops with a small lipid pool, a thick fibrous cap, and a preserved lumen. With inadequate control, however, a vulnerable plaque can manifest that is characterized by a thin fibrous cap, a large lipid pool, and many inflammatory cells. While multiple triggers exist, exposure to ongoing inflammation can lead to plaque disruption and thrombosis, resulting in progressive arterial narrowing and/or a major adverse cardiovascular event (MACE), such as a myocardial infarction (MI) (Fig. 17.1) (Libby 2002).

Acknowledging the widely accepted role of LDL-C in atherogenesis (Ridker 2012), accrued basic science and translational and clinical research have further elucidated multiple inflammatory pathways involved in ASCVD (Lawler et al. 2020). This has resulted in a paradigm shift for risk assessment and prevention, with recognition that a diverse group of inflammatory mediators may contribute to (a) progression of atherosclerosis in the clinically stable phase of ASCVD, (b) destabilization of plaque, prompting an acute coronary syndrome (ACS), and (c) extension of injury, following cardiomyocyte death with an MI. Therefore, if critical components of the innate and adaptive immune systems contribute to atherogenesis, then they may represent an important target for patients with ASCVD (Hansson and Libby 2006).

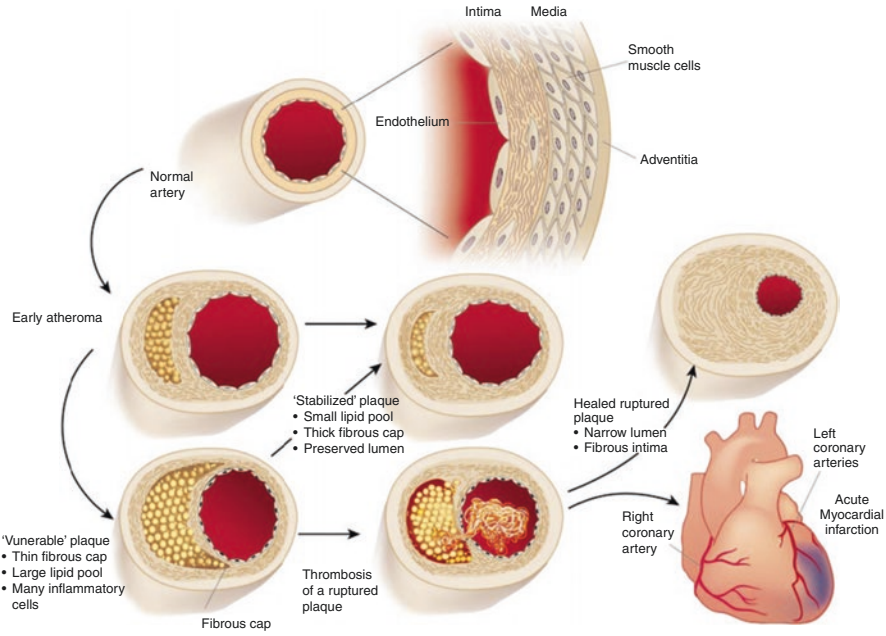

Fig. 17.1 Development and progression of atherosclerosis

Markers of Inflammation: High-Sensitivity C-Reactive Protein

The identification of specific markers of inflammation has been critical to improved understanding of atherosclerosis (Libby et al. 2009). A wide range of markers have been identified to date, including biomarkers (myeloperoxidase, lipoprotein-associated phospholipase A2, pentraxin-3), cytokines (interleukins, TNF-α), proteases (matrix metalloproteinase-9), adhesion molecules (intracellular adhesion molecule-1, vascular cellular adhesion molecule-1), and acute-phase reactants (C-reactive protein and fibrinogen).

C-reactive protein (CRP) is an annular, pentameric glycoprotein (23 kDa subunits). It is released into the circulation by hepatocytes in response to cytokine release (IL-6) and by macrophages and T cells in the setting of infection, trauma, or other acute inflammatory stimuli (Libby et al. 2009). Upstream mediators of CRP, including IL-6, also become activated following exposure to cholesterol or urate crystals, bacterial proteins, regional hypoxia, and local hemodynamic triggers at the site of an atheroma (Ridker 2016a).

In 1930, CRP was first identified as a blood protein that binds to the C-polysaccharide of pneumococcus in patients with pneumonia (Tillett and Francis 1930). CRP is usually quantified by assays with standard sensitivity. However, among individuals with chronic, low-level elevation, CRP may be detected by high-sensitivity assays (hsCRP).

CRP increases cytokine and adhesion molecule production, inhibits the survival and function of endothelial progenitor cells, induces endothelial cell apoptosis, decreases nitric oxide production, increases endothelin levels, and inhibits fibrinolysis through its effects on tissue plasminogen activator and plasminogen activator inhibitor-1 (Ridker et al. 2004). Despite this, it appears to have a less direct causal role in ASCVD and instead likely represents a by-product of upstream inflammation (Lawler et al. 2020). In fact, when measuring the concentration of various inflammatory markers at the site of a coronary occlusion, levels of CRP are typically not increased (Maier et al. 2005).

Nonetheless, hsCRP is widely accepted as the most common inflammatory biomarker used in the assessment of ASCVD risk. This, in part, is based on availability of a clinical assay with a well-described association between elevated levels and associated risk (Ridker 2016b). Currently, commercial assays for hsCRP are widely available and standardized for use in both outpatient and inpatient settings (Ridker et al. 2004). Of note, hsCRP is a distinct test from CRP, where the latter is typically utilized as part of a general evaluation during an infectious or rheumatologic disease workup.

Measurement of High-Sensitivity C-Reactive Protein: Cutpoints, Laboratory Testing, and Variation

In 2003, informed by data from multiple large, prospective cohort studies (Ridker et al. 1997, 2000, 2001a, b, 2002; Tracy et al. 1997; Koenig et al. 1999; Danesh et al. 2000), the Centers for Disease Control and Prevention and the American Heart

Association (AHA) issued the first clinical guideline incorporating hsCRP into the assessment of global risk. It was suggested that hsCRP levels <1, 1 to <3, and ≥ 3 mg/L be used to delineate groups as low, moderate, and high vascular risk, respectively (Pearson et al. 2003). While these cutpoints differ from those used in the Women's Health Study (<0.5, 0.5–1.0, 1.0–3.0, 3.0–5.0, >5 mg/L), both approaches improve risk discrimination (Ridker and Cook 2004).

Levels of hsCRP >10 mg/L suggest other underlying inflammatory processes. For these individuals, it is recommended that the hsCRP level be rechecked. If it persists in this range, then these individuals are still felt to be at increased cardiovascular (CV) risk. In fact, prospective data suggest that the predictive value of hsCRP is linear across a wide range of values, even in the presence of collagen vascular disease or other underlying chronic systemic inflammatory diseases (Ridker and Cook 2004).

Levels of hsCRP can vary but are not affected by fasting. Repeat or serial measurement of hsCRP does improve the predictive value but may be limited by financial cost (~$30 per test) and inconvenience (repeat blood draw). Ideally, hsCRP should be measured at times when other forms of inflammation are stable. However, as an acute-phase reactant, the levels of hsCRP can fluctuate widely based on the metabolic and inflammatory state of a given individual.

To improve hsCRP's value in refining ASCVD risk, factors that contribute to individual variability should be considered. Importantly, multiple factors influence hsCRP levels, including gender (women > men), race/ethnicity (African American > Latinos > South Asian > Caucasian > East Asian), age, geographic region, and education status (Woloshin and Schwartz 2005; Lakoski et al. 2006; Albert et al. 2004). Body mass index (BMI), diabetes status, blood pressure, and certain infections have also been shown to have an effect (Libby et al. 2002; Visser et al. 1999), with potentially significant alteration by physical exercise, dietary patterns, smoking, alcohol use, and exposure to environmental pollutants (LaMonte et al. 2002; Clark et al. 2011). In fact, environmental factors likely account for roughly 20% and 30% of interindividual hsCRP variability in women and men, respectively, with the remainder attributed to genetic differences (Pankow et al. 2001).

Risk Association of High-Sensitivity C-Reactive Protein

One of the first studies to describe an association between elevated levels of hsCRP and incident CV disease in primary prevention came from the Physicians' Health Study. Among the 1086 male participants, those in the highest quartile (hsCRP level ≥ 2.11 mg/L) of hsCRP had a 2.9-fold greater risk of MI ($p < 0.001$) and 1.9-fold greater risk of stroke ($p = 0.02$) compared to those in the lowest quartile (hsCRP level ≤ 0.55 mg/L) independent of traditional risk factors (Ridker et al. 1997). Likewise, in a nested case–control analysis from the Women's Health Study, each increase in quartile of plasma hsCRP was associated with a 1.5-fold increased risk of death from CHD, MI, stroke, or coronary revascularization (Ridker et al. 2000).

Further validation of the predictive value of hsCRP stems from a large 2010 meta-analysis of over 160,000 individuals without ASCVD. In this study, every standard deviation increase in log-normalized hsCRP was associated with a 37% increase in adjusted relative risk (RR) for CHD (RR 1.37, 95% confidence interval (CI) 1.27–1.48) – a magnitude comparable to other traditional risk factors, including non-high-density lipoprotein cholesterol (RR 1.28, 95% CI, 1.16–1.40) and systolic blood pressure (RR 1.35, 95% CI, 1.25–1.45) (Emerging Risk Factors Collaboration et al. 2010). Similar findings were noted for ischemic stroke (RR 1.27, 95% CI, 1.15–1.40) and CV disease mortality (RR 1.55, 95% CI, 1.37–1.76), even after adjustment for traditional risk factors including age, sex, systolic blood pressure, smoking, history of diabetes, BMI, triglycerides, and total cholesterol level (Emerging Risk Factors Collaboration et al. 2010).

In contrast to its use in primary prevention, the value afforded by measurement of hsCRP in secondary prevention is less well established (Koenig 2013). Data have, however, shown that hsCRP can help predict ASCVD events (including MI, revascularization, stroke, heart failure, and mortality) in individuals with stable coronary artery disease (CAD) and ACS (Liuzzo et al. 1994; Haverkate et al. 1997; Morrow et al. 1998, 2006; Sabatine et al. 2002; Aguilar et al. 2006; Arroyo-Espliguero et al. 2009; Horne et al. 2000; Sattar et al. 2007; de Winter et al. 2002; Zebrack et al. 2002; Blake and Ridker 2002; Haidari et al. 2001). For those who have been revascularized, it can also help predict the risk of coronary artery bypass graft failure or in-stent restenosis (Kangasniemi et al. 2006; Hong et al. 2006). Finally, among secondary prevention patients treated with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, hsCRP can help refine residual risk (Bohula et al. 2018; Pradhan et al. 2018).

Risk Discrimination, Reclassification, and Accuracy of High-Sensitivity C-Reactive Protein

Of key importance is understanding the ability of hsCRP to inform clinical decision-making above and beyond that provided by traditional risk factors. The American Heart Association released a scientific statement in 2010, outlining the criteria for evaluation of novel markers of CV risk (Hlatky et al. 2009). The six phases include proof of concept, prospective validation, incremental value, clinical utility, clinical outcomes, and cost-effectiveness.

Both proof of concept and prospective validation depend on a marker's ability to discriminate between those with and those without clinical events. Traditionally, this has been assessed using the C-statistic or the area under the curve (AUC) in a receiver operating characteristic (ROC) plot, comparing sensitivity to 1 – specificity (or true positives to true negatives).

In a 2006 analysis, global ASCVD risk prediction models were compared with and without hsCRP (Cook et al. 2006). The authors concluded that among healthy women without diabetes aged 45 years and older, hsCRP improved ASCVD risk

classification, particularly in those with a 10-year Framingham Risk Score (FRS) of 5–20%. However, adding hsCRP to the Framingham risk model, which includes variables like age, total cholesterol, high-density lipoprotein cholesterol, smoking, and blood pressure, only improved the AUC from 0.813 to 0.815 – a level less than the 0.05 increase in the AUC threshold set for moderate improvement in predictive ability (Lloyd-Jones et al. 2006).

Years later, a similar analysis was performed using data from the Multi-Ethnic Study of Atherosclerosis (MESA), where risk markers including hsCRP were studied to determine improvement in prediction of incident CHD and cardiovascular disease (CVD) among intermediate-risk participants (FRS 5–20%) (Yeboah et al. 2012). Very modest increases in predictive value were observed from addition of hsCRP to the FRS compared to the FRS alone for incident CHD (AUC 0.640 vs. 0.623) and CVD (AUC 0.637 vs 0.627), respectively (Fig. 17.2). Comparable findings were observed in an analysis of the Emerging Risk Factors Collaboration, where a small, clinically insignificant 0.004 increase in the AUC was noted ($p < 0.05$) (Emerging Risk Factors Collaboration et al. 2012).

Although discrimination is an important metric to consider when evaluating a novel risk marker, AUC alone may be too insensitive of a measure to assess the incremental value of adding a variable to a risk prediction model. For example, despite the significant role of lipids and blood pressure in risk prediction, they only modestly improve the AUC in risk models (Ridker et al. 2006).

It is also important to test a biomarker's ability to provide clinically meaningful reclassification of risk. In the Women's Health Study, when hsCRP was added to the

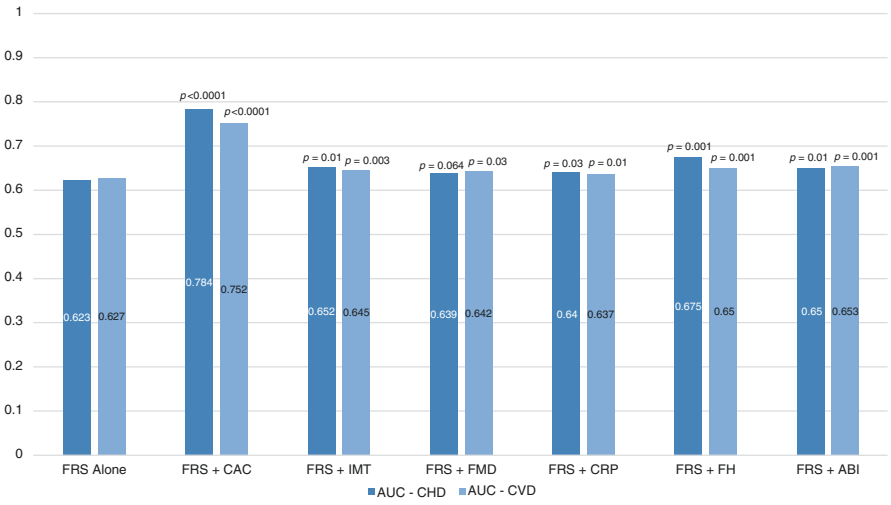

Fig. 17.2 AUC for the Framingham Risk Score + risk factors, laboratory tests, and imaging studies for incident CHD and CVD in MESA. ABI ankle–brachial index, AUC area under the curve, CAC coronary artery calcium, CHD coronary heart disease, CRP C-reactive protein, CVD cardiovascular disease, FH family history, FMD flow-mediated dilation, FRS Framingham Risk Score, IMT intima-media thickness, ROC receiver operating characteristic

Adult Treatment Panel III (ATP III) CHD risk score, approximately 40% of intermediate-risk women were reclassified into higher- or lower-risk categories (Cook et al. 2006). This led to development of the net reclassification index (NRI), which reflects changes in both risk classification and accuracy (Cook and Ridker 2009).

The NRI quantifies how many individuals are reclassified into a different risk group when adding a risk marker like hsCRP and appropriateness of the reclassification. Ultimately, the NRI is determined by net appropriate (reclassification into a higher-risk group followed by an event) and inappropriate (reclassification into a lower-risk group followed by an event) reclassifications.

The NRI for hsCRP has been evaluated in multiple older studies and has ranged from ~1 to 12%, depending on the clinical outcome. In the Framingham Heart Study, the NRI was 11.8% ($p = 0.009$) for CHD events and 5.6% ($p = 0.014$) for total CVD events (Wilson et al. 2005). A separate analysis of the Women's Health Study demonstrated an NRI of 5.7% (Cook 2008). Finally, in a case–control study from the European Prospective Investigation into Cancer and Nutrition in Norfolk, the NRI with addition of hsCRP was 12% for CHD events (Rana et al. 2009).

More recently, the NRIs from the Rotterdam (Kavousi et al. 2012) and MESA (Yeboah et al. 2012) studies have been 2% and 7.9% for CHD events, respectively. This was followed by a large meta-analysis of individuals without ASCVD, where addition of hsCRP to traditional risk factors yielded an NRI of only 1.5% for fatal and nonfatal CVD events ($p < 0.02$), corresponding to a very high number needed to test (400–500) to prevent one CVD event over 10 years (Emerging Risk Factors Collaboration et al. 2012).

In response to perceived limitations of the FRS and incremental value afforded by measurement of hsCRP, the Reynolds Risk Score (RRS) was developed. Addition of hsCRP (and family history of premature CHD) to traditional risk factors resulted in a risk score with better discrimination, calibration, and reclassification (Ridker et al. 2007). The contribution of hsCRP was small, however, compared to age, smoking, systolic blood pressure, and cholesterol. For context, a doubling of the hsCRP level equates roughly to a 3 mmHg increase in systolic blood pressure.

Additional analyses have been performed using the RRS. In a study that compared the RRS to the FRS for global CVD prediction in the Women's Health Initiative (Cook et al. 2012), the Framingham CVD model largely overestimated the risk for major CVD events. Not only did the RRS have adequate calibration but also it modestly improved discrimination (AUC 0.765 vs. 0.757) and increased the NRI (12.9% and 5.9%).

A separate analysis involving the MESA dataset utilized the FRS and RRS to predict the development and progression of subclinical atherosclerosis as assessed by coronary artery calcium (CAC) (DeFilippis et al. 2011). While the FRS and RRS were both significantly predictive of incident CAC and CAC progression, only the RRS consistently added predictive value for the incidence and progression of CAC when discordance between scoring systems was present.

Collectively, these data informed the 2013 American College of Cardiology/American Heart Association Guideline on the Assessment of Cardiovascular Risk

(Goff Jr et al. 2013). Even though a major portion of that document revolved around the introduction of the Pooled Cohort Equations (PCEs), measurement of hsCRP (along with other risk markers) was left as an option if risk-based treatment decision-making was uncertain following quantitative risk assessment.

A Review of the Evidence: Inflammatory Markers

Statin therapy represents the mainstay of ASCVD risk reduction in primary prevention (Shepherd et al. 1995; Downs et al. 1998; Sever et al. 2003). Despite this, ASCVD events continue to occur frequently, even among individuals with controlled LDL-C (Baigent et al. 2005). Hypotheses for additional targets of residual ASCVD risk include inadequately lowered LDL-C, other elevated lipoproteins (e.g., Lp(a)), hypertriglyceridemia, thrombosis, and systemic inflammation (Lawler et al. 2020).

In 2008, in an effort to determine whether additional LDL-C and hsCRP lowering with statin therapy could further reduce ASCVD risk, the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) was conducted (Ridker et al. 2008). This study followed a post hoc analysis of the Air Force/Texas Coronary Atherosclerosis Prevention Study where treatment with lovastatin conveyed a 42% relative risk reduction in fatal or nonfatal MI, unstable angina, or sudden death from cardiac causes among primary prevention patients with an LDL-C < 149 mg/dL and hsCRP >1.6 mg/L compared to placebo ($p = 0.04$) (Ridker et al. 2001a).

The JUPITER Trial

JUPITER enrolled 17,802 individuals without known ASCVD or diabetes, an LDL-C < 130 mg/dL, and an hsCRP ≥2 mg/L, randomizing them to rosuvastatin (20 mg daily) or placebo. Rosuvastatin reduced the levels of LDL-C and hsCRP by 50% and 37%, respectively. The trial was stopped prematurely after a median of 1.9 years because of differences in the CV event rate. Rates of the primary endpoint (MI, stroke, unstable angina, CV death, or revascularization) per 100 person-years were 0.77 and 1.36 in those receiving rosuvastatin and placebo, respectively (hazard ratio (HR), for rosuvastatin 0.56; 95% CI, 0.46–0.69, $p < 0.00001$).

While benefits from statin therapy are thought to largely result from reduction of LDL-C, on-treatment levels of LDL-C and hsCRP are, in fact, prognostically equivalent (Ridker et al. 1998, 2001a, 2005; Morrow et al. 2006; Nissen et al. 2005; Bohula et al. 2015). Even though findings from the JUPITER trial validate the benefits of high-intensity statin therapy in apparently healthy individuals with LDL-C levels <130 mg/dL and hsCRP levels ≥2 mg/L, secondary analyses have revealed several limitations. First, baseline hsCRP levels did not independently predict a preferential benefit with statin therapy (Kaul et al. 2010). In addition, the relative

risk reduction from rosuvastatin was consistent across three separate hsCRP cut-points (Kaul et al. 2010). Second, interaction testing between hsCRP levels and benefits from statin therapy was negative. Third, treatment response with rosuvastatin was limited to those with elevated hsCRP levels along with at least one traditional risk factor. This not only reinforces the importance of traditional risk factors in ASCVD risk assessment but also highlights the link between absolute risk and benefit with statin therapy.

In an attempt to further improve risk assessment, CAC scores were used to identify a JUPITER-like subgroup most likely to benefit from statin therapy in MESA (Blaha et al. 2011). Among 950 participants in this analysis, CAC scores further stratified risk and helped identify those likely to derive the greatest absolute benefit. For CHD events, the predicted 5-year number needed to treat (NNT) for CAC scores of 0 and > 100 was 549 and 24, respectively. For CVD events, the predicted 5-year NNT for CAC scores of 0 and > 100 was 124 and 19, respectively. Thus, CAC scoring provides a much more effective means to identify JUPITER-like patients most likely to benefit from high-intensity statin therapy.

The Low-Dose Colchicine (LoDoCo) Trial

While most commonly used for the treatment of gout and pericarditis, colchicine is a microtubule inhibitor that also interferes with the NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasome/IL-1ß signaling pathway. In the Low-Dose Colchicine (LoDoCo) trial, 532 patients with stable CHD on antiplatelet and statin therapy were randomized to colchicine (0.5 mg/day) or placebo for a median of 3 years (Nidorf et al. 2013). Rates of the primary composite endpoint of ACS, out-of-hospital cardiac arrest, or noncardioembolic ischemic stroke were 5.4% and 16.0% among those receiving colchicine or placebo, respectively (HR 0.33, 95% CI, 0.18–0.59, $p < 0.001$). In a prespecified secondary on-treatment analysis excluding patients unable to tolerate or start colchicine, rates of the primary composite outcome occurred in 4.5% and 16.0% of those receiving colchicine or placebo, respectively (HR 0.29, 95% CI, 0.15–0.56, $p < 0.001$).

Most of colchicine's benefits were driven by a reduction in nonfatal CV events. The exact mechanism underlying its benefits is not completely clear, as inflammatory markers, including hsCRP, were not collected. Importantly, 11% of patients treated with colchicine stopped therapy after a mean of 2.4 years, most commonly for gastrointestinal intolerance.

The CANTOS Trial

The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) sought to expand available therapies targeting residual inflammation in patients with ASCVD on statin therapy (Ridker et al. 2017a). Canakinumab, a therapeutic monoclonal antibody targeting IL-1ß, exerts its effects upstream in the inflammatory

signaling pathway, ultimately reducing IL-6 and CRP production. CANTOS enrolled 10,061 patients with previous MI and an hsCRP level ≥ 2 mg/L, randomizing them to subcutaneous canakinumab at one of three doses (50 mg, 150 mg, or 300 mg) or placebo every 3 months. Median hsCRP levels were reduced by 26–41% in the canakinumab group compared to those receiving placebo.

During a follow-up of 3.7 years, rates of the primary composite endpoint of nonfatal MI, nonfatal stroke, or CVD death were 4.1, 3.9, 3.9, and 4.5 per 100 person-years among those receiving the 50 mg, 150 mg, and 300 mg doses of canakinumab or placebo, respectively. The HRs for canakinumab compared to placebo at the 50 mg, 150 mg, and 300 mg doses were 0.93 (95% CI, 0.80–1.07, $p = 0.30$), 0.85 (95% CI, 0.74–0.98, $p = 0.021$), and 0.86 (95% CI, 0.75–0.99, $p = 0.031$), respectively.

The relative risk reduction for the primary composite endpoint was most pronounced among those who attained an hsCRP in the lowest tertile on canakinumab (HR 0.73, 95% CI, 0.62–0.85, $p < 0.0001$). There was also a strong relationship between reduction in the levels of IL-6 and CV benefits. Treatment with canakinumab was, however, associated with a higher incidence of fatal infection (incidence rate, 0.31 vs. 0.18 events per 100 person-years, $p = 0.02$).

CANTOS represents the first large outcomes study to validate the importance of attenuating inflammation in those with ASCVD already receiving statin therapy (Ridker et al. 2018a). Given the absence of any effect on LDL-C, the benefit of canakinumab directly results from a reduction in the levels of IL-6 and hsCRP (Ridker et al. 2018b, 2018c). Importantly, the effect size with canakinumab is comparable to that observed with PCSK9 inhibitors – a therapy capable of producing large reductions in LDL-C, but no appreciable decrease in IL-6 and hsCRP (Ridker et al. 2018a).

Further support for this approach is provided by the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) and Studies of PCSK9 Inhibition and the Reduction of Vascular Events (SPIRE) trials (Bohula et al. 2018; Pradhan et al. 2018). In these studies, persistence of elevated hsCRP among those with LDL-C levels ≤20 mg/dL on a statin and PCSK9 inhibitor was associated with significant residual risk.

The Cardiovascular Inflammation Reduction Trial (CIRT)

Additional studies have sought to reduce CV risk through use of alternative anti-inflammatory therapies. One such example is methotrexate, which has been associated with fewer MACEs when used in patients with psoriatic and rheumatoid arthritis (Choi et al. 2002; Westlake et al. 2010; Micha et al. 2011). This was the basis for the Cardiovascular Inflammation Reduction Trial (CIRT), which randomized 4786 participants with previous MI or multivessel CAD along with either diabetes or metabolic syndrome to low-dose methotrexate (target dose of 15–20 mg weekly) or placebo for a median of 2.3 years (Ridker et al. 2019).

Patients randomized to methotrexate, however, did not achieve lower levels of IL-1ß, IL-6, or hsCRP compared to placebo. Accordingly, occurrence of the primary endpoint, a composite of nonfatal MI, nonfatal stroke, CV death, or hospitalization for unstable angina that led to urgent revascularization, was not significantly different (incidence rate, 4.13 vs. 4.31 per 100 person-years for methotrexate and placebo arms, respectively; HR 0.96, 95% CI, 0.79–1.16). Patients receiving methotrexate, however, did experience an elevation in hepatic transaminases, reduction in leukocyte count and hematocrit, and a higher incidence of nonbasal cell skin cancer.

Various explanations have been put forth about the disappointing results of CIRT. While individuals included in the study had known ASCVD with additional CV risk factors, residual inflammatory risk with an elevated hsCRP level was not required for enrollment. As such, some believe that the negative findings relate to the absence of an enrichment strategy with hsCRP.

Reflective of this, the baseline median hsCRP levels in CIRT and CANTOS were 1.6 mg/L and 4.2 mg/L, respectively. While methotrexate can provide benefits in inflammatory conditions, its use in the CIRT did not result in decreased levels of measured inflammatory biomarkers (Lawler et al. 2020), underscoring the need to target specific inflammatory pathways in order to achieve CV benefits (Ridker 2020).

The Colchicine Cardiovascular Outcomes Trial (COLCOT)

In 2019, following discordant trial findings with CANTOS and CIRT, the Colchicine Cardiovascular Outcomes Trial (COLCOT) was published (Tardif et al. 2019). This study randomized 4745 patients within a median of 14 days following an acute MI to either low-dose colchicine (0.5 mg once daily) or placebo. After a median of ~2 years, treatment with colchicine was associated with a significant reduction in the primary composite endpoint of death from CV causes, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina leading to coronary revascularization. This was noted in 5.5% of those treated with colchicine and in 7.1% of those treated with placebo (HR 0.77, 95% CI, 0.61–0.96, $p = 0.02$). The greatest effect with colchicine was on rates of stroke (HR 0.26, 95% CI, 0.10–0.70) and urgent hospitalization for angina leading to coronary revascularization (HR 0.50, 95% CI, 0.31–0.81). Importantly, pneumonia was observed more often in those receiving colchicine (0.9% vs. 0.4%, $p = 0.03$).

While hsCRP and IL-6 levels were not measured in the COLCOT, they were assessed in a subgroup of the Colchicine in Percutaneous Coronary Intervention (COLCHICINE-PCI) study, which randomized patients referred for possible percutaneous coronary intervention (PCI) to acute preprocedural oral colchicine (1.8 mg) or placebo (Shah et al. 2020). Among 280 individuals included in this nested inflammatory biomarker substudy, there was no change in IL-6 concentrations 1 hour post PCI. After 24 hours, however, treatment with colchicine resulted in a less-pronounced increase in the levels of both IL-6 (76% vs. 338%, $p = 0.02$) and hsCRP (11% vs. 66%, $p = 0.001$) compared to placebo.

The LoDoCo2 Trial

Building off of favorable effects with colchicine in those with an acute MI, the LoDoCo2 trial sought to evaluate colchicine's impact on a large cohort of patients with stable ischemic heart disease. The study randomized 5522 patients with chronic CHD to daily colchicine (0.5 mg) or placebo for a median of 29 months (Nidorf et al. 2020). Rates of the primary composite endpoint of CV death, spontaneous (nonprocedural) MI, ischemic stroke, or ischemia-driven coronary revascularization occurred in 6.8% and 9.6% of those receiving colchicine or placebo, respectively (incidence rate, 2.5 vs. 3.6 events per 100 person-years; HR 0.69, 95% CI, 0.57–0.83, $p < 0.001$). Colchicine also significantly reduced multiple secondary composite endpoints including CV death, MI, or ischemic stroke (HR 0.72, 95% CI, 0.57–0.92, $p = 0.007$).

Treatment with colchicine, however, was associated with a strong trend toward increased risk of non-CV death (HR 1.51, 95% CI, 0.99–2.31) and a significantly higher rate of myalgia (HR 1.15, 95% CI, 1.01–1.31). Similar to findings observed in the original LoDoCo trial, 15.4% of patients enrolled in the run-in phase did not undergo randomization because of intolerance to colchicine, most commonly from gastrointestinal upset. Also, without baseline data on lipids and inflammatory markers, the benefits of colchicine could not be correlated with risk factor control. Accordingly, more investigation is needed to fully determine the populations most likely to benefit from its use in secondary prevention.

hsCRP and Inflammatory Markers in Clinical Practice

Although data from JUPITER, LoDoCo, CANTOS, COLCOT, and LoDOCo2 support a role for targeted anti-inflammatory therapy (Fig. 17.3), multiple questions persist as it relates to regular adoption in clinical practice. Importantly, there is a need to further understand how these biomarkers should be used to identify patients warranting treatment initiation and intensification (Yousuf et al. 2013).

Advocates for use of anti-inflammatory therapy to mitigate risk note that clinicians must first measure it. Simply put, without measuring hsCRP, it is difficult to identify those most likely to benefit from its lowering (Ridker et al. 2020). To

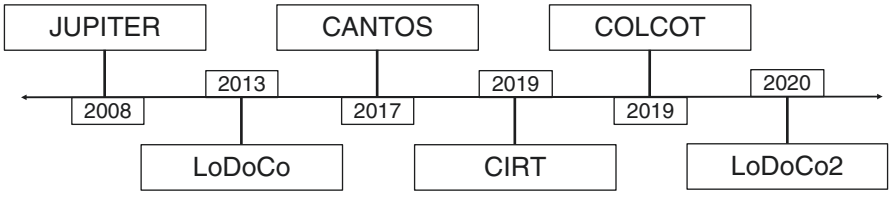

Fig. 17.3 Landmark anti-inflammatory and cardiovascular outcome trials

address hesitation about the expense associated with routinely incorporating hsCRP into clinical practice, recommendations have been proposed (Ridker et al. 2020).

In primary prevention, hsCRP represents an established risk enhancer that can help guide treatment decisions in individuals at borderline risk. Data suggest, however, that it is less useful than a zero CAC score (Fig. 17.4). Nonetheless, the presence of an hsCRP level ≥ 2 mg/L suggests ongoing inflammation of a sufficient degree so as to warrant reclassification of an individual's ASCVD risk, with consideration of statin therapy.

In secondary prevention, a personalized approach to identify residual risk through judicious use of biomarker measurement can offer potential value. Because canakinumab is not Food and Drug Administration (FDA) approved for CV risk reduction and the benefit of colchicine in LoDoCo, COLCOT, and LoDoCo2 was not based on hsCRP levels, further trial data are needed to guide decision-making.

To gauge the prevalence of residual inflammatory risk in secondary prevention, populations from the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) (high-intensity statin therapy), Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) (moderate-intensity statin therapy + ezetimibe), and SPIRE-1/SPIRE-2 (high-intensity statin therapy + PCSK9 inhibitor) trials were analyzed. Individuals in these studies were stratified based on (a) residual inflammatory risk (an hsCRP ≥2 mg/L), (b) residual cholesterol risk (an LDL-C ≥ 70 mg/dL), (c) residual inflammatory and cholesterol risk, or (d) neither

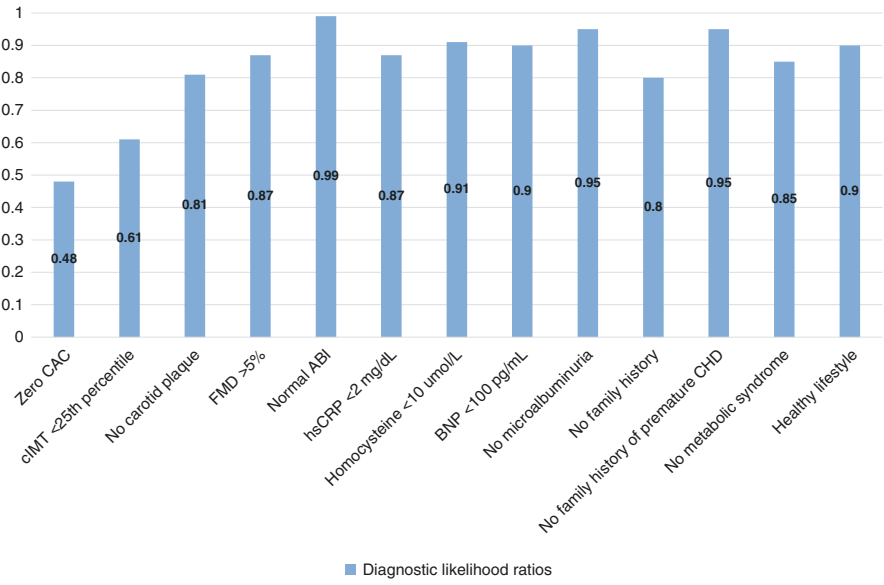

Fig. 17.4 Relationship between the pretest and posttest CVD risk after knowledge of the negative result of each risk marker. ABI ankle–brachial index, BNP B-type natriuretic peptide, CAC coronary artery calcium, CHD coronary heart disease, cIMT carotid intima-media thickness, FMD flow-mediated dilation, hsCRP high-sensitivity C-reactive protein

(Ridker 2018; Murphy et al. 2009; Cannon et al. 2015; Ridker et al. 2017b). The prevalence of residual inflammatory risk alone was 29–37%; the prevalence of residual inflammatory or cholesterol risk approached 50%.

While the search for novel anti-inflammatory therapies to reduce CV risk persists (Table 17.1), statin therapy represents the mainstay for all at-risk individuals in primary and secondary prevention. To date, studies have demonstrated an ~17–21%

Table 17.1 Anti-inflammatory drugs, their mechanism of action, and trial data highlighting a possible role in targeting inflammatory risk in CVD

Drug	Mechanism of action	Trial data
Allopurinol	Purine analogue inhibiting xanthine oxidase	*PGRx MI group:* (Grimaldi-Bensouda et al. 2015) Reduction in recurrent MI *Rentoukas et al.:* (Rentoukas et al. 2010). Reduction in CV events following ST-elevation myocardial infarction (STEMI)
Anakinra	Humanized monoclonal antibody against IL-1	Reduction in hsCRP and IL-6 following non-ST-elevation myocardial infarction (NSTEMI) *VCU-ART/VCU-ART 2:* (Abbate et al. 2010; Abbate et al. 2013). Reduction in left ventricular remodeling and heart failure following STEMI
Canakinumab	Fully human monoclonal antibody against IL-1ß	*CANTOS:* (Ridker et al. 2017a). 10,061 patients with previous MI and high hsCRP (≥2 mg/L) randomized to 3 doses of canakinumab or placebo Reduction in hsCRP ranging from 26 to 41%; no reduction in LDL-C Significant reduction in nonfatal MI, nonfatal stroke, CV death, or hospitalization for unstable angina leading to urgent revascularization with canakinumab (150 mg every 3 months)
Colchicine	Inhibits microtubule polymerization Prevents activation of the NLRP3 inflammasome Reduces release of IL-1ß	Reduction in hsCRP, IL-1ß, IL-6, and IL-18 (Nidorf and Thompson 2007; Martínez et al. 2015) *LoDoCo:* (Nidorf et al. 2013). 532 patients with stable CAD randomized to colchicine (0.5 mg/day) or placebo Significant reduction in ACS, noncardioembolic stroke, or out-of-hospital cardiac arrest *COLCOT:* (Tardif et al. 2019). 4745 patients within 30 days of MI randomized to colchicine (0.5 mg/day) or placebo Significant reduction in the composite endpoint of death from CV causes, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina leading to coronary revascularization *LoDoCo2:* (Nidorf et al. 2020). 5522 patients with chronic coronary disease randomized to colchicine (0.5 mg/day) or placebo Significant reduction in CV death, spontaneous MI, ischemic stroke, or ischemia-driven coronary revascularization

Table 17.1 (continued)

Drug	Mechanism of action	Trial data
Methotrexate	Folic acid antagonist Reduced T-cell proliferation Reduced cytokine release Reduced expression of cell-surface adhesion molecules	*CIRT:* (Ridker et al. 2019). 4786 patients with previous MI or multivessel CAD and either type 2 diabetes mellitus or metabolic syndrome randomized to low-dose methotrexate (target dose of 15–20 mg weekly) or placebo Methotrexate did not lower IL-1ß, IL-6, or CRP Methotrexate did not result in fewer CV events
MLN1202	Neutralizing monoclonal antibody against CC-chemokine receptor 2 (CCR2)	*MLN1202 Study Group:* (Gilbert et al. 2011). Reduction in hsCRP
Salsalate	NF-kB inhibitor	*TINSAL-T2D:* (Goldfine et al. 2013a). No reduction in hsCRP *TINSAL-FMD:* (Goldfine et al. 2013b). No impact on flow-mediated dilation *TINSAL-CVD:* (Hauser et al. 2016). No change in hsCRP or coronary plaque volume
Sarilumab	Monoclonal antibody against IL-6	*Kawashiri et al.:* (Kawashiri et al. 2011). Reduction in hsCRP
Tocilizumab	Monoclonal antibody against IL-6	*Kleveland et al.:* (Kleveland et al. 2016). Increased clearance of hsCRP after acute NSTEMI *Holte et al.:* (Holte et al. 2017). No change in coronary flow reserve after NSTEMI *ENTRACTE:* (Giles et al. 2020). 3080 patients with active seropositive rheumatoid arthritis +1 CV risk factor randomized to tocilizumab (8 mg/kg/month) or etanercept (50 mg/week) Increased LDL-C, HDL-C, and triglyceride levels Noninferior to TNF-α inhibitor in the occurrence of major adverse CV events

CAD coronary artery disease, *CCR2* chemokine CC receptor type 2, *CV* cardiovascular, *CVD* cardiovascular disease, *hsCRP* high-sensitivity C-reactive protein, *IL* interleukin, *LDL-C* low-density lipoprotein cholesterol, *MI* myocardial infarction, *NLRP3* NOD-, LRR-, and pyrin domain-containing protein 3, *NSTEMI* non-ST-elevation myocardial infarction, *STEMI* ST-elevation myocardial infarction, *TNF* tumor necrosis factor

reduction in hsCRP concentrations with moderate-intensity statin therapy and an ~37% reduction with high-intensity statin therapy (Ridker et al. 2001a; Albert et al. 2001; Ridker et al. 2009). Bempedoic acid, which inhibits adenosine triphosphate citrate lyase, has been shown to significantly reduce both LDL-C and hsCRP by ~16% and ~ 19%, respectively (Goldberg et al. 2019; Ray et al. 2019). The impact of other nonstatin therapies, including ezetimibe and PCSK9 inhibitors, on hsCRP levels has been much more modest (Fig. 17.5) (Pradhan et al. 2018; Bohula et al. 2015, 2018).

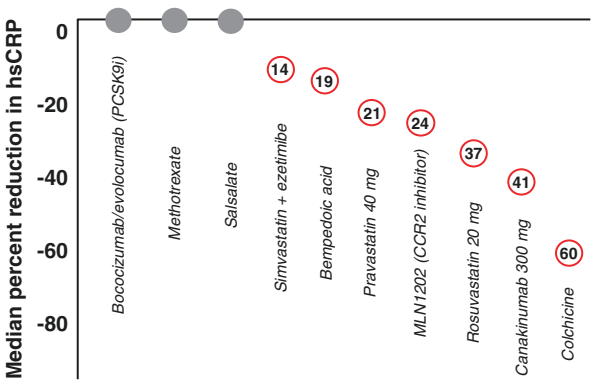

Fig. 17.5 Median percentage change in hsCRP with various pharmacotherapies

hsCRP and Inflammatory Markers: The Guidelines

For more than a decade, varying recommendations have been issued related to the measurement of hsCRP for CV risk assessment (Table 17.2).

The US Preventive Services Task Force (2009)

In 2009, the US Preventive Services Task Force (USPSTF) released its first set of guidelines related to use of hsCRP in follow-up to the JUPITER trial (U.S. Preventive Services Task Force 2009). They stated that (a) hsCRP is associated with incident CHD (strong evidence); (b) hsCRP improves risk stratification of intermediate-risk patients (moderate evidence); and (c) reducing hsCRP can prevent CHD events (insufficient evidence) (Buckley et al. 2009).

Despite moderate evidence supporting the use of hsCRP for risk stratification, the USPSTF did not formally endorse hsCRP testing in this capacity (Helfand et al. 2009). They, along with the Canadian Cardiovascular Society, instead emphasized the significant correlation between hsCRP and traditional risk factors, noting that there was minimal incremental value afforded by hsCRP testing (Genest et al. 2009).

American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) (2010)

Similar to the USPSTF, the 2010 ACCF/AHA Guideline provided a Class III (no benefit) recommendation for the measurement of hsCRP as part of CV risk assessment in asymptomatic high-risk adults as well as low-risk men ≤50 years of age and women ≤60 years of age (Greenland et al. 2010). A slightly higher Class IIb (may be considered) recommendation was given to the measurement of hsCRP in asymptomatic intermediate-risk men ≤50 years of age and women ≤60 years of age.

Table 17.2 Guideline recommendations for measuring hsCRP for cardiovascular risk assessment

Guideline	Year	Recommendations
USPSTF	2009	hsCRP is associated with incident CHD *Strong evidence* hsCRP improves risk stratification of intermediate-risk patients *Moderate evidence* Reducing hsCRP can prevent CHD events *Insufficient evidence*
ACCF/AHA	2010	In men ≥50 years of age and women ≥60 years of age with an LDL-C < 130 mg/dL, not on lipid-lowering therapy, and without clinical CHD, diabetes, chronic kidney disease, severe inflammatory conditions, or contraindications to statin therapy, measurement of hsCRP can be useful in the selection of patients for statin therapy *Class IIa recommendation* In asymptomatic intermediate-risk men ≤50 years of age and women ≤60 years of age, measurement of hsCRP may be reasonable for cardiovascular risk assessment *Class IIb recommendation* In asymptomatic high-risk adults, measurement of hsCRP is not recommended for CV risk assessment *Class III recommendation* In low-risk men ≤50 years of age and women ≤60 years of age, measurement of hsCRP is not recommended for CV risk assessment *Class III recommendation*
ACC/AHA	2013	In primary prevention adults not on statin therapy with an LDL-C 70–189 mg/dL, without diabetes, and a 10-year ASCVD risk estimate of 5 to <7.5% or ≥ 7.5%, if the decision to initiate statin therapy is unclear, then the clinician–patient discussion should consider an hsCRP ≥2 mg/L to support revising risk assessment upward and help guide further management *Class IIb recommendation*
AHA/ACC Multisociety	2018	In primary prevention adults not on statin therapy with an LDL-C 70–189 mg/dL, without diabetes, and a 10-year ASCVD risk estimate of 5 to <7.5% or ≥ 7.5%, the risk discussion should consider ASCVD risk enhancers, including an hsCRP ≥2 mg/L in selected individuals if measured In intermediate risk (≥7.5 to <20%), the presence of risk enhancers favors initiating moderate-intensity statin therapy to reduce LDL-C by 30–49% *Class I recommendation* In borderline risk (5 to <7.5%), if a risk enhancer is present, then a risk discussion regarding moderate-intensity statin therapy should be considered *Class IIb recommendation*

(continued)

Table 17.2 (continued)

Guideline	Year	Recommendations
ACC/AHA	2019	In primary prevention adults not on statin therapy with an LDL-C 70–189 mg/dL, without diabetes, and a 10-year ASCVD risk estimate of 5 to <7.5% or ≥ 7.5%, the risk discussion should consider ASCVD risk enhancers, including an hsCRP ≥2 mg/L in selected individuals if measured In intermediate risk (≥7.5 to <20%), the presence of risk enhancers favors initiating moderate-intensity statin therapy to reduce LDL-C by 30–49% *Class I recommendation* In borderline risk (5 to <7.5%), if a risk enhancer is present, then a risk discussion regarding moderate-intensity statin therapy should be considered *Class IIb recommendation*

ACC American College of Cardiology, *ACCF* American College of Cardiology Foundation, *AHA* American Heart Association, *ASCVD* atherosclerotic cardiovascular disease, *CHD* coronary heart disease, *CV* cardiovascular, *hsCRP* high-sensitivity, *LDL-C* low-density lipoprotein cholesterol, *USPSTF* United States Preventive Services Task Force

The most notable difference between these two guidelines, however, revolves around use of hsCRP in individuals meeting the JUPITER trial enrollment criteria. This includes men ≥50 years of age and women ≥60 years of age with an LDL-C < 130 mg/dL that were not on lipid-lowering therapy and without clinical CHD, diabetes, chronic kidney disease, severe inflammatory conditions, or statin contraindications. In this population, the ACCF/AHA guideline gave a Class IIa (it is reasonable) recommendation to measure hsCRP as part of guiding the determination of statin therapy initiation.

The ACC/AHA Prevention Guidelines (2013)

In 2013, the PCE was introduced, providing sex- and race-specific estimates of 10-year risk for fatal and nonfatal MI and stroke among African American and White men and women 40–79 years of age (Goff Jr et al. 2013; Stone et al. 2013). Because the PCE does not include hsCRP, it is not considered part of routine CV risk assessment. It was, however, included as an optional screening test when risk-based decisions regarding initiation of statin therapy were uncertain following quantitative risk assessment. Class IIb recommendations (may be considered) were provided to both (a) revise risk assessment upward with hsCRP levels ≥2 mg/L and (b) to not revise risk assessment with hsCRP levels <2 mg/L.

The AHA/ACC Multisociety Blood Cholesterol Guideline (2018)

The 2018 AHA/ACC Multisociety Blood Cholesterol Guideline recommended that CV risk assessment begins with the PCE for men and women aged 40–75 years, without ASCVD or diabetes and with LDL-C levels between 70 and 189 mg/dL

(Grundy et al. 2018). Risk enhancers, including an hsCRP level ≥ 2 mg/L, may be considered in those estimated to be at borderline (5 to <7.5%) or intermediate (≥7.5 to <20%) risk to help guide initiation of statin therapy (Class I for those at intermediate risk and Class IIb for those at borderline risk).

The ACC/AHA Primary Prevention Guideline (2019)

The 2019 ACC/AHA Primary Prevention Guideline recommended that individual risk assessment begins with estimation of 10-year ASCVD risk to guide decision-making. Similar to the 2018 AHA/ACC Multisociety Blood Cholesterol Guideline, adults at borderline or intermediate risk for ASCVD should consider additional risk-enhancing factors, including an hsCRP level ≥ 2 mg/L, to better inform use of preventive interventions such as statin therapy (Arnett et al. 2019).

Future Directions

To date, development of cholesterol-lowering and anti-inflammatory therapies to reduce CV risk has largely occurred separately. While statins represent the mainstay of treatment, further studies evaluating novel therapies affecting one or both pathways are needed. This would best be studied in a 2 × 2 factorial trial with one arm targeting LDL-C production directly and another arm targeting IL-1, IL-6, or the NLRP3 inflammasome (Fig. 17.6) (Ridker 2020; Yousuf et al. 2013).

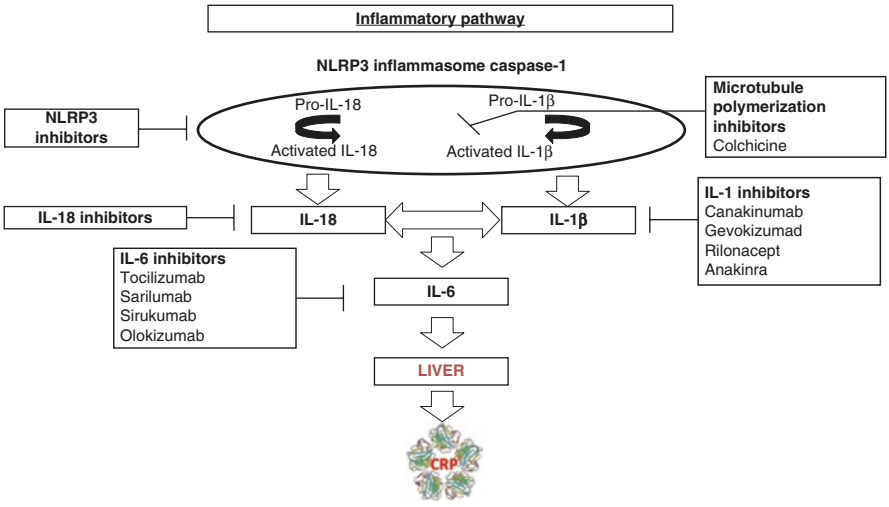

Fig. 17.6 The inflammatory pathway – inflammatory biomarkers and targeted pharmacotherapies. *CRP* C-reactive protein, *IL* interleukin, *NLRP3* NOD-, LRR-, and pyrin domain-containing protein 3

One therapeutic option currently being evaluated in an outcomes trial is bempedoic acid, which lowers both LDL-C and hsCRP. Beyond this, a number of other therapies are being investigated; most either lower LDL-C (e.g., small-interfering RNA to PCSK9 (inclisiran)) or reduce inflammation (e.g., IL-1 inhibitors (canakinumab, gevokizumab, anakinra, rilonacept) and IL-6 inhibitors (tocilizumab, sarilumab, sirukumab, olokizumab)). Future studies will be needed to determine the optimal use of these agents either alone or in combination.

Conclusions

For over 30 years, hsCRP has been used to refine risk prediction given its ability to independently predict future CV events. In primary prevention, it serves as a risk enhancer, helping guide decision-making around statin use. In secondary prevention, it can help identify residual inflammatory risk among those treated with optimal medical therapy. While statin therapy remains the first-line treatment to help mitigate CV risk, a number of anti-inflammatory therapies have the potential to help as well. Additional data around efficacy, safety, and cost-effectiveness will be needed, however, before routinely incorporating these therapies into clinical practice.

References

Abbate A, Kontos MC, Grizzard JD, Biondi-Zoccai GG, Van Tassell BW, Robati R, Roach LM, Arena RA, Roberts CS, Varma A, Gelwix CC, Salloum FN, Hastillo A, Dinarello CA, Vetrovec GW, VCU-ART Investigators. Interleukin-1 blockade with anakinra to prevent adverse cardiac remodeling after acute myocardial infarction (Virginia Commonwealth University Anakinra Remodeling Trial [VCU-ART] Pilot study). Am J Cardiol. 2010;105(10):1371–1377.e1. https://doi.org/10.1016/j.amjcard.2009.12.059.

Abbate A, Van Tassell BW, Biondi-Zoccai G, Kontos MC, Grizzard JD, Spillman DW, Oddi C, Roberts CS, Melchior RD, Mueller GH, Abouzaki NA, Rengel LR, Varma A, Gambill ML, Falcao RA, Voelkel NF, Dinarello CA, Vetrovec GW. Effects of interleukin-1 blockade with anakinra on adverse cardiac remodeling and heart failure after acute myocardial infarction [from the Virginia Commonwealth University-Anakinra Remodeling Trial (2) (VCU-ART2) pilot study]. Am J Cardiol. 2013;111(10):1394–400. https://doi.org/10.1016/j.amjcard.2013.01.287.

Aguilar D, Fisher MR, O'Connor CM, Dunne MW, Muhlestein JB, Yao L, Gupta S, Benner RJ, Cook TD, Edwards D, Pfeffer MA. Investigators in the weekly intervention with zithromax for atherosclerosis and its related disorder study. Metabolic syndrome, C-reactive protein, and prognosis in patients with established coronary artery disease. Am Heart J. 2006;152(2):298–304. https://doi.org/10.1016/j.ahj.2005.11.011.

Albert MA, Danielson E, Rifai N, Ridker PM, PRINCE Investigators. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. JAMA. 2001;286(1):64–70. https://doi.org/10.1001/jama.286.1.64.

Albert MA, Glynn RJ, Buring J, Ridker PM. C-reactive protein levels among women of various ethnic groups living in the United States (from the Women's Health Study). Am J Cardiol. 2004;93(10):1238–42. https://doi.org/10.1016/j.amjcard.2004.01.067.

Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, Michos ED, Miedema MD, Muñoz D, Smith SC Jr, Virani SS, Williams KA Sr, Yeboah J, Ziaeian B. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Circulation. 2019;140(11):e596–646. https://doi.org/10.1161/CIR.0000000000000678. Erratum in: Circulation. 2019;140(11):e649-e650. Erratum in: Circulation. 2020;141(4):e60. Erratum in: Circulation. 2020;141(16):e774.

Arroyo-Espliguero R, Avanzas P, Quiles J, Kaski JC. Predictive value of coronary artery stenoses and C-reactive protein levels in patients with stable coronary artery disease. Atherosclerosis. 2009;204(1):239–43. https://doi.org/10.1016/j.atherosclerosis.2008.08.009.

Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R, Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005;366(9493):1267–78. https://doi.org/10.1016/S0140-6736(05)67394-1. Erratum in: Lancet. 2005;366(9494):1358. Erratum in: Lancet. 2008;371(9630):2084

Blaha MJ, Budoff MJ, DeFilippis AP, Blankstein R, Rivera JJ, Agatston A, O'Leary DH, Lima J, Blumenthal RS, Nasir K. Associations between C-reactive protein, coronary artery calcium, and cardiovascular events: implications for the JUPITER population from MESA, a population-based cohort study. Lancet. 2011;378(9792):684–92. https://doi.org/10.1016/S0140-6736(11)60784-8.

Blake GJ, Ridker PM. C-reactive protein and prognosis after percutaneous coronary intervention. Eur Heart J. 2002;23(12):923–5. https://doi.org/10.1053/euhj.2001.3130.

Bohula EA, Giugliano RP, Cannon CP, Zhou J, Murphy SA, White JA, Tershakovec AM, Blazing MA, Braunwald E. Achievement of dual low-density lipoprotein cholesterol and high-sensitivity C-reactive protein targets more frequent with the addition of ezetimibe to simvastatin and associated with better outcomes in IMPROVE-IT. Circulation. 2015;132(13):1224–33. https://doi.org/10.1161/CIRCULATIONAHA.115.018381.

Bohula EA, Giugliano RP, Leiter LA, Verma S, Park JG, Sever PS, Lira Pineda A, Honarpour N, Wang H, Murphy SA, Keech A, Pedersen TR, Sabatine MS. Inflammatory and cholesterol risk in the FOURIER trial. Circulation. 2018;138(2):131–40. https://doi.org/10.1161/CIRCULATIONAHA.118.034032.

Buckley DI, Fu R, Freeman M, Rogers K, Helfand M. C-reactive protein as a risk factor for coronary heart disease: a systematic review and meta-analyses for the U.S. Preventive Services Task Force. Ann Intern Med. 2009;151(7):483–95. https://doi.org/10.7326/0003-4819-151-7-200910060-00009.

Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM, IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372(25):2387–97. https://doi.org/10.1056/NEJMoa1410489.

Choi HK, Hernán MA, Seeger JD, Robins JM, Wolfe F. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. Lancet. 2002;359(9313):1173–7. https://doi.org/10.1016/S0140-6736(02)08213-2.

Clark CR, Coull B, Berkman LF, Buring JE, Ridker PM. Geographic variation in cardiovascular inflammation among healthy women in the Women's Health Study. PLoS One. 2011;6(11):e27468. https://doi.org/10.1371/journal.pone.0027468.

Cook NR. Comments on 'Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond' by M. J. Pencina et al., Statistics in Medicine (DOI: 10.1002/sim.2929). Stat Med. 2008;27(2):191–5. https://doi.org/10.1002/sim.2987.

Cook NR, Ridker PM. Advances in measuring the effect of individual predictors of cardiovascular risk: the role of reclassification measures. Ann Intern Med. 2009;150(11):795–802. https://doi.org/10.7326/0003-4819-150-11-200906020-00007.

Cook NR, Buring JE, Ridker PM. The effect of including C-reactive protein in cardiovascular risk prediction models for women. Ann Intern Med. 2006;145(1):21–9. https://doi.org/10.7326/0003-4819-145-1-200607040-00128.

Cook NR, Paynter NP, Eaton CB, Manson JE, Martin LW, Robinson JG, Rossouw JE, Wassertheil-Smoller S, Ridker PM. Comparison of the Framingham and Reynolds Risk scores for global cardiovascular risk prediction in the multiethnic Women's Health Initiative. Circulation. 2012;125(14):1748–56., S1-11. https://doi.org/10.1161/CIRCULATIONAHA.111.075929.

Danesh J, Whincup P, Walker M, Lennon L, Thomson A, Appleby P, Gallimore JR, Pepys MB. Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. BMJ. 2000;321(7255):199–204. https://doi.org/10.1136/bmj.321.7255.199.

DeFilippis AP, Blaha MJ, Ndumele CE, Budoff MJ, Lloyd-Jones DM, McClelland RL, Lakoski SG, Cushman M, Wong ND, Blumenthal RS, Lima J, Nasir K. The association of Framingham and Reynolds risk scores with incidence and progression of coronary artery calcification in MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol. 2011;58(20):2076–83. https://doi.org/10.1016/j.jacc.2011.08.022.

Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto AM Jr. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA. 1998;279(20):1615–22. https://doi.org/10.1001/jama.279.20.1615.

Emerging Risk Factors Collaboration, Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, Collins R, Danesh J. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet. 2010;375(9709):132–40. https://doi.org/10.1016/S0140-6736(09)61717-7.

Emerging Risk Factors Collaboration, Kaptoge S, Di Angelantonio E, Pennells L, Wood AM, White IR, Gao P, Walker M, Thompson A, Sarwar N, Caslake M, Butterworth AS, Amouyel P, Assmann G, Bakker SJ, Barr EL, Barrett-Connor E, Benjamin EJ, Björkelund C, Brenner H, Brunner E, Clarke R, Cooper JA, Cremer P, Cushman M, Dagenais GR, D'Agostino RB Sr, Dankner R, Davey-Smith G, Deeg D, Dekker JM, Engström G, Folsom AR, Fowkes FG, Gallacher J, Gaziano JM, Giampaoli S, Gillum RF, Hofman A, Howard BV, Ingelsson E, Iso H, Jørgensen T, Kiechl S, Kitamura A, Kiyohara Y, Koenig W, Kromhout D, Kuller LH, Lawlor DA, Meade TW, Nissinen A, Nordestgaard BG, Onat A, Panagiotakos DB, Psaty BM, Rodriguez B, Rosengren A, Salomaa V, Kauhanen J, Salonen JT, Shaffer JA, Shea S, Ford I, Stehouwer CD, Strandberg TE, Tipping RW, Tosetto A, Wassertheil-Smoller S, Wennberg P, Westendorp RG, Whincup PH, Wilhelmsen L, Woodward M, Lowe GD, Wareham NJ, Khaw KT, Sattar N, Packard CJ, Gudnason V, Ridker PM, Pepys MB, Thompson SG, Danesh J. C-reactive protein, fibrinogen, and cardiovascular disease prediction. N Engl J Med. 2012;367(14):1310–20. https://doi.org/10.1056/NEJMoa1107477.

Genest J, McPherson R, Frohlich J, Anderson T, Campbell N, Carpentier A, Couture P, Dufour R, Fodor G, Francis GA, Grover S, Gupta M, Hegele RA, Lau DC, Leiter L, Lewis GF, Lonn E, Mancini GB, Ng D, Pearson GJ, Sniderman A, Stone JA, Ur E. 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult – 2009 recommendations. Can J Cardiol. 2009;25(10):567–79. https://doi.org/10.1016/s0828-282x(09)70715-9.

Gilbert J, Lekstrom-Himes J, Donaldson D, Lee Y, Hu M, Xu J, Wyant T, Davidson M, MLN1202 Study Group. Effect of CC chemokine receptor 2 CCR2 blockade on serum C-reactive protein in individuals at atherosclerotic risk and with a single nucleotide polymorphism of the monocyte chemoattractant protein-1 promoter region. Am J Cardiol. 2011;107(6):906–11. https://doi.org/10.1016/j.amjcard.2010.11.005.

Giles JT, Sattar N, Gabriel S, Ridker PM, Gay S, Warne C, Musselman D, Brockwell L, Shittu E, Klearman M, Fleming TR. Cardiovascular safety of tocilizumab versus etanercept in rheumatoid arthritis: a randomized controlled trial. Arthritis Rheumatol. 2020;72(1):31–40. https://doi.org/10.1002/art.41095.

Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC Jr, Sorlie P, Stone NJ, Wilson PW, Jordan HS, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr, Tomaselli GF, American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(25 Suppl 2):S49–73. https://doi.org/10.1161/01.cir.0000437741.48606.98. Erratum in: Circulation. 2014;129(25 Suppl 2):S74-5

Goldberg AC, Leiter LA, Stroes ESG, Baum SJ, Hanselman JC, Bloedon LT, Lalwani ND, Patel PM, Zhao X, Duell PB. Effect of bempedoic acid vs placebo added to maximally tolerated statins on low-density lipoprotein cholesterol in patients at high risk for cardiovascular disease: the CLEAR wisdom randomized clinical trial. JAMA. 2019;322(18):1780–8. https://doi.org/10.1001/jama.2019.16585. Erratum in: JAMA. 2020;323(3):282.

Goldfine AB, Fonseca V, Jablonski KA, Chen YD, Tipton L, Staten MA, Shoelson SE, Targeting Inflammation Using Salsalate in Type 2 Diabetes Study Team. Salicylate (salsalate) in patients with type 2 diabetes: a randomized trial. Ann Intern Med. 2013a;159(1):1–12. https://doi.org/10.7326/0003-4819-159-1-201307020-00003.

Goldfine AB, Buck JS, Desouza C, Fonseca V, Chen YD, Shoelson SE, Jablonski KA, Creager MA. TINSAL-FMD (Targeting Inflammation Using Salsalate in Type 2 Diabetes–Flow-Mediated Dilation) Ancillary Study Team. Targeting inflammation using salsalate in patients with type 2 diabetes: effects on flow-mediated dilation (TINSAL-FMD). Diabetes Care. 2013b;36(12):4132–9. https://doi.org/10.2337/dc13-0859.

Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, Foster E, Hlatky MA, Hodgson JM, Kushner FG, Lauer MS, Shaw LJ, Smith SC Jr, Taylor AJ, Weintraub WS, Wenger NK, Jacobs AK, Smith SC Jr, Anderson JL, Albert N, Buller CE, Creager MA, Ettinger SM, Guyton RA, Halperin JL, Hochman JS, Kushner FG, Nishimura R, Ohman EM, Page RL, Stevenson WG, Tarkington LG, Yancy CW, American College of Cardiology Foundation; American Heart Association. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2010;56(25):e50–103. https://doi.org/10.1016/j.jacc.2010.09.001.

Grimaldi-Bensouda L, Alpérovitch A, Aubrun E, Danchin N, Rossignol M, Abenhaim L, Richette P, PGRx MI Group. Impact of allopurinol on risk of myocardial infarction. Ann Rheum Dis. 2015;74(5):836–42. https://doi.org/10.1136/annrheumdis-2012-202972.

Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC Jr, Sperling L, Virani SS, Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019;73(24):e285–350. https://doi.org/10.1016/j.jacc.2018.11.003. Erratum in: J Am Coll Cardiol. 2019;73(24):3237-3241.

Haidari M, Javadi E, Sadeghi B, Hajilooi M, Ghanbili J. Evaluation of C-reactive protein, a sensitive marker of inflammation, as a risk factor for stable coronary artery disease. Clin Biochem. 2001;34(4):309–15. https://doi.org/10.1016/s0009-9120(01)00227-2.

Hansson GK, Libby P. The immune response in atherosclerosis: a double-edged sword. Nat Rev Immunol. 2006;6:508–19.

Hauser TH, Salastekar N, Schaefer EJ, Desai T, Goldfine HL, Fowler KM, Weber GM, Welty F, Clouse M, Shoelson SE, Goldfine AB, Targeting Inflammation Using Salsalate in Cardiovascular Disease (TINSAL-CVD) Study Team. Effect of targeting inflammation with salsalate: the TINSAL-CVD randomized clinical trial on progression of coronary plaque in

overweight and obese patients using statins. JAMA Cardiol. 2016;1(4):413–23. https://doi.org/10.1001/jamacardio.2016.0605.

Haverkate F, Thompson SG, Pyke SD, Gallimore JR, Pepys MB. Production of C-reactive protein and risk of coronary events in stable and unstable angina. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. Lancet. 1997;349(9050):462–6. https://doi.org/10.1016/s0140-6736(96)07591-5.

Helfand M, Buckley DI, Freeman M, Fu R, Rogers K, Fleming C, Humphrey LL. Emerging risk factors for coronary heart disease: a summary of systematic reviews conducted for the U.S. Preventive Services Task Force. Ann Intern Med. 2009;151(7):496–507. https://doi.org/10.7326/0003-4819-151-7-200910060-00010.

Hlatky MA, Greenland P, Arnett DK, Ballantyne CM, Criqui MH, Elkind MS, Go AS, Harrell FE Jr, Hong Y, Howard BV, Howard VJ, Hsue PY, Kramer CM, JP MC, Normand SL, O'Donnell CJ, Smith SC Jr, Wilson PW, American Heart Association Expert Panel on Subclinical Atherosclerotic Diseases and Emerging Risk Factors and the Stroke Council. Criteria for evaluation of novel markers of cardiovascular risk: a scientific statement from the American Heart Association. Circulation. 2009;119(17):2408–16. https://doi.org/10.1161/CIRCULATIONAHA.109.192278.

Holte E, Kleveland O, Ueland T, Kunszt G, Bratlie M, Broch K, Michelsen AE, Bendz B, Amundsen BH, Aakhus S, Damås JK, Gullestad L, Aukrust P, Wiseth R. Effect of interleukin-6 inhibition on coronary microvascular and endothelial function in myocardial infarction. Heart. 2017;103(19):1521–7. https://doi.org/10.1136/heartjnl-2016-310875.

Hong YJ, Jeong MH, Lim SY, Lee SR, Hong SN, Kim KH, Sohn IS, Park HW, Kim JH, Kim W, Ahn Y, Cho JG, Park JC, Kang JC. Relation of soft plaque and elevated preprocedural high-sensitivity C-reactive protein levels to incidence of in-stent restenosis after successful coronary artery stenting. Am J Cardiol. 2006;98(3):341–5. https://doi.org/10.1016/j.amjcard.2006.02.037.

Horne BD, Muhlestein JB, Carlquist JF, Bair TL, Madsen TE, Hart NI, Anderson JL. Statin therapy, lipid levels, C-reactive protein and the survival of patients with angiographically severe coronary artery disease. J Am Coll Cardiol. 2000;36(6):1774–80. https://doi.org/10.1016/s0735-1097(00)00950-5.

Kangasniemi OP, Biancari F, Luukkonen J, Vuorisalo S, Satta J, Pokela R, Juvonen T. Preoperative C-reactive protein is predictive of long-term outcome after coronary artery bypass surgery. Eur J Cardiothorac Surg. 2006;29(6):983–5. https://doi.org/10.1016/j.ejcts.2006.02.022.

Kaul S, Morrissey RP, Diamond GA. By Jove! What is a clinician to make of JUPITER? Arch Intern Med. 2010;170(12):1073–7. https://doi.org/10.1001/archinternmed.2010.189.

Kavousi M, Elias-Smale S, Rutten JH, Leening MJ, Vliegenthart R, Verwoert GC, Krestin GP, Oudkerk M, de Maat MP, Leebeek FW, Mattace-Raso FU, Lindemans J, Hofman A, Steyerberg EW, van der Lugt A, van den Meiracker AH, Witteman JC. Evaluation of newer risk markers for coronary heart disease risk classification: a cohort study. Ann Intern Med. 2012;156(6):438–44. https://doi.org/10.7326/0003-4819-156-6-201203200-00006.

Kawashiri SY, Kawakami A, Yamasaki S, Imazato T, Iwamoto N, Fujikawa K, Aramaki T, Tamai M, Nakamura H, Ida H, Origuchi T, Ueki Y, Eguchi K. Effects of the anti-interleukin-6 receptor antibody, tocilizumab, on serum lipid levels in patients with rheumatoid arthritis. Rheumatol Int. 2011;31(4):451–6. https://doi.org/10.1007/s00296-009-1303-y.

Kleveland O, Kunszt G, Bratlie M, Ueland T, Broch K, Holte E, Michelsen AE, Bendz B, Amundsen BH, Espevik T, Aakhus S, Damås JK, Aukrust P, Wiseth R, Gullestad L. Effect of a single dose of the interleukin-6 receptor antagonist tocilizumab on inflammation and troponin T release in patients with non-ST-elevation myocardial infarction: a double-blind, randomized, placebo-controlled phase 2 trial. Eur Heart J. 2016;37(30):2406–13. https://doi.org/10.1093/eurheartj/ehw171.

Koenig W. High-sensitivity C-reactive protein and atherosclerotic disease: from improved risk prediction to risk-guided therapy. Int J Cardiol. 2013;168(6):5126–34. https://doi.org/10.1016/j.ijcard.2013.07.113.

Koenig W, Sund M, Fröhlich M, Fischer HG, Löwel H, Döring A, Hutchinson WL, Pepys MB. C-Reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. Circulation. 1999;99(2):237–42. https://doi.org/10.1161/01.cir.99.2.237.

Lakoski SG, Cushman M, Criqui M, Rundek T, Blumenthal RS, D'Agostino RB Jr, Herrington DM. Gender and C-reactive protein: data from the Multiethnic Study of Atherosclerosis (MESA) cohort. Am Heart J. 2006;152(3):593–8. https://doi.org/10.1016/j.ahj.2006.02.015.

LaMonte MJ, Durstine JL, Yanowitz FG, Lim T, DuBose KD, Davis P, Ainsworth BE. Cardiorespiratory fitness and C-reactive protein among a tri-ethnic sample of women. Circulation. 2002;106(4):403–6. https://doi.org/10.1161/01.cir.0000025425.20606.69.

Lawler PR, Bhatt DL, Godoy LC, Lüscher TF, Bonow RO, Verma S, Ridker PM. Targeting cardiovascular inflammation: next steps in clinical translation. Eur Heart J. 2020:ehaa099. https://doi.org/10.1093/eurheartj/ehaa099. [Epub ahead of print].

Libby P. Inflammation in atherosclerosis. Nature. 2002;420(6917):868–74. https://doi.org/10.1038/nature01323.

Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation. 2002;105(9):1135–43. https://doi.org/10.1161/hc0902.104353.

Libby P, Ridker PM, Hansson GK, Leducq Transatlantic Network on Atherothrombosis. Inflammation in atherosclerosis: from pathophysiology to practice. J Am Coll Cardiol. 2009;54(23):2129–38. https://doi.org/10.1016/j.jacc.2009.09.009.

Liuzzo G, Biasucci LM, Gallimore JR, Grillo RL, Rebuzzi AG, Pepys MB, Maseri A. The prognostic value of C-reactive protein and serum amyloid a protein in severe unstable angina. N Engl J Med. 1994;331(7):417–24. https://doi.org/10.1056/NEJM199408183310701.

Lloyd-Jones DM, Liu K, Tian L, Greenland P. Narrative review: assessment of C-reactive protein in risk prediction for cardiovascular disease. Ann Intern Med. 2006;145(1):35–42. https://doi.org/10.7326/0003-4819-145-1-200607040-00129.

Maier W, Altwegg LA, Corti R, Gay S, Hersberger M, Maly FE, Sütsch G, Roffi M, Neidhart M, Eberli FR, Tanner FC, Gobbi S, von Eckardstein A, Lüscher TF. Inflammatory markers at the site of ruptured plaque in acute myocardial infarction: locally increased interleukin-6 and serum amyloid A but decreased C-reactive protein. Circulation. 2005;111(11):1355–61. https://doi.org/10.1161/01.CIR.0000158479.58589.0A.

Martínez GJ, Robertson S, Barraclough J, Xia Q, Mallat Z, Bursill C, Celermajer DS, Patel S. Colchicine acutely suppresses local cardiac production of inflammatory cytokines in patients with an acute coronary syndrome. J Am Heart Assoc. 2015;4(8):e002128. https://doi.org/10.1161/JAHA.115.002128.

Micha R, Imamura F, Wyler von Ballmoos M, Solomon DH, Hernán MA, Ridker PM, Mozaffarian D. Systematic review and meta-analysis of methotrexate use and risk of cardiovascular disease. Am J Cardiol. 2011;108(9):1362–70. https://doi.org/10.1016/j.amjcard.2011.06.054.

Morrow DA, Rifai N, Antman EM, Weiner DL, CH MC, Cannon CP, Braunwald E. C-reactive protein is a potent predictor of mortality independently of and in combination with troponin T in acute coronary syndromes: a TIMI 11A substudy. Thrombolysis in myocardial infarction. J Am Coll Cardiol. 1998;31(7):1460–5. https://doi.org/10.1016/s0735-1097(98)00136-3.

Morrow DA, de Lemos JA, Sabatine MS, Wiviott SD, Blazing MA, Shui A, Rifai N, Califf RM, Braunwald E. Clinical relevance of C-reactive protein during follow-up of patients with acute coronary syndromes in the Aggrastat-to-Zocor trial. Circulation. 2006;114(4):281–8. https://doi.org/10.1161/CIRCULATIONAHA.106.628909.

Murphy SA, Cannon CP, Wiviott SD, McCabe CH, Braunwald E. Reduction in recurrent cardiovascular events with intensive lipid-lowering statin therapy compared with moderate lipid-lowering statin therapy after acute coronary syndromes from the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22) trial. J Am Coll Cardiol. 2009;54(25):2358–62. https://doi.org/10.1016/j.jacc.2009.10.005.

Nidorf M, Thompson PL. Effect of colchicine (0.5 mg twice daily) on high-sensitivity C-reactive protein independent of aspirin and atorvastatin in patients with stable coronary artery disease. Am J Cardiol. 2007;99(6):805–7. https://doi.org/10.1016/j.amjcard.2006.10.039.

Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL. Low-dose colchicine for secondary prevention of cardiovascular disease. J Am Coll Cardiol. 2013;61(4):404–10. https://doi.org/10.1016/j.jacc.2012.10.027.

Nidorf SM, ATL F, Mosterd A, Eikelboom JW, Schut A, TSJ O, SHK T, Xu XF, Ireland MA, Lenderink T, Latchem D, Hoogslag P, Jerzewski A, Nierop P, Whelan A, Hendriks R, Swart H, Schaap J, AFM K, van MWJ H, Saklani P, Tan I, Thompson AG, Morton A, Judkins C, Bax WA, Dirksen M, Alings M, Hankey GJ, Budgeon CA, JGP T, Cornel JH, Thompson PL, LoDoCo2 Trial Investigators. Colchicine in patients with chronic coronary disease. N Engl J Med. 2020;383(19):1838–47. https://doi.org/10.1056/NEJMoa2021372.

Nissen SE, Tuzcu EM, Schoenhagen P, Crowe T, Sasiela WJ, Tsai J, Orazem J, Magorien RD, O'Shaughnessy C, Ganz P, Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) Investigators. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. N Engl J Med. 2005;352(1):29–38. https://doi.org/10.1056/NEJMoa042000.

Pankow JS, Folsom AR, Cushman M, Borecki IB, Hopkins PN, Eckfeldt JH, Tracy RP. Familial and genetic determinants of systemic markers of inflammation: the NHLBI family heart study. Atherosclerosis. 2001;154(3):681–9. https://doi.org/10.1016/s0021-9150(00)00586-4.

Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC Jr, Taubert K, Tracy RP, Vinicor F, Centers for Disease Control and Prevention, American Heart Association. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation. 2003;107(3):499–511. https://doi.org/10.1161/01.cir.0000052939.59093.45.

Pradhan AD, Aday AW, Rose LM, Ridker PM. Residual inflammatory risk on treatment with PCSK9 inhibition and statin therapy. Circulation. 2018;138(2):141–9. https://doi.org/10.1161/CIRCULATIONAHA.118.034645.

Rana JS, Cote M, Després JP, Sandhu MS, Talmud PJ, Ninio E, Wareham NJ, Kastelein JJ, Zwinderman AH, Khaw KT, Boekholdt SM. Inflammatory biomarkers and the prediction of coronary events among people at intermediate risk: the EPIC-Norfolk prospective population study. Heart. 2009;95(20):1682–7. https://doi.org/10.1136/hrt.2009.170134.

Ray KK, Bays HE, Catapano AL, Lalwani ND, Bloedon LT, Sterling LR, Robinson PL, Ballantyne CM, CLEAR Harmony Trial. Safety and efficacy of bempedoic acid to reduce LDL cholesterol. N Engl J Med. 2019;380(11):1022–32. https://doi.org/10.1056/NEJMoa1803917.

Rentoukas E, Tsarouhas K, Tsitsimpikou C, Lazaros G, Deftereos S, Vavetsi S. The prognostic impact of allopurinol in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention. Int J Cardiol. 2010;145(2):257–8. https://doi.org/10.1016/j.ijcard.2009.08.037.

Ridker PM. Hyperlipidemia as an instigator of inflammation: inaugurating new approaches to vascular prevention. J Am Heart Assoc. 2012;1(1):3–5. https://doi.org/10.1161/JAHA.112.000497.

Ridker PM. From C-reactive protein to interleukin-6 to interleukin-1: moving upstream to identify novel targets for atheroprotection. Circ Res. 2016a;118(1):145–56. https://doi.org/10.1161/CIRCRESAHA.115.306656.

Ridker PM. A test in context: high-sensitivity C-reactive protein. J Am Coll Cardiol. 2016b;67(6):712–23. https://doi.org/10.1016/j.jacc.2015.11.037.

Ridker PM. Clinician's guide to reducing inflammation to reduce atherothrombotic risk: JACC review topic of the week. J Am Coll Cardiol. 2018;72(25):3320–31. https://doi.org/10.1016/j.jacc.2018.06.082.

Ridker PM. From CANTOS to CIRT to COLCOT to clinic: will all atherosclerosis patients soon be treated with combination lipid-lowering and inflammation-inhibiting agents? Circulation. 2020;141(10):787–9. https://doi.org/10.1161/CIRCULATIONAHA.119.045256.

Ridker PM, Cook N. Clinical usefulness of very high and very low levels of C-reactive protein across the full range of Framingham Risk Scores. Circulation. 2004;109(16):1955–9. https://doi.org/10.1161/01.CIR.0000125690.80303.A8.

Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med. 1997;336(14):973–9. https://doi.org/10.1056/NEJM199704033361401. Erratum in: N Engl J Med 1997;337(5):356

Ridker PM, Rifai N, Pfeffer MA, Sacks FM, Moye LA, Goldman S, Flaker GC, Braunwald E. Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events (CARE) Investigators. Circulation. 1998;98(9):839–44. https://doi.org/10.1161/01.cir.98.9.839.

Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med. 2000;342(12):836–43. https://doi.org/10.1056/NEJM200003233421202.

Ridker PM, Rifai N, Clearfield M, Downs JR, Weis SE, Miles JS, Gotto AM Jr, Air Force/Texas Coronary Atherosclerosis Prevention Study Investigators. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. N Engl J Med. 2001a;344(26):1959–65. https://doi.org/10.1056/NEJM200106283442601.

Ridker PM, Stampfer MJ, Rifai N. Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. JAMA. 2001b;285(19):2481–5. https://doi.org/10.1001/jama.285.19.2481.

Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med. 2002;347(20):1557–65. https://doi.org/10.1056/NEJMoa021993.

Ridker PM, Wilson PW, Grundy SM. Should C-reactive protein be added to metabolic syndrome and to assessment of global cardiovascular risk? Circulation. 2004;109(23):2818–25. https://doi.org/10.1161/01.CIR.0000132467.45278.59.

Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, Pfeffer MA, Braunwald E, Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) Investigators. C-reactive protein levels and outcomes after statin therapy. N Engl J Med. 2005;352(1):20–8. https://doi.org/10.1056/NEJMoa042378.

Ridker P, Rifai N, Koenig W, Blumenthal RS. C-reactive protein and cardiovascular risk in the Framingham Study. Arch Intern Med. 2006;166(12):1327–8.; ; author reply 1328. https://doi.org/10.1001/archinte.166.12.1327-b.

Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. JAMA. 2007;297(6):611–9. https://doi.org/10.1001/jama.297.6.611. Erratum in: JAMA. 2007;297(13):1433

Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ, JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359(21):2195–207. https://doi.org/10.1056/NEJMoa0807646.

Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, Macfadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ, JUPITER Trial Study Group. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. Lancet. 2009;373(9670):1175–82. https://doi.org/10.1016/S0140-6736(09)60447-5.

Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF, Troquay RPT, Libby P, Glynn RJ, CANTOS Trial Group. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med. 2017a;377(12):1119–31. https://doi.org/10.1056/NEJMoa1707914.

Ridker PM, Revkin J, Amarenco P, Brunell R, Curto M, Civeira F, Flather M, Glynn RJ, Gregoire J, Jukema JW, Karpov Y, JJP K, Koenig W, Lorenzatti A, Manga P, Masiukiewicz U, Miller M, Mosterd A, Murin J, Nicolau JC, Nissen S, Ponikowski P, Santos RD, Schwartz PF, Soran H, White H, Wright RS, Vrablik M, Yunis C, Shear CL, Tardif JC, SPIRE Cardiovascular Outcome Investigators. Cardiovascular efficacy and safety of bococizumab in high-risk patients. N Engl J Med. 2017b;376(16):1527–39. https://doi.org/10.1056/NEJMoa1701488.

Ridker PM, Koenig W, Kastelein JJ, Mach F, Lüscher TF. Has the time finally come to measure hsCRP universally in primary and secondary cardiovascular prevention? Eur Heart J. 2018a;39(46):4109–11. https://doi.org/10.1093/eurheartj/ehy723.

Ridker PM, MacFadyen JG, Everett BM, Libby P, Thuren T, Glynn RJ, CANTOS Trial Group. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. Lancet. 2018b;391(10118):319–28. https://doi.org/10.1016/S0140-6736(17)32814-3.

Ridker PM, Libby P, MacFadyen JG, Thuren T, Ballantyne C, Fonseca F, Koenig W, Shimokawa H, Everett BM, Glynn RJ. Modulation of the interleukin-6 signalling pathway and incidence rates of atherosclerotic events and all-cause mortality: analyses from the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS). Eur Heart J. 2018c;39(38):3499–507. https://doi.org/10.1093/eurheartj/ehy310.

Ridker PM, Everett BM, Pradhan A, MacFadyen JG, Solomon DH, Zaharris E, Mam V, Hasan A, Rosenberg Y, Iturriaga E, Gupta M, Tsigoulis M, Verma S, Clearfield M, Libby P, Goldhaber SZ, Seagle R, Ofori C, Saklayen M, Butman S, Singh N, Le May M, Bertrand O, Johnston J, Paynter NP, Glynn RJ, CIRT Investigators. Low-dose methotrexate for the prevention of atherosclerotic events. N Engl J Med. 2019;380(8):752–62. https://doi.org/10.1056/NEJMoa1809798.

Ridker PM, MacFadyen JG, Glynn RJ, Bradwin G, Hasan AA, Rifai N. Comparison of interleukin-6, C-reactive protein, and low-density lipoprotein cholesterol as biomarkers of residual risk in contemporary practice: secondary analyses from the Cardiovascular Inflammation Reduction Trial. Eur Heart J. 2020;41(31):2952–61. https://doi.org/10.1093/eurheartj/ehaa160.

Sabatine MS, Morrow DA, de Lemos JA, Gibson CM, Murphy SA, Rifai N, McCabe C, Antman EM, Cannon CP, Braunwald E. Multimarker approach to risk stratification in non-ST elevation acute coronary syndromes: simultaneous assessment of troponin I, C-reactive protein, and B-type natriuretic peptide. Circulation. 2002;105(15):1760–3. https://doi.org/10.1161/01.cir.0000015464.18023.0a.

Sattar N, Murray HM, McConnachie A, Blauw GJ, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Murphy MB, Packard CJ, Perry IJ, Stott DJ, Sweeney BJ, Twomey C, Westendorp RG, Shepherd J, PROSPER Study Group. C-reactive protein and prediction of coronary heart disease and global vascular events in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER). Circulation. 2007;115(8):981–9. https://doi.org/10.1161/CIRCULATIONAHA.106.643114.

Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, GT MI, Mehlsen J, Nieminen M, O'Brien E, Ostergren J, ASCOT Investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet. 2003;361(9364):1149–58. https://doi.org/10.1016/S0140-6736(03)12948-0.

Shah B, Pillinger M, Zhong H, Cronstein B, Xia Y, Lorin JD, Smilowitz NR, Feit F, Ratnapala N, Keller NM, Katz SD. Effects of acute colchicine administration prior to percutaneous coronary intervention: COLCHICINE-PCI randomized trial. Circ Cardiovasc Interv. 2020;13(4):e008717. https://doi.org/10.1161/CIRCINTERVENTIONS.119.008717.

Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995;333(20):1301–7. https://doi.org/10.1056/NEJM199511163332001.

Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW, American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(25 Pt B):2889–934. https://doi.org/10.1016/j.jacc.2013.11.002. Erratum in: J Am Coll Cardiol. 2014;63(25 Pt B):3024-3025. Erratum in: J Am Coll Cardiol. 2015;66(24):2812.

Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, Pinto FJ, Ibrahim R, Gamra H, Kiwan GS, Berry C, López-Sendón J, Ostadal P, Koenig W, Angoulvant D, Grégoire JC, Lavoie MA, Dubé MP, Rhainds D, Provencher M, Blondeau L, Orfanos A, L'Allier PL, Guertin MC, Roubille F. Efficacy and safety of low-dose colchicine after myocardial infarction. N Engl J Med. 2019;381(26):2497–505. https://doi.org/10.1056/NEJMoa1912388.

Tillett WS, Francis T. Serological reactions in pneumonia with a non-protein somatic fraction of pneumococcus. J Exp Med. 1930;52(4):561–71. https://doi.org/10.1084/jem.52.4.561\.

Tracy RP, Lemaitre RN, Psaty BM, Ives DG, Evans RW, Cushman M, Meilahn EN, Kuller LH. Relationship of C-reactive protein to risk of cardiovascular disease in the elderly. Results from the Cardiovascular Health Study and the Rural Health Promotion Project. Arterioscler Thromb Vasc Biol. 1997;17(6):1121–7. https://doi.org/10.1161/01.atv.17.6.1121.

U.S. Preventive Services Task Force. Using nontraditional risk factors in coronary heart disease risk assessment: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2009;151(7):474–82. https://doi.org/10.7326/0003-4819-151-7-200910060-00008.

Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. JAMA. 1999;282(22):2131–5. https://doi.org/10.1001/jama.282.22.2131.

Westlake SL, Colebatch AN, Baird J, Kiely P, Quinn M, Choy E, Ostor AJ, Edwards CJ. The effect of methotrexate on cardiovascular disease in patients with rheumatoid arthritis: a systematic literature review. Rheumatology (Oxford). 2010;49(2):295–307. https://doi.org/10.1093/rheumatology/kep366.

Wilson PW, Nam BH, Pencina M, D'Agostino RB Sr, Benjamin EJ, O'Donnell CJ. C-reactive protein and risk of cardiovascular disease in men and women from the Framingham Heart Study. Arch Intern Med. 2005;165(21):2473–8. https://doi.org/10.1001/archinte.165.21.2473.

de Winter RJ, Heyde GS, Koch KT, Fischer J, van Straalen JP, Bax M, Schotborgh CE, Mulder KJ, Sanders GT, Piek JJ, Tijssen JG. The prognostic value of pre-procedural plasma C-reactive protein in patients undergoing elective coronary angioplasty. Eur Heart J. 2002;23(12):960–6. https://doi.org/10.1053/euhj.2001.2988.

Woloshin S, Schwartz LM. Distribution of C-reactive protein values in the United States. N Engl J Med. 2005;352(15):1611–3. https://doi.org/10.1056/NEJM200504143521525.

Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, Carr JJ, Goff DC, Greenland P, Herrington DM. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. JAMA. 2012;308(8):788–95. https://doi.org/10.1001/jama.2012.9624.

Yousuf O, Mohanty BD, Martin SS, Joshi PH, Blaha MJ, Nasir K, Blumenthal RS, Budoff MJ. High-sensitivity C-reactive protein and cardiovascular disease: a resolute belief or an elusive link? J Am Coll Cardiol. 2013;62(5):397–408. https://doi.org/10.1016/j.jacc.2013.05.016.

Zebrack JS, Anderson JL, Maycock CA, Horne BD, Bair TL, Muhlestein JB, Intermountain Heart Collaborative (IHC) Study Group. Usefulness of high-sensitivity C-reactive protein in predicting long-term risk of death or acute myocardial infarction in patients with unstable or stable angina pectoris or acute myocardial infarction. Am J Cardiol. 2002;89(2):145–9. https://doi.org/10.1016/s0002-9149(01)02190-7.

Chapter 18
Apolipoprotein B in Primary Prevention: Ready for Time Prime?

Renato Quispe, Bibin Varghese, and Seth S. Martin

Introduction

Over a century ago, Nikolai Anitschkow proposed the role of cholesterol deposition carried by atherogenic lipoproteins, in particular low-density lipoprotein (LDL), for the initiation and progression of atherosclerosis. This hypothesis has prevailed since then, supported by a large body of evidence ranging from conventional epidemiological studies to genetic studies to large-scale randomized clinical trials. As such, major guidelines on primary prevention and cholesterol management worldwide recommend the use of LDL cholesterol (LDL-C) as a primary target of therapy and multiple effective therapies are now available (Jacobson et al. 2014; Jellinger et al. 2017; Mach et al. 2020; Grundy et al. 2019).

It is postulated that trapping of atherogenic apolipoprotein B (apoB)-containing lipoproteins, of which LDL is the primary lipoprotein representing ~90% of total circulating apoB, is a critical step in the formation of atherogenesis. The cholesterol content within each of these apoB-containing lipoproteins can vary over the lifetime course of these particles. Therefore, discordance can arise between apoB and

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cholesterol-based measures, such as LDL-C or non-high-density lipoprotein cholesterol (non-HDL-C).

In this chapter, we will review the pathophysiology of apoB in the context of related cholesterol-based measures, as well as the evidence that supports its role in prediction of cardiovascular events. Finally, we will review recommendations by major worldwide clinical guidelines for its use and indications for measurement.

Apolipoprotein B and Metabolism of Cholesterol

ApoB-containing lipoproteins include very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), LDL and lipoprotein (a) [Lp(a)] particles, as well as chylomicrons (Sniderman et al. 2019). Their surface is enveloped by one apoB molecule per particle (apoB 48 in the case of chylomicrons and apoB100 in the rest of particles); therefore, plasma level of apoB represents the concentration of these particles. Under most circumstances, the total number of apoB48 particles is much smaller than apoB100 particles, for which apoB assays mostly measure apoB100 particles (Sniderman et al. 2019).

The core of apoB-containing particles is constituted by cholesterol esters (CE) and triglycerides (TG), which significantly vary throughout their metabolic lifetime (Elovson et al. 1988). By action of the CE transfer protein (CETP), TG can be transferred from VLDL to an LDL particle in exchange of CE. This metabolic process occurs more frequently in the presence of hypertriglyceridemia (Griffin et al. 1990), and results in a cholesterol-enriched VLDL particle and a TG-enriched LDL particle (Fig. 18.1). The latter undergo hydrolysis of the TG content by action of hepatic lipase, which produces smaller (a.k.a. “dense”) cholesterol-depleted LDL particles (Berneis and Krauss 2002).

The circulating levels of LDL-C and non-HDL-C, estimated from the standard lipid panel, represent the sum of the cholesterol content in LDL and all non-HDL particles, respectively, at a given point in time. These levels are the result of multiple dynamic and complex interacting metabolic processes, such as the rates at which TG are hydrolyzed or CE and TG are exchanged among lipoproteins. On the other hand, the apoB molecule remains on each of the apoB-containing lipoprotein for their lifetime.

Evidence from Epidemiological Studies

Major guidelines generally use total cholesterol and HDL cholesterol (HDL-C) in estimating cardiovascular risk, following evidence from epidemiologic studies. An example is the Pooled Cohort Equations in the AHA/ACC prevention guidelines. The risk estimate serves as a key step in guiding shared decision-making through clinician–patient discussion on lipid-lowering therapy. This is a critically

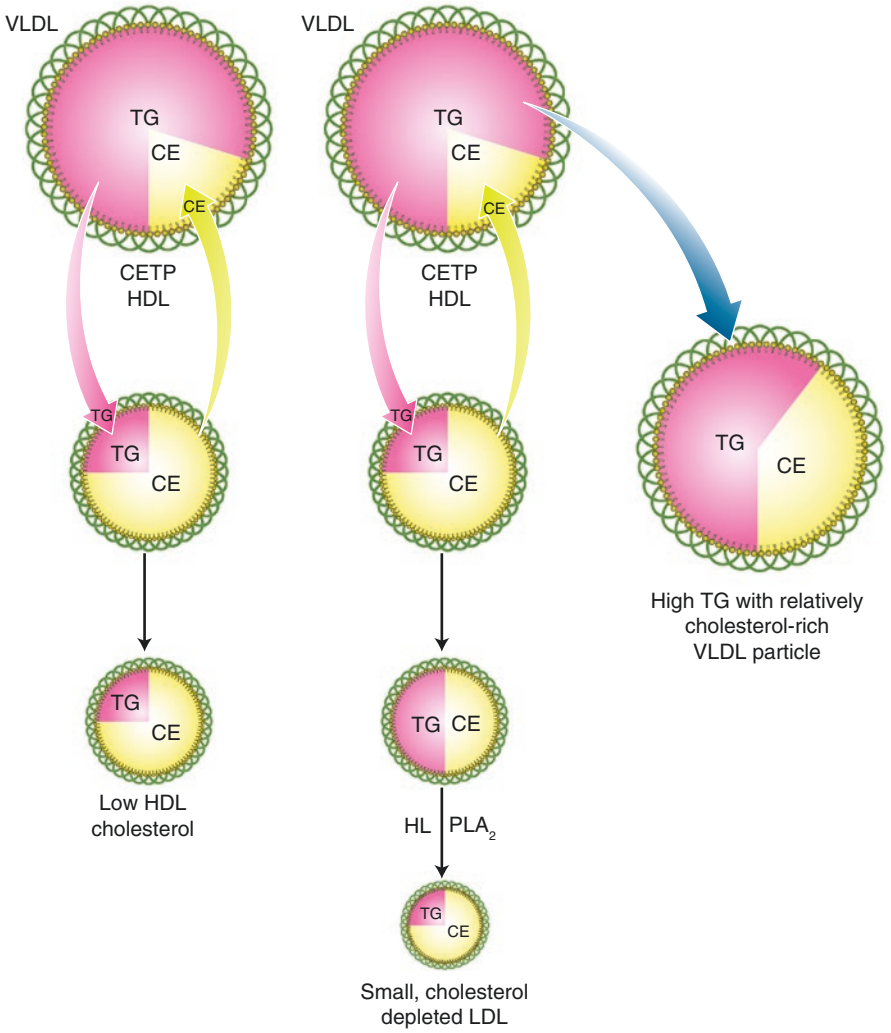

Fig. 18.1 Cholesteryl ester transfer protein (CETP) exchange and the atherogenic lipoprotein phenotype. CE cholesterol ester, TG triglycerides, LDL low-density lipoprotein, VLDL very low-density lipoprotein, HL hepatic lipase, PLA2 phospholipase A2, CETP cholesteryl ester transfer protein, HDL high-density lipoprotein

important step as the absolute risk reduction with therapy depends on the absolute cardiovascular risk. It also depends on the amount of LDL-C lowering, or atherogenic lipoprotein lowering, that can be achieved with therapy. Thus, estimating risk at baseline and treating a target are fundamentally different, but related, endeavors.

An increasingly challenging aspect of interpreting such literature is the introduction of effective LDL-C lowering therapies during the course of participant

follow-up and the inability to fully account for this in analyses. That is, if a certain individual with high baseline LDL-C is not on statin therapy at baseline and then is started on a statin during follow-up, the reduction of risk from statin therapy will lower the probability of that individual having a cardiovascular event below what would have been the natural association. This can make the epidemiological evidence more difficult to interpret.

With caveats such as this in mind, a number of studies have sought to understand the risk prediction performance of LDL-C, non-HDL-C, and apoB. Overall, each of the markers is typically highly related and is an important predictor of cardiovascular risk. In many of the epidemiological studies, the point estimates for risk are fairly similar and confidence intervals are overlapping. However, some studies have documented apoB's unique strength in risk prediction and its ability to potentially provide information beyond lipoprotein cholesterol levels. This was first suggested in a cross-sectional study that showed that apoB was a particularly strong predictive risk factor in patients who experienced a myocardial infarction (Avogaro et al. 1979). This has been further supported by the prospective observational studies including the Quebec Cardiovascular Study, the Apolipoprotein-related MOrtality RISk (AMORIS) Study, the Thrombo Study, the Thrombo Metabolic Syndrome Study, the Northwick park Heart Study, the Nurses' Health Study, and patients with type 2 diabetes in the Health Professional's Follow-up Study (Barter et al. 2006; Sniderman et al. 1980; Sniderman and Robinson 2019).

Among 18- to 30-year-old individuals free of ASCVD from the CARDIA study, a discordantly high apoB level was strongly predictive of coronary artery calcification in midlife (Wilkins et al. 2016). Analysis of the Framingham Offspring Cohort study suggested that apoB levels had an association with risk of coronary events beyond LDL-C or non-HDL-C (Pencina et al. 2015). In the Quebec cardiovascular study following 2155 men ages 45–76 for 5 years, apoB levels were independently linked to ischemic heart disease (Lamarche et al. 1996). In the AMORIS Study including 175,553 participants who were followed for greater than 3 years, apoB levels added power to traditional lipid markers to predict fatal myocardial infarction (Walldius et al. 2001).

However, contrary to the prior studies that suggested additional utility with apoB, a few studies suggested that apoB did not enhance risk prediction over non-HDL-C. In the Emerging Risk Factor Collaboration (ERFC), 302,430 patients without vascular disease from 68 prospective studies were included. In this study, non-HDL-C and apoB were equivalent predictors of risk (Emerging Risk Factors et al. 2009). In the Copenhagen City Heart Study, 9231 Danish patients were followed for 8 years. While apoB was superior to LDL-C in predictive ability, it was equivalent to non-HDL-C in predicting risk (Benn et al. 2007). Similarly, in the Women's Health Study including 27,673 initially healthy women who were followed for 11 years, and the UK Biobank study including 346,686 patients, apoB was equivalent to non-HDL-C which were both superior to LDL-C (Mora et al. 2009; Welsh et al. 2019). In order to clearly delineate the additional value of apoB

from non-HDL-C and LDL-C, Mendelian randomization studies and randomized controlled trials (RCT) were necessary.

Evidence from Randomized Clinical Trials and Mendelian Randomization Studies

Several large RCTs have shown that LDL-C lowering, with a combination of statins, ezetimibe, and proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors, can significantly lower cardiovascular risk (Ference et al. 2017). In the Cholesterol Treatment Trialists' data, pooling individual level data from statin trials, the reduction in cardiovascular risk is closely tied to the amount of LDL-C lowering, with a ~25% relative risk reduction per ~40 mg/dL lowering in LDL-C (Collins et al. 2016).

There has also been interest assessing the risk reduction related to non-HDL-C and apoB. In a meta-analysis of individual patient data from 8 randomized statin trials including 38,153 patients, non-HDL-C seemed to have a stronger association than LDL-C and apoB with cardiovascular risk reduction (Boekholdt et al. 2012). There was no significant difference between apoB and LDL-C (Boekholdt et al. 2012). In a Bayesian random effect trial-level meta-analysis that included 25 statin trials with 131,134 participants, each 10 mg/dL decrease in apoB was associated with a 9% decreased risk of coronary artery disease (CAD), but no decrease in stroke risk, which is surprising given that Cholesterol Treatment Trialist data clearly link LDL-C reduction with stroke reduction. The addition of apoB reduction to LDL-C and non-HDL-C reduction improved the accuracy of predicting coronary heart disease events, although this did not hold for overall cardiovascular risk or stroke risk (Robinson et al. 2012).

Yet another meta-analysis of seven statin trials employing frequentist biostatistical methodology suggested that apoB was more strongly associated with risk than LDL-C and non-HDL-C, including risk of coronary artery disease (CAD) and overall cardiovascular disease (Thanassoulis et al. 2014). In an attempt to further delineate the role of apoB, an analysis of the Simvastatin plus Fenofibrate for Combined Hyperlipidemia (SAFARI) trial assessed the association of non-HDL-C and LDL-C with apoB in patients treated with simvastatin and/or fenofibrate (Grundy et al. 2009). Non-HDL-C and LDL-C seemed to correlate highly with apoB in patients with lower rather than higher TG levels (Grundy et al. 2009) and as such, the value of apoB may be greatest in patients with higher TG levels (Grundy et al. 2009).

Mendelian randomization studies serve as "nature's RCTs" comparing inherited variants of a gene (Thanassoulis and O'Donnell 2009). The "randomization" is achieved through the random assortment of the gene variants from parents to offspring during gamete formation and conception, which can provide insight into mechanistic links in disease processes. For example, genetic variants that lead to higher LDL-C are associated with increased cardiovascular risk (Linsel-Nitschke et al. 2008). Two recent studies have suggested that CAD risk is proportional to apoB (Richardson et al. 2020; Ference et al. 2019). Genome-wide association

studies (GWAS) that combine genomic profiling with molecular measurement to evaluate genetic regulation of molecular processes have also suggested that apoB levels are a primary determinant of CAD (Zuber et al. 2021).

Apolipoprotein Versus Traditional Cholesterol Measures: The Relevance of Discordance

ApoB Versus LDL-C

LDL particles (each of which has one molecule of apoB100) represent ~90% of total circulating apoB. In a majority of patients, apoB correlates closely with LDL-C. However, discordance between LDL-C and apoB (i.e., high apoB without necessarily having high LDL-C) may occur in the presence of small cholesterol-depleted LDL particles that typically predominate in patients with hypertriglyceridemia and/or metabolic syndrome/diabetes mellitus (Fig. 18.2). Generally, when apoB is discordantly higher, cardiovascular may be higher. This suggests the strength and complementary information that apoB can provide and opens the possibility that patients with discordantly elevated apoB may benefit from more intensive treatment (Lawler et al. 2017a; Mora et al. 2014). It is important to note, however, that much of the

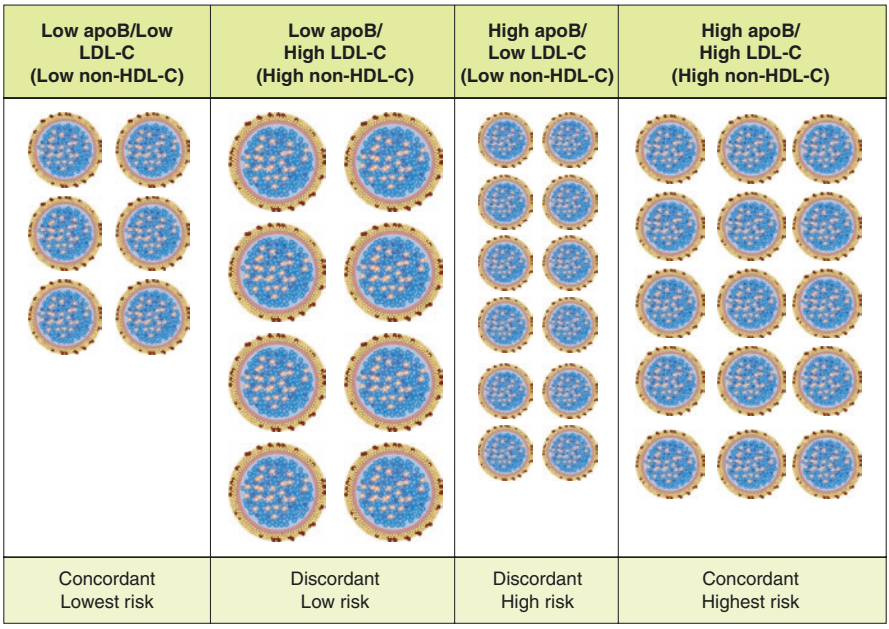

Fig. 18.2 Pathophysiological basis for discordance analysis (PMID: 26791067; Wilkins et al). ApoB apolipoprotein B, LDL-C low-density lipoprotein cholesterol, non-HDL-C non-high-density lipoprotein cholesterol

literature has focused on LDL-C estimated by the Friedewald equation, which is now known to underestimate LDL-C. This can create discordance between LDL-C and apoB, not due to inherent discordance, but due to inaccurate estimation of LDL-C. A newer method to estimate LDL-C is now available, providing better accuracy in LDL-C estimation and correlating more strongly with apoB (Brownstein and Martin 2020; Whelton et al. 2017).

LDL particle number (LDL-P), as opposed to LDL-C, represents a measure of particle concentration and not of cholesterol content. Therefore, LDL-P and LDL-C can be discordant by the same mechanisms seen in apoB vs. LDL-C discordance (i.e., effect of hypertriglyceridemia and statin use). The definition of discordance varies from study to study. When a difference of 12 population percentile units or more was used as the definition of discordance, ~50% of ASCVD-free individuals from the Multi-Ethnic Study of Atherosclerosis (MESA) were discordant between LDL-C and LDL-P (Otvos et al. 2011). Like many studies, this MESA study is limited by the use of Friedewald LDL-C. Given the predominance of LDL particles in plasma, apoB and LDL-P are usually expected to be discordant (Garvey et al. 2003), depending on the quality of measurement. However, patients with type III hyperlipidemia have a larger proportion of apoB48 particles because of the remarkably elevated concentration of remnant lipoproteins (Sniderman et al. 2018). In these patients, apoB100 particles (including LDL) represent ~50% of the total apoB particles, which increases the magnitude of discordance between apoB and LDL-P (Sniderman et al. 2007).

ApoB Versus Non-HDL-C

Non-HDL-C represents the aggregate cholesterol content within all the apoB-containing particles known to cause ASCVD, and can be easily calculated from the standard lipid profile as TC minus HDL-C. Non-HDL-C includes LDL-C as well as the cholesterol content in TG-rich VLDL and chylomicron-derived apoB48-containing particles (Langlois et al. 2020; Nordestgaard 2017). The ERFC showed that hazard ratios for coronary heart disease risk were similar for both non-HDL-C and apoB (Emerging Risk Factors et al. 2009). On the other hand, a recent large-scale meta-analysis suggested that apoB had better predictive power than LDL-C and non-HDL-C (Sniderman et al. 2011).

Although plasma apoB and non-HDL-C are strongly correlated at a *population*-scale, discordance may still arise at an *individual*-level because they represent different measures (cholesterol vs. particle) (Langlois and Sniderman 2020; Langlois et al. 2018). Discordance between non-HDL-C and apoB may be even more common in patients taking medications that reduce non-HDL-C to a greater extent than apoB (i.e., statins, PCSK9 inhibitors) (Rosenson et al. 2016; Ridker et al. 2016; Sniderman 2008), with on-treatment levels of LDL and VLDL particles that remain elevated and can explain residual risk (Lawler et al. 2017b; Mora et al. 2015).

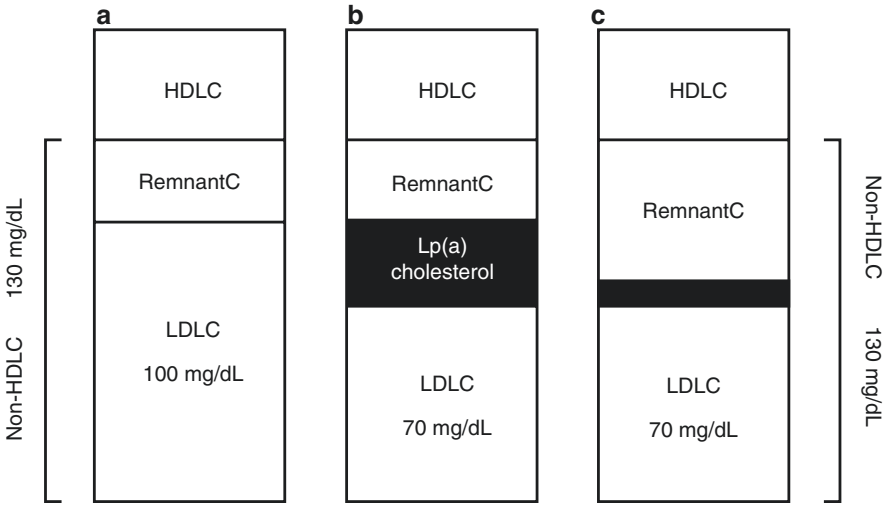

Fig. 18.3 Differences in relative composition of lipoproteincholesterol fractions in three patients with identical non-HDL-C levels. HDL-C high-density lipoprotein cholesterol, RemnantC remnant lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, Lp(a) lipoprotein (a), non-HDL-C non-high-density lipoprotein cholesterol

Non-HDL-C may carry some disadvantages. First, non-HDL-C can be affected by metabolic fluctuations in cholesterol content within non-HDL lipoproteins and if there is a preponderance of small dense particles, then non-HDL-C may underestimate the risk due to elevated atherogenic lipoproteins. Second, non-HDL-C itself does not differentiate between its components, for which it may not accurately represent or distinguish phenotypes of individuals with (a) high LDL-C but normal remnant and Lp(a)-C, (b) low LDL-C but high Lp(a)-C, (c) low LDL-C but high remnant cholesterol (Fig. 18.3).

Apolipoprotein B for Precision Diagnosis of Dyslipidemia Phenotypes

Fredrickson, Levy, and Lees (FLL) first defined the five familial lipoprotein phenotypes (types I–V) in 1967 based on the presence of lipoprotein classes and their associated clinical manifestations (Fredrickson et al. 1967). For example, types I and V, which were characterized by elevated chylomicrons, were associated with high pancreatitis risk, whereas type IIb and type III which were characterized by elevated cholesterol and triglyceride enriched particles were associated with premature CAD and acute coronary syndrome. However, part of the challenge in identifying these disorders is the requirement for ultracentrifugation, gel electrophoresis, and genetic testing that is not readily available.

Sniderman et al. have developed an algorithm using an apoB level and a traditional lipid panel to differentiate the five lipoprotein phenotypes with high sensitivity and specificity (de Graaf et al. 2008). Of these, elevated apoB levels generally correlate with elevated cardiovascular risk, as seen with familial hypercholesterolemia (type IIa) and familial combined hypercholesterolemia (type IIb). The exception to the rule is hyperlipoproteinemia type III (HLP3). HLP3, or familial dysbetalipoproteinemia, is characterized by cholesterol and triglyceride enriched remnant cholesterol particles and is associated with high risk of premature CAD and peripheral artery disease. However, patients with HLP3 have normal apoB levels, and the disorder cannot be diagnosed using a traditional lipid panel. In a study of 128,485 patients, the apoB algorithm was shown to reliably identify the HLP3 phenotype with high specificity even in patients with mild mixed hyperlipidemia (Varghese et al. 2021). Although multiple algorithms to screen for HLP3 have been proposed (Varghese et al. 2021), the apoB algorithm allows assessment of the five FLL phenotypes using an apoB level and a lipid panel.

Apolipoprotein B in Contemporary Clinical Guidelines

In light of evidence supporting the role of apoB in atherosclerosis and risk prediction, worldwide guidelines have incorporated apoB in their recommendations, although with different emphases and/or cutpoints. In general, cutpoints for apoB to guide clinical management are less well established than for LDL-C and differ considerably between the various recommendations of professional societies around the globe.

The 2018 American Heart Association/American College of Cardiology (AHA/ACC) multisociety Cholesterol Guideline uses LDL-C as the main lipid target for primary prevention (Grundy et al. 2019). As opposed to prior guidelines, the most recent iteration introduced elevated apoB as a risk-enhancing factor, and gave a relative indication for apoB measurement when TG levels are ≥200 mg/dL. The AHA/ACC multisociety guideline favors initiation of statin therapy for apoB levels ≥130 mg/dL in primary prevention. Of note, they do not recommend measurement of apoB to determine efficacy of therapy. Based on NHANES III data, AHA/ACC guidelines state that the corresponding cutpoint for apoB of 130 mg/dL would be 160 mg/dL for LDL-C (Grundy et al. 2019).

On the other hand, the National Lipid Association (NLA) introduced apoB goals: <80 mg/dL for high-risk patients and <90 mg/dL for primary prevention. Additionally, the NLA expert guidance suggests that an apoB level of 110 mg/dL corresponds approximately to an LDL-C level of 130 mg/dL (Jacobson et al. 2014). The American Association of Clinical Endocrinologists (AACE) recommended slightly higher apoB goals for therapy: <90 mg/dL for patients at high risk, <80 mg/dL for patients at very high risk, and <70 mg/dL for patients at extreme risk (Jellinger et al. 2017).

Table 18.1 Estimated percentiles of LDL-C, non-HDL-C, and apoB from NHANES 2015–2016

	Percentiles						
	5th	10th	25th	50th	75th	90th	95th
LDL-C (mg/dL)	59	67	83	106	132	156	172
Non-HDL-C (mg/dL)	72	81	100	126	155	186	206
ApoB (mg/dL)	54	60	72	88	106	126	138

The European Society of Cardiology and the European Atherosclerosis Society (ESC/EAS) guidelines proposed apoB targets for very high- and high-risk patients of <65 and <80 mg/dL, respectively (Mach et al. 2020). Of note, these apoB goals are higher than their population equivalent levels of LDL-C. For instance, the recommended apoB goal for high-risk patients corresponds to ~25th percentile of the population, whereas an LDL-C of 70 mg/dL corresponds to seventh to ninth percentiles (Sathiyakumar et al. 2018) for which apoB targets may need to be readjusted to, for instance, the population equivalent level for LDL-C (Langlois et al. 2020). For further reference, percentiles of LDL-C, non-HDL-C, and apoB estimated from NHANES 2015–2016 are shown in Table 18.1.

As apoB is progressively incorporated into worldwide guidelines, it is still not a part of routine clinical practice. A cost-analysis study suggested that using apoB in patients' care would only produce a trivial increase in the cost of care (Kohli-Lynch et al. 2020). However, the main limitations for its widespread implementation are lack of clinician familiarity, lack of randomized trial evidence, and concern that measurement has not been adequately standardized to date.

Apolipoprotein B Measurement

To date, a key barrier to increasing the utilization of apoB is the lack of standardized methods (Contois and Delatour 2018). A recent study from MESA showed a significant discordance in three apoB assay results at apoB >100 mg/dL (Cao et al. 2018). Another study showed that measurement across ten laboratories were not equivalent for assays of non-HDL particles and apoB100, and suggested that liquid chromatography–mass spectrometry/mass spectrometry may be the most accurate method (Delatour et al. 2018).

Although currently there is no apoB reference method, clinical laboratories typically measure apoB using an immunonephelometry assay (INA), which is based on light scattering measurements following apoB antigen–antibody complex formation. However, given that all apoB-containing lipoproteins have different sizes and compositions, INA results may not be highly accurate because apoB antigenic sites may be masked on larger particles.

Due to these reasons, accuracy and improved between-method comparability require standardized calibration and result traceability to the International System of Units. In the 1990s, the International Federation for Clinical Chemistry (IFCC)

and the World Heart Organization (WHO) developed a reference material aiming to standardize and harmonize apoB measurements. A working group of the IFCC, Apolipoprotein Standardization by Mass Spectrometry is addressing this issue (International Federation for Clinical Chemistry (IFCC) 2017).

Conclusions

We reviewed the metabolism of apoB-containing lipoproteins, supporting evidence for their role in cardiovascular risk prediction, and the current guideline's recommendations for use and implementation of apoB in clinical care. Atherogenic lipoprotein particle concentration – represented apoB – has a central role in atherogenesis. Epidemiological studies and lipid-lowering trials have shown that cardiovascular risk tracks with apoB, and it may provide additional risk information when discordant with LDL-C and non-HDL-C. ApoB also may aid in diagnostic assessment of dyslipidemic phenotypes when used along with triglycerides and total cholesterol. While apoB has been incorporated in various recommendations/guidelines of professional societies, views on clinically meaningful cutpoints differ considerably. Expanding apoB's role in the primary prevention of cardiovascular disease will require increased clinician familiarity and appreciation of the value that apoB can add beyond the standard lipid profile and improved standardization of measurement.

References

Avogaro P, Bon GB, Cazzolato G, Quinci GB. Are apolipoproteins better discriminators than lipids for atherosclerosis? Lancet. 1979;1(8122):901–3.

Barter PJ, Ballantyne CM, Carmena R, Castro Cabezas M, Chapman MJ, Couture P, et al. Apo B versus cholesterol in estimating cardiovascular risk and in guiding therapy: report of the thirty-person/ten-country panel. J Intern Med. 2006;259(3):247–58.

Benn M, Nordestgaard BG, Jensen GB, Tybjaerg-Hansen A. Improving prediction of ischemic cardiovascular disease in the general population using apolipoprotein B: the Copenhagen City Heart Study. Arterioscler Thromb Vasc Biol. 2007;27(3):661–70.

Berneis KK, Krauss RM. Metabolic origins and clinical significance of LDL heterogeneity. J Lipid Res. 2002;43(9):1363–79.

Boekholdt SM, Arsenault BJ, Mora S, Pedersen TR, LaRosa JC, Nestel PJ, et al. Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins: a meta-analysis. JAMA. 2012;307(12):1302–9.

Brownstein AJ, Martin SS. More accurate LDL-C calculation: externally validated, guideline endorsed. Clin Chim Acta. 2020;506:149–53.

Cao J, Steffen BT, Guan W, Remaley AT, McConnell JP, Palamalai V, et al. A comparison of three apolipoprotein B methods and their associations with incident coronary heart disease risk over a 12-year follow-up period: the Multi-Ethnic Study of Atherosclerosis. J Clin Lipidol. 2018;12(2):300–4.

Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet. 2016;388(10059):2532–61.

Contois JH, Delatour V. Apolipoprotein B measurement: need for standardization. J Clin Lipidol. 2018;12(2):264–5.

de Graaf J, Couture P, Sniderman A. A diagnostic algorithm for the atherogenic apolipoprotein B dyslipoproteinemias. Nat Clin Pract Endocrinol Metab. 2008;4(11):608–18.

Delatour V, Clouet-Foraison N, Gaie-Levrel F, Marcovina SM, Hoofnagle AN, Kuklenyik Z, et al. Comparability of lipoprotein particle number concentrations across ES-DMA, NMR, LC-MS/MS, immunonephelometry, and VAP: in search of a candidate reference measurement procedure for apoB and non-HDL-P standardization. Clin Chem. 2018;64(10):1485–95.

Elovson J, Chatterton JE, Bell GT, Schumaker VN, Reuben MA, Puppione DL, et al. Plasma very low density lipoproteins contain a single molecule of apolipoprotein B. J Lipid Res. 1988;29(11):1461–73.

Emerging Risk Factors C, Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, et al. Major lipids, apolipoproteins, and risk of vascular disease. JAMA. 2009;302(18):1993–2000.

Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2017;38(32):2459–72.

Ference BA, Kastelein JJP, Ray KK, Ginsberg HN, Chapman MJ, Packard CJ, et al. Association of triglyceride-lowering LPL variants and LDL-C-lowering LDLR variants with risk of coronary heart disease. JAMA. 2019;321(4):364–73.

Fredrickson DS, Levy RI, Lees RS. Fat transport in lipoproteins–an integrated approach to mechanisms and disorders. N Engl J Med. 1967;276(5):273–81. concl.

Garvey WT, Kwon S, Zheng D, Shaughnessy S, Wallace P, Hutto A, et al. Effects of insulin resistance and type 2 diabetes on lipoprotein subclass particle size and concentration determined by nuclear magnetic resonance. Diabetes. 2003;52(2):453–62.

Griffin BA, Caslake MJ, Yip B, Tait GW, Packard CJ, Shepherd J. Rapid isolation of low density lipoprotein (LDL) subfractions from plasma by density gradient ultracentrifugation. Atherosclerosis. 1990;83(1):59–67.

Grundy SM, Vega GL, Tomassini JE, Tershakovec AM. Correlation of non-high-density lipoprotein cholesterol and low-density lipoprotein cholesterol with apolipoprotein B during simvastatin + fenofibrate therapy in patients with combined hyperlipidemia (a subanalysis of the SAFARI trial). Am J Cardiol. 2009;104(4):548–53.

Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Circulation. 2019;139(25):e1082–e143.

International Federation for Clinical Chemistry (IFCC). IFCC working group on apolipoprotein standardization by mass spectrometry (WG-APO MS). 2017. http://www.ifcc.org/ifcc-scientific-division/sd-working-groups/wg-apo-ms/.

Jacobson TA, Ito MK, Maki KC, Orringer CE, Bays HE, Jones PH, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1 - executive summary. J Clin Lipidol. 2014;8(5):473–88.

Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, et al. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. Endocr Pract. 2017;23(Suppl 2):1–87.

Kohli-Lynch CN, Thanassoulis G, Moran AE, Sniderman AD. The clinical utility of apoB versus LDL-C/non-HDL-C. Clin Chim Acta. 2020;508:103–8.

Lamarche B, Moorjani S, Lupien PJ, Cantin B, Bernard PM, Dagenais GR, et al. Apolipoprotein A-I and B levels and the risk of ischemic heart disease during a five-year follow-up of men in the Quebec cardiovascular study. Circulation. 1996;94(3):273–8.

Langlois MR, Sniderman AD. Non-HDL cholesterol or apoB: which to prefer as a target for the prevention of atherosclerotic cardiovascular disease? Curr Cardiol Rep. 2020;22(8):67.

Langlois MR, Chapman MJ, Cobbaert C, Mora S, Remaley AT, Ros E, et al. Quantifying atherogenic lipoproteins: current and future challenges in the era of personalized medicine and very low concentrations of LDL cholesterol. A consensus statement from EAS and EFLM. Clin Chem. 2018;64(7):1006–33.

Langlois MR, Nordestgaard BG, Langsted A, Chapman MJ, Aakre KM, Baum H, et al. Quantifying atherogenic lipoproteins for lipid-lowering strategies: consensus-based recommendations from EAS and EFLM. Clin Chem Lab Med. 2020;58(4):496–517.

Lawler PR, Akinkuolie AO, Ridker PM, Sniderman AD, Buring JE, Glynn RJ, et al. Discordance between circulating atherogenic cholesterol mass and lipoprotein particle concentration in relation to future coronary events in women. Clin Chem. 2017a;63(4):870–9.

Lawler PR, Akinkuolie AO, Chu AY, Shah SH, Kraus WE, Craig D, et al. Atherogenic lipoprotein determinants of cardiovascular disease and residual risk among individuals with low low-density lipoprotein cholesterol. J Am Heart Assoc. 2017b;6(7):e005549.

Linsel-Nitschke P, Gotz A, Erdmann J, Braenne I, Braund P, Hengstenberg C, et al. Lifelong reduction of LDL-cholesterol related to a common variant in the LDL-receptor gene decreases the risk of coronary artery disease – a Mendelian Randomisation study. PLoS One. 2008;3(8):e2986.

Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111–88.

Mora S, Otvos JD, Rifai N, Rosenson RS, Buring JE, Ridker PM. Lipoprotein particle profiles by nuclear magnetic resonance compared with standard lipids and apolipoproteins in predicting incident cardiovascular disease in women. Circulation. 2009;119(7):931–9.

Mora S, Buring JE, Ridker PM. Discordance of low-density lipoprotein (LDL) cholesterol with alternative LDL-related measures and future coronary events. Circulation. 2014;129(5):553–61.

Mora S, Caulfield MP, Wohlgemuth J, Chen Z, Superko HR, Rowland CM, et al. Atherogenic lipoprotein subfractions determined by ion mobility and first cardiovascular events after random allocation to high-intensity statin or placebo: the justification for the use of statins in prevention: an intervention trial evaluating rosuvastatin (JUPITER) trial. Circulation. 2015;132(23):2220–9.

Nordestgaard BG. A test in context: lipid profile, fasting versus nonfasting. J Am Coll Cardiol. 2017;70(13):1637–46.

Otvos JD, Mora S, Shalaurova I, Greenland P, Mackey RH, Goff DC Jr. Clinical implications of discordance between low-density lipoprotein cholesterol and particle number. J Clin Lipidol. 2011;5(2):105–13.

Pencina MJ, D'Agostino RB, Zdrojewski T, Williams K, Thanassoulis G, Furberg CD, et al. Apolipoprotein B improves risk assessment of future coronary heart disease in the Framingham Heart Study beyond LDL-C and non-HDL-C. Eur J Prev Cardiol. 2015;22(10):1321–7.

Richardson TG, Sanderson E, Palmer TM, Ala-Korpela M, Ference BA, Davey Smith G, et al. Evaluating the relationship between circulating lipoprotein lipids and apolipoproteins with risk of coronary heart disease: a multivariable Mendelian randomisation analysis. PLoS Med. 2020;17(3):e1003062.

Ridker PM, Mora S, Rose L, Group JTS. Percent reduction in LDL cholesterol following high-intensity statin therapy: potential implications for guidelines and for the prescription of emerging lipid-lowering agents. Eur Heart J. 2016;37(17):1373–9.

Robinson JG, Wang S, Jacobson TA. Meta-analysis of comparison of effectiveness of lowering apolipoprotein B versus low-density lipoprotein cholesterol and nonhigh-density lipoprotein cholesterol for cardiovascular risk reduction in randomized trials. Am J Cardiol. 2012;110(10):1468–76.

Rosenson RS, Jacobson TA, Preiss D, Djedjos CS, Dent R, Bridges I, et al. Efficacy and safety of the PCSK9 inhibitor evolocumab in patients with mixed hyperlipidemia. Cardiovasc Drugs Ther. 2016;30(3):305–13.

Sathiyakumar V, Park J, Quispe R, Elshazly MB, Michos ED, Banach M, et al. Impact of novel low-density lipoprotein-cholesterol assessment on the utility of secondary non-high-density lipoprotein-C and apolipoprotein B targets in selected worldwide dyslipidemia guidelines. Circulation. 2018;138(3):244–54.

Sniderman AD. Differential response of cholesterol and particle measures of atherogenic lipoproteins to LDL-lowering therapy: implications for clinical practice. J Clin Lipidol. 2008;2(1):36–42.

Sniderman AD, Robinson JG. ApoB in clinical care: pro and con. Atherosclerosis. 2019; 282:169–75.

Sniderman A, Shapiro S, Marpole D, Skinner B, Teng B, Kwiterovich PO Jr. Association of coronary atherosclerosis with hyperapobetalipoproteinemia [increased protein but normal cholesterol levels in human plasma low density (beta) lipoproteins]. Proc Natl Acad Sci U S A. 1980;77(1):604–8.

Sniderman A, Tremblay A, Bergeron J, Gagne C, Couture P. Diagnosis of type III hyperlipoproteinemia from plasma total cholesterol, triglyceride, and apolipoprotein B. J Clin Lipidol. 2007;1(4):256–63.

Sniderman AD, Williams K, Contois JH, Monroe HM, McQueen MJ, de Graaf J, et al. A meta-analysis of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B as markers of cardiovascular risk. Circ Cardiovasc Qual Outcomes. 2011;4(3):337–45.

Sniderman AD, Couture P, Martin SS, DeGraaf J, Lawler PR, Cromwell WC, et al. Hypertriglyceridemia and cardiovascular risk: a cautionary note about metabolic confounding. J Lipid Res. 2018;59(7):1266–75.

Sniderman AD, Thanassoulis G, Glavinovic T, Navar AM, Pencina M, Catapano A, et al. Apolipoprotein B particles and cardiovascular disease: a narrative review. JAMA Cardiol. 2019;4(12):1287–95.

Thanassoulis G, O'Donnell CJ. Mendelian randomization: nature's randomized trial in the post-genome era. JAMA. 2009;301(22):2386–8.

Thanassoulis G, Williams K, Ye K, Brook R, Couture P, Lawler PR, et al. Relations of change in plasma levels of LDL-C, non-HDL-C and apoB with risk reduction from statin therapy: a meta-analysis of randomized trials. J Am Heart Assoc. 2014;3(2):e000759.

Varghese B, Park J, Chew E, Sajja A, Brownstein A, Pallazola VA, et al. Importance of the triglyceride level in identifying patients with a Type III Hyperlipoproteinemia phenotype using the ApoB algorithm. J Clin Lipidol. 2021;15(1):104–115.e9.

Walldius G, Jungner I, Holme I, Aastveit AH, Kolar W, Steiner E. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. Lancet. 2001;358(9298):2026–33.

Welsh C, Celis-Morales CA, Brown R, Mackay DF, Lewsey J, Mark PB, et al. Comparison of conventional lipoprotein tests and apolipoproteins in the prediction of cardiovascular disease. Circulation. 2019;140(7):542–52.

Whelton SP, Meeusen JW, Donato LJ, Jaffe AS, Saenger A, Sokoll LJ, et al. Evaluating the atherogenic burden of individuals with a Friedewald-estimated low-density lipoprotein cholesterol <70 mg/dL compared with a novel low-density lipoprotein estimation method. J Clin Lipidol. 2017;11(4):1065–72.

Wilkins JT, Li RC, Sniderman A, Chan C, Lloyd-Jones DM. Discordance between apolipoprotein B and LDL-cholesterol in young adults predicts coronary artery calcification: the CARDIA study. J Am Coll Cardiol. 2016;67(2):193–201.

Zuber V, Gill D, Ala-Korpela M, Langenberg C, Butterworth A, Bottolo L, et al. High-throughput multivariable Mendelian randomization analysis prioritizes apolipoprotein B as key lipid risk factor for coronary artery disease. Int J Epidemiol. 2021;50(3):893–901.

Chapter 19
Social Determinants of Cardiovascular Health

Melvin R. Echols, Rachel M. Bond, and Keith C. Ferdinand

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide and is expected to cause over 22 million deaths by 2030 (Virani et al. 2020). Although CVD mortality has significantly declined over several decades in the United States, the burden remains high and may even increase in the future, partly due to increasing burden of uncontrolled hypertension, overweight/obesity, physical inactivity, and type 2 diabetes (T2D) over recent decades. There are several social and environmental circumstances that influence mortality and outcomes related to the progression of CVD. Thus, understanding the relationship between social determinants of health (SDoH) and CVD is crucial in developing measures to manage and prevent adverse outcomes (Brondolo et al. 2011a; Reshetnyak et al. 2020; Moen et al. 2020; Suglia et al. 2020; Promotion. OoDPaH 2020; Pinheiro et al. 2020) (Fig. 19.1). The predominance of data documents essential relationships between the adverse effects

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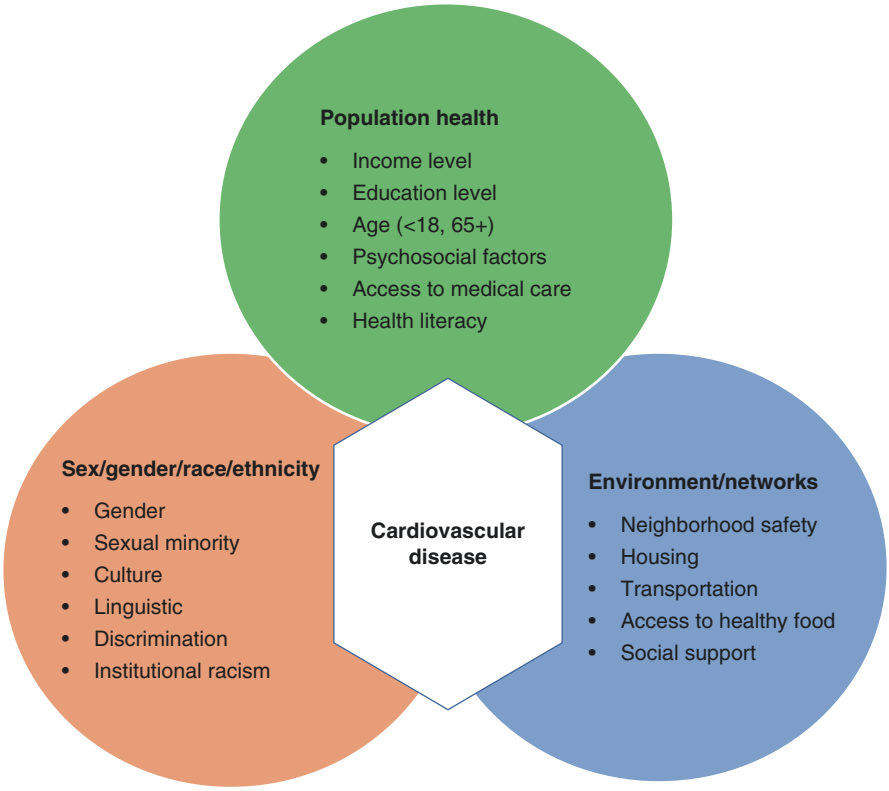

Fig. 19.1 Social determinants of cardiovascular health

of lower socioeconomic status on CVD in the United States and other high-income countries (HICs) (Schultz et al. 2018). Recent data also emphasize more novel variables of the SDoH that afford a greater understanding of lesser-known predictors of CVD outcomes (Milner and Franz 2020; Serchen et al. 2020; Churchwell et al. 2020). More recent research suggests that society's behavioral effects, such as structural or systemic racism, may also play a crucial role in SDoH-related CVD outcomes. The purpose of this chapter is to summarize the current knowledge of SDoH concerning CVD health and suggest an understanding of how these factors impact the management of CVD, strategies for prevention, and future research directions.

Definitions of Social Determinants of Health

The World Health Organization (WHO) has defined SDoH as the circumstances in which people are born, grow, live, work, and age (WHO 2020). Economic influences, power, and other resources determine many of these circumstances on a local

and global level. The 2015 American Heart Association (AHA) Scientific Statement denotes that socioeconomic position (SEP), which encompasses wealth and income, education, and employment/occupational status, is instrumental in affecting CVD outcomes (Havranek et al. 2015). Other factors such as race/ethnicity, social support, culture, access to medical care, and residential environments are also additional SDoH-related factors and are essential in the discussion of overall CVD health. The components of SDoH are not mutually exclusive factors, but rather interrelated based on local/global resources and distribution availability. Furthermore, measures of SDoH are likely multidimensional and require models that adequately reflect the complex relationships.

The Vulnerable Populations model of SDoH, developed by Flaskerud in 1998, was a concept linking resource availability, health status, and relative risk to disease outcomes (Flaskerud and Winslow 1998). The relationship between resource availability and relative risk was described as inversely proportional to one another, suggesting the lack of resources increased the relative risk for the disease outcomes of interest. Thus, the socioeconomic factors of resource availability heavily influence the avoidable risk of a population. The relationship of relative risk and health status is also an inverse proportion, suggesting that the increased exposure to risk will decrease a population's health and increase the mortality and morbidity of the related disease state. The final relationship of health status and resource availability suggests that the burden of mortality and morbidity of a disease within a community will likely inhibit the societal population's potential efforts to secure resources. This concept reflects in the ability, or lack thereof, of racial/ethnic minority populations to secure human capital. For example, the national poverty rates according to 2019 Census data are highest for Hispanics and blacks, with blacks also suffering from the highest rates of CVD mortality (Semaga et al. 2020). The markers of SEP include race and ethnicity, wealth and income, education, employment/occupational status, social connections, political voice, environment, and physical insecurity (Havranek et al. 2015). However, the importance of socioeconomic status (SES) often differs between race and ethnicity, culture, and/or location. Individual markers of SEP and production systems within the economy often determine the ability to define a population's SES. The measures of education, income, and occupation are well studied in their relationship to CVD. Moreover, the other areas such as race and ethnicity, political voice, and social connections may have key similarities that may contribute to racism, defined as the deliberate preferential treatment of one race or ethnicity over another. To an extent, this chapter will also explore the evidence of racism as a SDoH and how structural inequities contribute to CVD.

Socioeconomic Status and Cardiovascular Disease

Although many socioeconomic factors may associate with CVD outcomes, there are four markers of SEP/SES that have most consistently demonstrated associations with CVD in HICs: education, income, employment status, and environmental

factors. Although low- and middle-income countries (LMICs) have the highest global burden of CVD, the associations between SES are described with limitations and contain conflicting data (Schultz et al. 2018). This chapter, therefore, reviews and analyzes the data primarily from the United States and other HICs. Although the SDoH may impact CVD globally regardless of specific regions, in order to better understand the relationship of various CVD risk factors, the text will focus on HICs with reasonably similar environmental conditions.

Education

Educational attainment has an inverse relationship with CVD in HICs. Recent data from the United States suggest that educational attainment is associated with lower CVD risk, regardless of other SES markers. A large study by Kubota et al. in 2017 analyzed the associations of educational attainment with CVD in the Atherosclerosis Risk in Communities (ARIC) study (Kubota et al. 2017). In this study of 13,948 white and black individuals, aged 45 to 64 at baseline, the authors found a significant association with a higher lifetime risk for CVD between those individuals completing as compared to not completing high school. Specifically lifetime risk of CVD for men were 59.0% (95% CI, 54.0–64.1%) for grade school vs. 50.9% (95% CI, 47.3–53.9%) for high school graduation. Moreover, lifetime risk of CVD for women were 50.8% (95% CI, 45.7–55.8%) for grade school vs. 36.3% (95% CI, 33.4–39.1%) for high school graduation. Educational attainment was inversely associated with CVD, even within family income, income change, occupation, or parental educational level (Kubota et al. 2017).

Other studies have related educational attainment to important physiological CVD risk factors, such as hypertension (HTN), type 2 diabetes (DM), and obesity (Reshetnyak et al. 2020; Barnason et al. 2017; Dégano et al. 2017; Kershaw et al. 2013). Degano and colleagues analyzed data from the REgistre GIroni del COR, Catalan for Girona Heart Registry (REGICOR) study evaluating the effects of educational attainment with CVD incidence in a population cohort of 11,158 individuals (Dégano et al. 2017). Participants with a university degree had a 49% lower risk of CVD events over the study duration than participants with primary or lower education (HR 0.51, 95% CI, 0.30–0.85). The association between educational level and CVD was mediated by HTN, DM, and body mass index (BMI), which comprised approximately 26% of the association. Moreover, HTN was the most prominent mediator of the three risk factors (Dégano et al. 2017). The findings of these and other studies suggest educational attainment may adversely affect health through interrelated associations of health literacy and individual insight into the management of significant CVD risk factors.

The level of educational attainment a person achieves may be heavily correlated to health literacy, as individuals with low health literacy may not connect the reasoning of risk factor management through medication adherence and lifestyle interventions. Other behavioral risk factors such as smoking and physical inactivity are

also likely related to elevated CVD risk in those with lower educational levels (Kershaw et al. 2013). Research designed to improve health literacy in a low SES population may significantly reveal best practices to unlock the power of preventive efforts. Nevertheless, further investigations are required to understand how educational attainment specifically relates with biological risk factors.

Income Level

The current peer-reviewed literature well delineates the inverse association of income level with CVD. Compared with lower-income neighborhoods, higher-income groups reportedly have lower stress levels, lower rates of obesity, and fewer comorbidities (White-Williams et al. 2020). In 2016, Mosquera and colleagues analyzed data from a large Swedish cohort of 44,039 individuals followed for two decades, which recorded the first time to hospitalization for CVD events and averaged earned income (Mosquera et al. 2016). Although education and employment status played more dominant roles in explaining the inequalities related to health in the early observations, the role of stable income and age became more dominant in CVD events as the cohort matured. This study displayed the dynamic role of specific SEP markers and will require further investigations to determine how these markers' penetrance changes over time.

Although many studies display the significance of income inequality related to CVD, few data address interventions to change these findings. In a recent US study published in 2019 of low- and moderately low-income participants, Zhang and colleagues demonstrated that the expansion of federal funding may be useful in providing more health care access and management for chronic conditions (Zhang et al. 2019). In a nationally representative sample of 2866 nonpregnant hypertensive individuals aged 18 to 64 years with income up to 138% of the federal poverty level (FPL), both low- and moderately low-income groups, newly eligible for Medicaid, were associated with higher health care services use ($13,085 compared with $7582 without Medicaid) (Zhang et al. 2019). These data suggest that federal funding interventions in low-income populations can support the management of chronic CVD conditions and possibly decrease adverse events downstream.

Employment Status

Although the data are robust on the relationship between income and CVD, the relationship between employment status or employment type is less well defined. Data analyzed from the National Health and Nutrition Examination Survey (NHANES) of 6928 workers aged 20 years or older from 40 occupational groups reported protective service workers ranked among the lowest in awareness (50.6%), treatment (79.3%), and control (47.7%) of HTN management compared with executive/administrative/

managerial workers (Davila et al. 2012). In 2020, Mendy and colleagues analyzed combined 2013, 2015, and 2017 data from the Mississippi Behavioral Risk Factor Surveillance System for 6965 workers in ten Standard Occupational Classification System significant groups (Mendy et al. 2020). The study revealed that the prevalence of HTN was 31.4%, with a higher likelihood of HTN seen among workers aged 30–44 years, 45–64 years, blacks, and those classified as overweight and obese workers compared to their counterparts. The likelihood of having HTN among workers in the fields of installation, repair, maintenance (APR, 1.26; 95% CI, 1.03–1.55) and production (APR 1.33; 95% CI, 1.11–1.58) was higher when these workers were compared with workers in all other occupational groups (Mendy et al. 2020). The findings of this study continue to emphasize the need for innovative community-based or linked programs that may reduce the risk of HTN in targeted workers.

Some data suggest that diet may also play a crucial role CVD development of working individuals. Bortkiewicz et al. evaluated the differences in 243 occupationally active men admitted for an indexed myocardial infarction (MI) in Poland with a reference group of 473 men of various occupations without hospitalization for MI over 1 year. The MI patients reported significantly less fruit consumption, raw vegetables, cheese, vegetable oils, and fish. The consumption of salty ($p = 0.0226$) or fatty ($p < 0.0001$) foods was significantly higher in the workers who suffered MI during the observation period. After adjusting for age, education, and the type of work, the daily consumption of fish, salads, cooked vegetables, fruit, and vegetable oils, significantly reduced the risk of MI (Bortkiewicz et al. 2019). Therefore, this study indicated the importance of prevention activities and proper dietary habits among working people. However, other studies in other HICs suggest an elevated risk in the employed office working individual, possibly related to a higher risk of physical inactivity (Okuda et al. 2019; Strauss et al. 2020). Although the data suggest varying cardiovascular risk across the type of employment, prevention factors are likely beneficial for people of all occupations. Ideally, these prevention measures include proper dietary habits and physical activity and control of other risk factors such as HTN, hyperlipidemia, and smoking cessation.

In the United States, the differences between employment status and income in the form of federal assistance and their relationship to CVD events are also an understudied area that will require further investigations. Federally funded income in the form of unemployment assistance may not have the same inverse relationship with CVD as with employment income, possibly related to physical inactivity in those with federally funded income. Thus, the answer to this hypothesis may contradict the findings of studies that suggest federal funding in the form of medical healthcare and access may reduce outcomes related to CVD (Zhang et al. 2019).

Environment

Environmental factors, including neighborhood socioeconomic characteristics, are well-documented concerning CVD and mortality risk (Schultz et al. 2018; Powell-Wiley et al. 2013; Claudel et al. 2018; Mayne et al. 2018; Xiao et al. 2018; Andrews

et al. 2021). In a recent study, Xiao and colleagues examined the 10-year change in neighborhood socioeconomic deprivation with the mortality rate among 288,555 participants aged 51–70 who enrolled in the National Institutes of Health-AARP Diet and Health Study in 1995–1996 (baseline) and did not move to another neighborhood during the study (Xiao et al. 2018). Data for all-cause mortality, cardiovascular disease, and cancer deaths were attained through linkage to the Social Security Administration Death Master File between 2000 and 2011. The study results suggested that improvement in neighborhood socioeconomic status was associated with a lower mortality rate, while deterioration was associated with a higher mortality rate (Xiao et al. 2018).

Neighborhood safety, or the perception thereof, may also contribute to CVD risk. Mayne and colleagues recently evaluated longitudinal data from 528 participants of the Multi-Ethnic Study of Atherosclerosis (aged 45–84, normotensive at baseline) who lived in Chicago, Illinois. The investigators examined associations of changes in individual-level perceived safety, aggregated neighborhood-level perceived safety, and past-year rates of police-recorded crime in a 1, ½, or ¼ mile buffer per 1000 population with changes in systolic and diastolic BPs using fixed-effects linear regression. A standard deviation increase in individual-level perceived safety was associated with a nonsignificant 1.54 mm Hg reduction in systolic BP overall (95% confidence interval [CI]: 0.25, 2.83), and with a 1.24 mm Hg reduction in diastolic BP among women only (95% CI: 0.37, 2.12) in adjusted models (Mayne et al. 2018). Thus, increased neighborhood-level safety was not associated with BP change. An increase in police-recorded crime was associated with a reduction in systolic and diastolic BPs among women only, but results were sensitive to the neighborhood buffer size. These results suggest that individual perception of neighborhood safety may be particularly salient for systolic BP reduction relative to more objective neighborhood exposures (Mayne et al. 2018). As neighborhood variables can change with time, some studies suggest increased risk factors for CVD with other risk characteristics such as obesity, physical inactivity, and health care utilization (Powell-Wiley et al. 2013; Powell-Wiley et al. 2017; Claudel et al. 2019; Ceasar et al. 2020).

Race and Ethnicity, Structural Racism, and Social Determinants of Health

Although previous studies document the relationship between racial and ethnic differences in CVD outcomes, the impact of racism toward CVD burden in specific groups is less clear. Yet, the association of race and racism with SDoH likely has devastating effects on CVD (Fig. 19.2). While studies have investigated links between certain CVD conditions and racial discrimination, the studies evaluating HTN-related outcomes suggest higher blood pressure and cardiovascular reactivity among those with significant self-reported racism experiences (Brondolo et al. 2011a; Havranek et al. 2015; Brondolo et al. 2008; Brondolo et al. 2011b; Greer et al. 2014). The data are less defined in the link between observed and objective

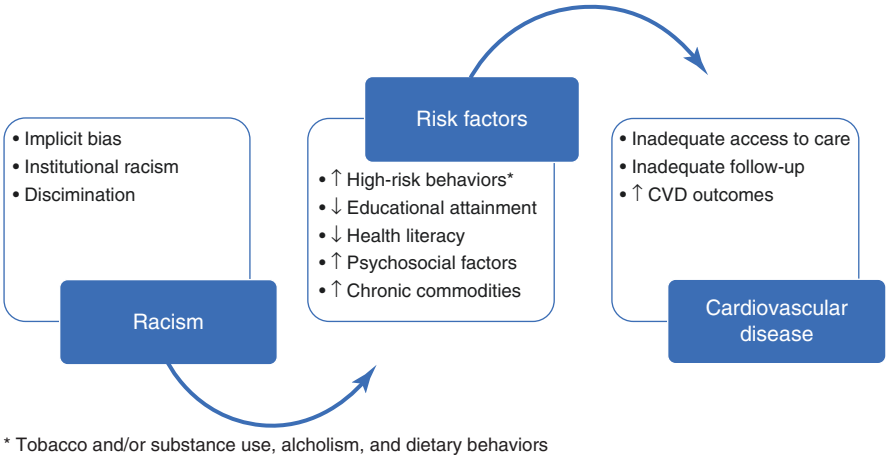

Fig. 19.2 Racism and social determinants of cardiovascular health

overt racism and CVD. More recently, the concept of lifetime discrimination among various racial and ethnic groups has revealed significant findings related to ambulatory blood pressure (ABP) and overall CVD risk. In a study from Beatty-Moody et al., the investigators evaluated the link between lifetime discrimination exposure and ambulatory blood pressure using Perceived Ethnic Discrimination Questionnaire-Community Version (PEDQ-CV). The study evaluated the ambulatory blood pressure of 607 black (n = 318) and Hispanic (n = 289) adults after completing the PEDQ-CV. The participants were outfitted with an ABP monitor to assess systolic and diastolic blood pressure (SBP, DBP) across a 24-hr period. The statistical analysis of mixed-level modeling examined potential interactive effects of lifetime discrimination and age to 24-hr, daytime, and nighttime ABP after adjustment for demographic, socioeconomic, personality and life stress characteristics, and substance consumption covariates (e.g., smoking, alcohol). The study results were significant between the interactions of age and lifetime discrimination on 24-hr and daytime DBP ($p \leq 0.04$), as well as significant interactions for the assessments of the social exclusion component of lifetime discrimination (Beatty Moody et al. 2016). Thus, lifetime discrimination may impose a negative association with nocturnal blood pressure, not moderated by the effects of age.

Other studies suggest health inequalities and quality of life significantly correlate to racism exposure of individuals living in the United States (Milner and Franz 2020; Bailey et al. 2017; Brondolo 2018; Molina et al. 2019). In a recent systematic review of 84 studies between 1984 and 2017, 86% of the reviewed studies demonstrated a link between cardiovascular disease and socially stigmatized groups (Panza et al. 2019). Although most of these studies are cross-sectional, most stigmatization emphasized racial discrimination (79%) with various measurements assessing social discrimination and cardiovascular health. These data emphasize the need for further investigations to include more longitudinal assessments of racial and ethnic discrimination in CVD. To this end, several health organizations are now

recognizing the detrimental effects of racism on the psychological, physical, and environmental conditions that increase CVD risk.

More recent data also suggest a greater burden of SDoH is associated with a graded increase in risk of incident coronary heart disease (CHD), particularly in blacks. Safford and colleagues analyzed data from the prospective longitudinal Reasons for Geographic and Racial Differences in Stroke cohort study, a national US population-based sample of community-dwelling black and white adults ≥45 years of age from 2003 to 2007 (Safford et al. 2021). Seven of the SDoH subdomains from the five Health People 2020 domains included black race, social isolation (Social and Community Context), educational attainment (Education), annual household income (Economic Stability), living in an area with high prevalence of poverty (Neighborhood and Built Environment), and no health insurance, living in an area with poor health infrastructure (Health and Healthcare) were associated with fatal incident CHD and MI. In individuals with fewer SDoH, there was significantly less fatal incident CHD. Compared to those without SDoH, the adjusted risk was significantly higher among those with ≥3 SDoH factors (HR 1.67, 95% CI, 1.18–2.37). Three or more SDoH were found in 84.5% of the black population, which comprised 42% of the entire cohort. These data provide hypothesis-provoking findings possibly related to structural racism that exists in relation to the presents of SDoH, particularly in blacks. However, further investigation is warranted to correlate these findings to other underrepresented populations.

The 2020 American College of Physicians scientific statement addresses some sources of institutional racism and harm through transparency and accountability measures in SDoH, which is the first of many steps required to begin correcting historical racial injustices (Serchen et al. 2020). Likely, other professional organizations may soon follow suit as public injustices related to racism and discrimination are highlighted over time. As recent as November 2020, the American Heart Association (AHA) published a call to action which emphasized structural racism as a fundamental driver of health disparities (Churchwell et al. 2020). This AHA report recognizes that the path forward will require a commitment to transforming the conditions of historically marginalized environments of racial and ethnic minorities, which in part will target the improvement of housing quality, neighborhood environments, as well as advocating for policies that eliminate inequities of economic opportunities, quality education, and health care (Churchwell et al. 2020).

Age and Sex–Gender Relationships to Cardiovascular Health

Age

At times, the extremes of age are most impacted by the conditions in the social and physical environments in which they are born, live, and work (Schultz et al. 2018; Havranek et al. 2015). Early milestones in life from childhood, adolescents, and

even young adulthood provide the physical, cognitive, and social-emotional foundation for lifelong health, learning, and well-being. The history of exposure to adverse childhood experiences, including exposure to violence and maltreatment, is associated with health risk behaviors such as smoking, alcohol, drug use, and chronic health problems such as obesity, diabetes, and CVD (Suglia et al. 2020). Black, Hispanic, and all children of lower SES have a higher prevalence of the more common CVD risk factors such as obesity, diabetes, and HTN (Goff Jr. et al. 2019). Age disparities also exist, beyond the obvious effects of physiology with aging, with the incidence of CVD, increasingly for those adults over the age of 65. For instance, older people may have more severe disease and may be prone to adverse effects of social isolation and other SDOH that would portend poor cardiovascular outcomes (Díez-Villanueva and Alfonso 2016). The availability of community-based resources is imperative, even in the United States, as two-thirds of Americans ≥65 years of age have low health literacy skills (Cuthbertson et al. 2018). Particularly for older adults, access or availability to other support services such as healthier food availability, transportation options for food, and medical care procurement can positively affect their health status. Studies have shown that increased social support levels are associated with a lower risk for chronic disease or mortality from CVD conditions (Havranek et al. 2015). However, frequently, little or no support is available to assist such vulnerable populations as the elderly, at least beyond the initial transition from a hospital or rehabilitation facility. This situation presents an obstacle for patients living with chronic conditions like CVD, suggesting the need for newer roles to support an aging population's needs (Table 19.1).

Table 19.1 Solutions to effects of social determinants of health in vulnerable populations

	Vulnerable Populations	Solutions to Overcome SDOH Effects

Extremes of Age	• High-risk behaviors in childhood
	• Chronic comorbidities naturally ↑ as we age
	• Healthcare maintenance
		• **Increasing community-based resources**
		  • Access to healkthier food
		  • Transportation
		  • Medical care
		• **Improving social support**
		  • Physical networks
		  • Social media
		• **Diversifying the healthcare work force**
		• **Ensuring universal Healthcare**
		• **Increasing transparency and accountability**
		  • Institutional racism
		  • Discrimination

Sex/Gender	• Accompanying symptoms ♀> ♂ • Cardiovascular disorders of pregnancy • ♀ >MI risk if HTN, T2DM, Obesity, Smoking • Gender bias → underdiagnosis in ♀	
Sexula Minority	• Psychosocial stressors • More common high-risk behaviors* • Discrimination • The Role of Hormone Therapy?	

SDOH social determinants of health, ♀ female, ♂ male, *MI* myocardial infarction, *HTN* hypertension, *T2DM* type II diabetes mellitus

Sex-Related Cardiovascular Health

Sex and gender are increasingly important determinants of health for women and men. Although aspects of sex will not vary substantially between different human societies, the aspects of gender may vary greatly; they both impact health outcomes, especially for chronic conditions (World Health Organization 2010). Multiple sex differences in disease prevalence, manifestation, and treatment response are rooted in the genetic differences between men and women (Mauvais-Jarvis et al. 2020). Women often have sex-specific risk factors for CVD, including adverse pregnancy outcomes, higher rates of rheumatic autoimmune disease, mental health disorders, and cancer therapies that may be cardiotoxic. However, more traditional cardiovascular risk factors clearly define the strength of this association. For example, HTN, smoking, obesity, and T2D are associated with higher hazard ratios for MI in women than in men (Millett et al. 2018).

To the same point, ischemic heart disease (IHD) is the most recognized example of distinct disease outcomes based on sex. Men are more likely to be affected by obstructive coronary artery disease (CAD) of large vessels. In contrast, the more diffuse, nonobstructive, or microvascular disease has a higher prevalence in women (Bairey Merz et al. 2017). Compared with men, women suffering from IHD present at an older age, which historically relates to endogenous estrogens' potential protective effects (Mehta et al. 2016). Furthermore, a meta-analysis looking at symptoms at presentation of acute MI demonstrated that both sexes most often presented with chest pain, but compared with men, women were more likely to present with the atypical pain symptoms between the shoulder blades, nausea or vomiting, and shortness of breath. Beyond the biological sex differences, gender roles, norms, and behavior influence how women, men, girls, and boys access health services and how health systems respond to their different needs. Gender inequality leads to health risks for women and girls globally and is clearly defined when it comes to CVD (Suglia et al. 2020).

Women suffering from IHD are underdiagnosed (Bugiardini et al. 2017; Dreyer et al. 2013), with gender bias appearing to be responsible for the absence of recognition of IHD in women with higher mortality rates. Women tend to suffer more from acute MI adverse effects when treated by male emergency medicine physicians (Greenwood et al. 2018). Other studies suggest both men and women with IHD who score high on feminine roles and personality traits are at an equally increased risk of recurrent ischemic heart disease, independent of female sex (Pelletier et al. 2016).

Studies also reveal that male physicians are more effective at treating female patients with acute MI when working with female colleagues and have experience in treating female patients (Mauvais-Jarvis et al. 2020). Therefore, diversifying the cardiology workforce may correct emergency recognition of ST-elevation myocardial infarction in women and accelerate the use of percutaneous coronary intervention or other reperfusion strategies (Roswell et al. 2017). Addressing these sex and gender roles may lead to a better understanding of how the social construction of identity and unbalanced power relations between men and women affect the risks, health-seeking behavior, and health outcomes of men and women in different groups.

Sexual Minority and Cardiovascular Disease

There is mounting evidence that sexual minorities such as lesbian, gay, bisexual, transgender, and queer or questioning (LGBTQ) adults experience more disparities across several cardiovascular risk factors than their cisgender (individuals with a gender identity that matches their sex assigned at birth) heterosexual peers (Caceres et al. 2020). These disparities are thought to be primarily driven by exposure to psychosocial stressors across the life span. While the cardiovascular risks and outcomes on sexual and gender minority groups are an evolving research area with limited information to date, a few risk factors stand out from existing data. For one, LGBTQ adults are more likely to report tobacco, alcohol, and substance use than their cisgender heterosexual peers, with lesbian and bisexual women reporting a higher prevalence of obesity (McCabe et al. 2019). A study found that transgender individuals taking gender-affirming hormones had greater body satisfaction and was associated with higher physical activity (Jones et al. 2018). These data suggest that gender-affirming care might play a role in promoting physical activity among transgender people.

Although studies have identified an increased risk for venous thromboembolism among transgender women taking estrogen (Roswell et al. 2017), data on other CVD outcomes and their causes are limited. Data are conflicting, with some data suggesting that changes in lipid profiles are related to the use of gender-affirming hormones. Systematic reviews demonstrate higher triglyceride levels in transgender women and men taking gender-affirming hormones, lower high-density lipoproteins and low-density lipoproteins in transgender men, while others demonstrate no change in lipid profiles (Connelly et al. 2019; Maraka et al. 2017). To the same point, when looking at blood pressure and glycemic control, there are studies more recently demonstrating a potential increase in both systolic and diastolic BP, along with greater risk for poorer glycemic control in transgender men and women on gender-affirming hormones (Roswell et al. 2017). Although evidence remains limited, and the data are generally inconsistent, this information highlights the crucial need for future investigation on CVD outcomes in these marginalized populations.

One consistent theme in the sexual and gender minorities is strong evidence linking discrimination with poor cardiovascular health in racial and ethnic minorities (Maraka et al. 2017). With sexual minority women, interpersonal violence is associated with higher obesity, hypertension, and diabetes (Caceres et al. 2019). As such, discriminatory policies evaluating antidiscrimination laws and interpersonal discrimination and intrapersonal stressors should be the focus, in part, of future SDoH research in the population.

Social Support and Cardiovascular Disease

Social support, best defined as information leading the subject to believe that he/she is cared for, loved, esteemed, and a member of a network of mutual obligations

(Havranek et al. 2015) involves lively emotional exchange linked to better cardiovascular health outcomes. The concept of social networks overlaps with the concept of social support but differs in that it focuses on a group of individuals rather than a single individual. The best examples include churches and houses of worship, beauty salons or barbershops, and social media networks.

Physical Networks

Environmental, behavioral, and psychosocial factors play a more significant role than genetics in the higher prevalence of CVD in particular patient populations. While at times challenging to implement, community-based interventions have been proven successful in increasing trust, engagement, and access to adequate care and self-management. Although classically, individuals might use members of their social networks for material assistance, such as for transportation, fulfilling obligations while hospitalized, or accessing health expertise, social networks also influence health through behavior.

Two prominent examples of community-based interventions using social networks came from two National Heart, Lung, and Blood Institute (NHLBI) projects. The first, Faith-based Approaches in the Treatment of Hypertension (FAITH) in Blacks study (Schoenthaler et al. 2018), was a church-based program in New York that randomized 32 Black churches to 1 of 2 church-based interventions with trained fellow parishioners or outside health experts. These interventions focused on behavioral changes. After the 6-month program, participants had a notable improvement in systolic blood pressure with their fellow parishioners compared to the outside health expert group. The second, the Los Angeles Barbershop Blood Pressure (LABBP) study (Victor et al. 2018), demonstrated successful BP control in a difficult-to-reach population. This study enrolled males who attended barbershops with a systolic blood pressure of 140 mm Hg or more and randomly assigned them to a pharmacist-led intervention site vs. collaboration and routine follow-up care with the participants' primary care providers. Within the community, trusted barbers encouraged meetings with specialty-trained pharmacists who prescribed drug therapy under a collaborative practice agreement with the participants' doctors, compared with an active behavioral control approach in which barbers encouraged lifestyle modification and doctor appointments. This 6-month trial led to a stunning 21.6 mm Hg difference in SBP and an additional 14.9 mm Hg difference in DBP between the intervention and control groups, sustained for a year (Victor et al. 2018). Despite the notable differences in the trials, both significantly advanced the field of community-based interventions, leading to a better understanding of potentially successful intervention research. Ultimately, future community-based interventions of this nature may improve health outcomes, especially of the highest-risk populations through the use of trusted members of their community social network.

Social Media

As social media utilization and online social networking continue to increase, it is becoming apparent how vital access to mass media and emerging technologies such as cell phones, the internet, and social media can play a role in the SDOH. Internet use is not limited to the millennial generation, as many seniors participate in online activities, especially to access health information (Chen and Schulz 2016). A systematic review of over 98 publications on the use of social media found significant benefits when used in medicine such as increased meaningful interactions with colleagues; more available, tailored, and shared information; increased accessibility and widening access to health information; increased peer/emotional/social support; public health surveillance; and potential to influence healthcare policy (Moorhead et al. 2013). There are countless websites and apps dispensing health information, tracking nutrition and fitness, offering encouragement and inspiration, linking people to support one another, even providing real-time medical advice.

The rapidly expanding growth of social media presents opportunities for public health to increase the influence and impact on the social determinants of health and health equity (Cushman et al. 2020). Public health may increase awareness of CVD in the most-at-risk populations through online campaigns. These efforts, such as those shown with the AHA's Go Red for Women Campaign using the #GoRed to change public perception, give investigators some direction on conducting outreach for chronic diseases more effective public health campaigns. The campaign has seen a notable increase in women's social media posting about heart disease after the initial launch in 2004. However, unfortunately, a recent report released by the AHA in September 2020 demonstrated that heart disease, the leading cause of death for women, declined from 2009 to 2019, yet CVD mortality was not as strongly affected in Hispanic, non-Hispanic black, and younger women (Ndumbe-Eyoh and Mazzucco 2016). Therefore, an opportunity is available where social media's efforts can be more potent by explicitly targeting these vulnerable populations, including those in low socioeconomic strata and lower health literacy, to improve health equity (Zwas 2018).

Health Literacy

Education, the most used indicator of socioeconomic status (SES) in the United States, provides the most consistent data in CVD-related SDoH outcomes. Furthermore, although those with less than a high school education also tend to have lower health literacy (Berkman et al. 2011), health literacy remains an independent predictor of CVD outcomes as well. Health literacy is best defined by the US Department of Health and Human Services (HHS) as the degree to which individuals can obtain, process, and understand necessary health information needed to make appropriate health decisions (National action plan to improve health literacy

2010). Many factors may influence an individual's health literacy, including living in poverty, education, race/ethnicity, age, and disability. For adults living below the poverty level, they are more likely to have lower health literacy than those living above it (Promotion. OoDPaH 2020). Specific characteristics influenced by poverty, including insurance status, may impact health literacy in that uninsured and publicly insured (e.g., Medicaid) individuals are at higher risk of having low health literacy. Individuals with low health literacy have higher medical costs, increased emergency room visits and hospital admissions, and decreased healthcare access.

Interventions that improve self-care behavior, risk factor control, or cardiovascular outcomes in low health literacy are generally lacking (Goff Jr. et al. 2019). However, interventions are indicated for the most at-risk groups where the most significant health literacy disparities occur among racial and ethnic minority groups from different cultural backgrounds and those who do not speak English as a first language.

Culture and Language

Linguistic and cultural differences contribute to poorer cardiovascular health, most notably in the most marginalized groups. People with limited English proficiency are twice as likely as individuals without to report low health status. One study found that 74% of Spanish-speaking patients have less-than-adequate health literacy versus 7% of English-speaking patients (National action plan to improve health literacy 2010). Culture, perhaps best described as a system of beliefs and behaviors characteristic of a definable group that transmits without biological inheritance, may also impact communication between patients and providers and affect a patient's ability to understand or follow a clinician's instructions (Havranek et al. 2015).

To counteract this, the US Department of HHS has published a revised version of its National Standards for Culturally and Linguistically Appropriate Services in Health and Health Care (US Department of Health and Human Services OoMH 2013). Of these revised standards, healthcare providers must inform and offer language assistance options to individuals who have limited English proficiency or other communication needs, at no cost to the patient, to facilitate timely access to all healthcare and services.

Other ways to counteract language barriers at the community level involve training laypeople who are members of the target population with similar cultural and linguistic practices to prevent and control CVD (Brownstein et al. 2005). Community health workers have contributed to significant improvements in community members' access to and continuity of care and adherence to treatment to control hypertension, as documented with the NHBLI studies FAITH (Caceres et al. 2019) and LABBP (Schoenthaler et al. 2018). These community health workers assume multiple roles, including educating patients and communities, counseling patients,

monitoring patient health status, linking people with health and social services, and enhancing provider–patient communication, trust, and adherence to care.

Access to Care

Healthy People 2020 and the Institute of Medicine define access to health services as the timely use of personal health services to achieve the best possible health outcomes (Press 1993). Access to care is a complex concept that incorporates five characteristics or dimensions: approachability, acceptability, availability and accommodation, affordability, and appropriateness (Havranek et al. 2015). These concepts can lead to disparities in access and delays in cardiovascular care.

Approachability

Approachability captures one's ability to identify the existence of healthcare services and the potential health impact of service use; it places that responsibility on the patient to utilize this health, and many times, preventive services by being transparent and educating them on the importance of screening and follow-up (Havranek et al. 2015).

Availability, Accommodation, Affordability, Acceptability

Availability and accommodation involve the existence of healthcare services that are physically available and convenient to one's geographic location, flexible hours of opening, availability, and timing of appointments. For example, a study analyzing the cardiology workforce found an uneven geographic distribution of cardiologists, with many rural regions having poor local access.

Affordability represents an individual's economic capacity to spend resources and time on healthcare— direct, indirect, and opportunity costs (Levesque et al. 2013). Apart from this, affordability relates to access and healthcare quality. Public health insurance plans such as Medicaid with low reimbursement may exacerbate disparities as some clinicians do not favor seeing such patients (Havranek et al. 2015). However, clinicians have also voiced a bias, implicit or explicit, toward such patients identifying them as more likely to miss appointments and be less adherent with treatment (Press 1993). Although universal healthcare is one solution to targeting SDoH and poor CV outcomes, it is probably not sufficient on its own.

Up-front costs often deter high-risk, vulnerable patients from initially filling necessary prescriptions, especially when dealing with chronic medical conditions like cardiovascular disease, specifically congestive heart failure. Some cost-sharing

programs have reduced out-of-pocket costs, but reduced costs have had little impact on long-term access to medications (White-Williams et al. 2020). Social workers/case managers can evaluate patient eligibility for different programs to make a prescribed regimen affordable. Acceptability involves cultural and social factors shaping an individual's perception of the various aspects of services and appropriateness of care services (Brownstein et al. 2005). One important example in the current political climate is Hispanic undocumented immigrants who may be more fearful of using health services due to their immigration status, possible language barrier, and fear of perceived racial bias. These challenges are multifaceted and will require improved provisions of insurance coverage and a better distribution of services. These challenges will continue to depend on the value placed on appropriate healthcare for society in light of ever-changing political, economic, and cultural adaptations.

COVID-19, Social Determinants of Health, and Cardiovascular Disease

The Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has had a profound, but unfortunately disparate effect on hospitalization, mortality and economic distress in the United States. Among necessary interventions to overcome this pandemic, especially in HIC, the growth policies which focus on telemedicine may help control CVD risk, even in areas where the population density does not support specialists (Aneja et al. 2011), something particularly more feasible in the days of the novel pandemic. Other interventions included targeted culturally sensitive, literacy-level appropriate education of continued social distancing, wearing masks, and hand washing to minimize exposure (Ferdinand and Nasser 2020), and now effective vaccinations. Although the long-term effects of COVID-19 on the complex relationship of SDoH and CVD are yet undefined, it is likely the pandemic will continue to affect this relationship for decades to come.

Summary

The associations of SDoH and CVD are complex and continue to evolve in relation to ongoing investigations. There are well-delineated data for various areas of focus, yet more research is warranted for others in order to fully establish the role of contemporary findings. Although descriptive findings are essential to understand the relationship between SDoH and CVD, further study of innovative interventions are likely to become the focus of future investigations. As this chapter focused primarily on HICs, work to further define the SDoH–CVD relation in LMICs will likely provide insight into the goals of care for all populations.

References

Access to health care in America. In: Press NA, editor. Washington, DC: Institute of Medicine; 1993.

Andrews MR, Ceasar J, Tamura K, et al. Neighborhood environment perceptions associate with depression levels and cardiovascular risk among middle-aged and older adults: data from the Washington, DC cardiovascular health and needs assessment. Aging Ment Health. 2021;25(11):2078–89.

Aneja S, Ross JS, Wang Y, et al. US cardiologist workforce from 1995 to 2007: modest growth, lasting geographic maldistribution especially in rural areas. Health Aff (Millwood). 2011;30:2301–9.

Bailey ZD, Krieger N, Agénor M, Graves J, Linos N, Bassett MT. Structural racism and health inequities in the USA: evidence and interventions. Lancet. 2017;389:1453–63.

Bairey Merz CN, Pepine CJ, Walsh MN, Fleg JL. Ischemia and no obstructive coronary artery disease (INOCA): developing evidence-based therapies and research agenda for the next decade. Circulation. 2017;135:1075–92.

Barnason S, White-Williams C, Rossi LP, et al. Evidence for therapeutic patient education interventions to promote cardiovascular patient self-management: a scientific statement for healthcare professionals from the American Heart Association. Circ Cardiovasc Qual Outcomes. 2017;10:e000025.

Beatty Moody DL, Waldstein SR, Tobin JN, Cassells A, Schwartz JC, Brondolo E. Lifetime racial/ethnic discrimination and ambulatory blood pressure: the moderating effect of age. Health Psychol. 2016;35:333–42.

Berkman ND, Sheridan SL, Donahue KE, Halpern DJ, Crotty K. Low health literacy and health outcomes: an updated systematic review. Ann Intern Med. 2011;155:97–107.

Bortkiewicz A, Gadzicka E, Siedlecka J, et al. Dietary habits and myocardial infarction in occupationally active men. Int J Occup Med Environ Health. 2019;32:853–63.

Brondolo E. Considering social processes when examining mediators of the effects of discrimination on health. Soc Sci Med. 2018;215:160–2.

Brondolo E, Libby DJ, Denton EG, et al. Racism and ambulatory blood pressure in a community sample. Psychosom Med. 2008;70:49–56.

Brondolo E, Love EE, Pencille M, Schoenthaler A, Ogedegbe G. Racism and hypertension: a review of the empirical evidence and implications for clinical practice. Am J Hypertens. 2011a;24:518–29.

Brondolo E, Hausmann LR, Jhalani J, et al. Dimensions of perceived racism and self-reported health: examination of racial/ethnic differences and potential mediators. Ann Behav Med. 2011b;42:14–28.

Brownstein JN, Bone LR, Dennison CR, Hill MN, Kim MT, Levine DM. Community health workers as interventionists in the prevention and control of heart disease and stroke. Am J Prev Med. 2005;29:128–33.

Bugiardini R, Ricci B, Cenko E, et al. Delayed care and mortality among women and men with myocardial infarction. J Am Heart Assoc. 2017;6:e005968.

Caceres BA, Veldhuis CB, Hickey KT, Hughes TL. Lifetime trauma and cardiometabolic risk in sexual minority women. J Womens Health (Larchmt). 2019;28:1200–17.

Caceres BA, Streed CG Jr, Corliss HL, et al. Assessing and addressing cardiovascular health in LGBTQ adults: a scientific statement from the American Heart Association. Circulation. 2020;142(19):e321–32. https://doi.org/10.1161/Cir.0000000000000914.

Ceasar JN, Ayers C, Andrews MR, et al. Unfavorable perceived neighborhood environment associates with less routine healthcare utilization: data from the Dallas Heart Study. PLoS One. 2020;15:e0230041.

Chen YR, Schulz PJ. The effect of information communication technology interventions on reducing social isolation in the elderly: a systematic review. J Med Internet Res. 2016;18:e18.

Churchwell K, Elkind MSV, Benjamin RM, et al. Call to action: structural racism as a fundamental driver of health disparities: a presidential advisory from the American Heart Association. Circulation. 2020;142(24):e454–68. https://doi.org/10.1161/CIR.0000000000000936.

Claudel SE, Adu-Brimpong J, Banks A, et al. Association between neighborhood-level socioeconomic deprivation and incident hypertension: a longitudinal analysis of data from the Dallas heart study. Am Heart J. 2018;204:109–18.

Claudel SE, Shiroma EJ, Harris TB, et al. Cross-sectional associations of neighborhood perception, physical activity, and sedentary time in community-dwelling, socioeconomically diverse adults. Front Public Health. 2019;7:256.

Connelly PJ, Marie Freel E, Perry C, et al. Gender-affirming hormone therapy, vascular health and cardiovascular disease in transgender adults. Hypertension. 2019;74:1266–74.

Cushman M, Shay CM, Howard VJ, et al. Ten-year differences in women's awareness related to coronary heart disease: results of the 2019 American Heart Association National Survey: a special report from the American Heart Association. Circulation. 2020. https://doi.org/10.1161/Cir.0000000000000907.

Cuthbertson CC, Heiss G, Wright JD, et al. Socioeconomic status and access to care and the incidence of a heart failure diagnosis in the inpatient and outpatient settings. Ann Epidemiol. 2018;28:350–5.

Davila EP, Kuklina EV, Valderrama AL, Yoon PW, Rolle I, Nsubuga P. Prevalence, management, and control of hypertension among US workers: does occupation matter? J Occup Environ Med. 2012;54:1150–6.

Dégano IR, Marrugat J, Grau M, et al. The association between education and cardiovascular disease incidence is mediated by hypertension, diabetes, and body mass index. Sci Rep. 2017;7:12370.

Díez-Villanueva P, Alfonso F. Heart failure in the elderly. J Geriatr Cardiol. 2016;13:115–7.

Dreyer RP, Beltrame JF, Tavella R, et al. Evaluation of gender differences in Door-to-Balloon time in ST-elevation myocardial infarction. Heart Lung Circ. 2013;22:861–9.

Ferdinand KC, Nasser SA. African-American COVID-19 mortality: a sentinel event. J Am Coll Cardiol. 2020;75:2746–8.

Flaskerud JH, Winslow BJ. Conceptualizing vulnerable populations health-related research. Nurs Res. 1998;47:69–78.

Goff DC Jr, Buxton DB, Pearson GD, et al. Implementing the national heart, lung, and blood institute's strategic vision in the division of cardiovascular sciences. Circ Res. 2019;124:491–7.

Greenwood BN, Carnahan S, Huang L. Patient-physician gender concordance and increased mortality among female heart attack patients. Proc Natl Acad Sci U S A. 2018;115:8569–74.

Greer TM, Brondolo E, Brown P. Systemic racism moderates effects of provider racial biases on adherence to hypertension treatment for African Americans. Health Psychol. 2014;33:35–42.

Havranek EP, Mujahid MS, Barr DA, et al. Social determinants of risk and outcomes for cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2015;132:873–98.

Jones BA, Haycraft E, Bouman WP, Arcelus J. The levels and predictors of physical activity engagement within the treatment-seeking transgender population: a matched control study. J Phys Act Health. 2018;15:99–107.

Kershaw KN, Droomers M, Robinson WR, Carnethon MR, Daviglus ML, Monique Verschuren WM. Quantifying the contributions of behavioral and biological risk factors to socioeconomic disparities in coronary heart disease incidence: the MORGEN study. Eur J Epidemiol. 2013;28:807–14.

Kubota Y, Heiss G, MacLehose RF, Roetker NS, Folsom AR. Association of Educational Attainment with lifetime risk of cardiovascular disease: the atherosclerosis risk in communities study. JAMA Intern Med. 2017;177:1165–72.

Levesque JF, Harris MF, Russell G. Patient-centred access to health care: conceptualising access at the interface of health systems and populations. Int J Equity Health. 2013;12:18.

Maraka S, Singh Ospina N, Rodriguez-Gutierrez R, et al. Sex steroids and cardiovascular outcomes in transgender individuals: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2017;102:3914–23.

Mauvais-Jarvis F, Bairey Merz N, Barnes PJ, et al. Sex and gender: modifiers of health, disease, and medicine. Lancet. 2020;396:565–82.

Mayne SL, Moore KA, Powell-Wiley TM, Evenson KR, Block R, Kershaw KN. Longitudinal associations of neighborhood crime and perceived safety with blood pressure: the multi-ethnic study of atherosclerosis (MESA). Am J Hypertens. 2018;31:1024–32.

McCabe SE, Hughes TL, Matthews AK, et al. Sexual orientation discrimination and tobacco use disparities in the United States. Nicotine Tob Res. 2019;21:523–31.

Mehta LS, Beckie TM, DeVon HA, et al. Acute myocardial infarction in women: a scientific statement from the American Heart Association. Circulation. 2016;133:916–47.

Mendy VL, Vargas R, Ogungbe O, Zhang L. Hypertension among Mississippi workers by sociodemographic characteristics and occupation, behavioral risk factor surveillance system. Int J Hypertens. 2020;2020:2401747.

Millett ERC, Peters SAE, Woodward M. Sex differences in risk factors for myocardial infarction: cohort study of UK Biobank participants. BMJ. 2018;363:k4247.

Milner A, Franz B. Anti-black attitudes are a threat to health equity in the United States. J Racial Ethn Health Disparities. 2020;7:169–76.

Moen M, Storr C, German D, Friedmann E, Johantgen M. A review of tools to screen for social determinants of health in the United States: a practice brief. Popul Health Manag. 2020;23(6):422–9.

Molina KM, Estrella ML, Durazo-Arvizu R, et al. Perceived discrimination and physical health-related quality of life: the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) Sociocultural Ancillary Study. Soc Sci Med. 2019;222:91–100.

Moorhead SA, Hazlett DE, Harrison L, Carroll JK, Irwin A, Hoving C. A new dimension of health care: systematic review of the uses, benefits, and limitations of social media for health communication. J Med Internet Res. 2013;15:e85.

Mosquera PA, San Sebastian M, Waenerlund AK, Ivarsson A, Weinehall L, Gustafsson PE. Income-related inequalities in cardiovascular disease from mid-life to old age in a Northern Swedish cohort: a decomposition analysis. Soc Sci Med. 2016;149:135–44.

National action plan to improve health literacy. Washington, DC: U.S. Department of Health and Human Services, Office of Disease Prevention and Health Promotion; 2010.

National standards for culturally and linguistically appropriate services in health and health care. In: US Department of Health and Human Services OoMH, editor. Washington, DC, 2013.

Ndumbe-Eyoh S, Mazzucco A. Social media, knowledge translation, and action on the social determinants of health and health equity: a survey of public health practices. J Public Health Policy. 2016;37:249–59.

Okuda N, Kadota A, Nishi N, et al. Association of work situation with cardiovascular disease mortality risk among working-age Japanese men - a 20-year follow-up of NIPPON DATA90. Circ J. 2019;83:1506–13.

Panza GA, Puhl RM, Taylor BA, Zaleski AL, Livingston J, Pescatello LS. Links between discrimination and cardiovascular health among socially stigmatized groups: a systematic review. PLoS One. 2019;14:e0217623.

Pelletier R, Khan NA, Cox J, et al. Sex versus gender-related characteristics: which predicts outcome after acute coronary syndrome in the young? J Am Coll Cardiol. 2016;67:127–35.

Pinheiro LC, Reshetnyak E, Sterling MR, Levitan EB, Safford MM, Goyal P. Multiple vulnerabilities to health disparities and incident heart failure hospitalization in the REGARDS study. Circ Cardiovasc Qual Outcomes. 2020;13:e006438.

Powell-Wiley TM, Ayers CR, de Lemos JA, et al. Relationship between perceptions about neighborhood environment and prevalent obesity: data from the Dallas Heart Study. Obesity (Silver Spring). 2013;21:E14–21.

Powell-Wiley TM, Moore K, Allen N, et al. Associations of neighborhood crime and safety and with changes in body mass index and waist circumference: the multi-ethnic study of atherosclerosis. Am J Epidemiol. 2017;186:280–8.

Promotion. OoDPaH. Healthy people 2020: social determinants of health; health literacy. Washington, DC: U.S. Department of Health and Human Services; 2020.

Reshetnyak E, Ntamatungiro M, Pinheiro LC, et al. Impact of multiple social determinants of health on incident stroke. Stroke. 2020;51:2445–53.

Roswell RO, Kunkes J, Chen AY, et al. Impact of sex and contact-to-device time on clinical outcomes in acute ST-segment elevation myocardial infarction-findings from the National Cardiovascular Data Registry. J Am Heart Assoc. 2017;6:e004521.

Safford MM, Reshetnyak E, Sterling MR, et al. Number of social determinants of health and fatal and nonfatal incident coronary heart disease in the reasons for geographic and racial differences in stroke (REGARDS) study. Circulation. 2021;143(3):244–53.

Schoenthaler AM, Lancaster KJ, Chaplin W, Butler M, Forsyth J, Ogedegbe G. Cluster randomized clinical trial of FAITH (FAITH-based approaches in the treatment of hypertension) in blacks. Circ Cardiovasc Qual Outcomes. 2018;11:e004691.

Schultz WM, Kelli HM, Lisko JC, et al. Socioeconomic status and cardiovascular outcomes: challenges and interventions. Circulation. 2018;137:2166–78.

Semaga J KM, Shrider EA, Creamer J. Income and poverty in the United States: 2019. United States Census Bureau; 2020.

Serchen J, Doherty R, Atiq O, Hilden D. Racism and health in the United States: a policy statement from the American College of Physicians. Ann Intern Med. 2020;173:556–7.

Strauss M, Foshag P, Leischik R. Prospective evaluation of cardiovascular, cardiorespiratory, and metabolic risk of German office workers in comparison to international data. Int J Environ Res Public Health. 2020;17:1590.

Suglia SF, Campo RA, Brown AGM, et al. Social determinants of cardiovascular health: early life adversity as a contributor to disparities in cardiovascular diseases. J Pediatr. 2020;219:267–73.

Victor RG, Lynch K, Li N, et al. A cluster-randomized trial of blood-pressure reduction in black barbershops. N Engl J Med. 2018;378:1291–301.

Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke statistics-2020 update: a report from the American Heart Association. Circulation. 2020;141:e139–596.

What do we mean by "sex" and "gender". Geneva: Department of Gender, Women and Health, World Health Organization; 2010.

White-Williams C, Rossi LP, Bittner VA, et al. Addressing social determinants of health in the care of patients with heart failure: a scientific statement from the American Heart Association. Circulation. 2020;141:e841–63.

WHO. Closing the Gap in a Generation: Health equity through action on the social determinants of health. World Health Organization, Commission on Social Determinants of Health; 2020.

Xiao Q, Berrigan D, Powell-Wiley TM, Matthews CE. Ten-year change in neighborhood socioeconomic deprivation and rates of total, cardiovascular disease, and cancer mortality in older US adults. Am J Epidemiol. 2018;187:2642–50.

Zhang D, Ritchey MR, Park C, Li J, Chapel J, Wang G. Association between medicaid coverage and income status on health care use and costs among hypertensive adults after enactment of the affordable care act. Am J Hypertens. 2019;32:1030–8.

Zwas DR. Redressing the red dress: rethinking the campaign. Circulation. 2018;137:763–5.

Chapter 20
Stress and Cardiovascular Disease

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Introduction

Cardiovascular disease (CVD) is the leading global cause of death. As of 2019, it accounts for over 17.8 million deaths per year, which is approximately 20% higher than in 2007 (Virani et al. 2021). Furthermore, the burden of risk factors for CVD continues to remain alarmingly high. While there are ample data on common risk factors such as diabetes, hypertension, smoking, and others, the increase in global CVD mortality suggests that novel risk factors and targets for intervention need to be identified. There is growing evidence to suggest that psychosocial stress is significantly associated with CVD. A number of studies have demonstrated the role of stress in both the progression of CVD and the precipitation of acute CVD events.

However, psychosocial stress is complex and heterogeneous, arising from interpersonal relationships, previous trauma, financial constraints, employment-related issues, politics, and discrimination based on race, and gender and other perceived disparities (Fig. 20.1) (Hatch and Dohrenwend 2007; Sternthal et al. 2011).

Even though the association between psychosocial stress and CVD is being increasingly recognized, there continues to be a lack of its adoption in clinical practice as well as development of effective and scalable interventions.

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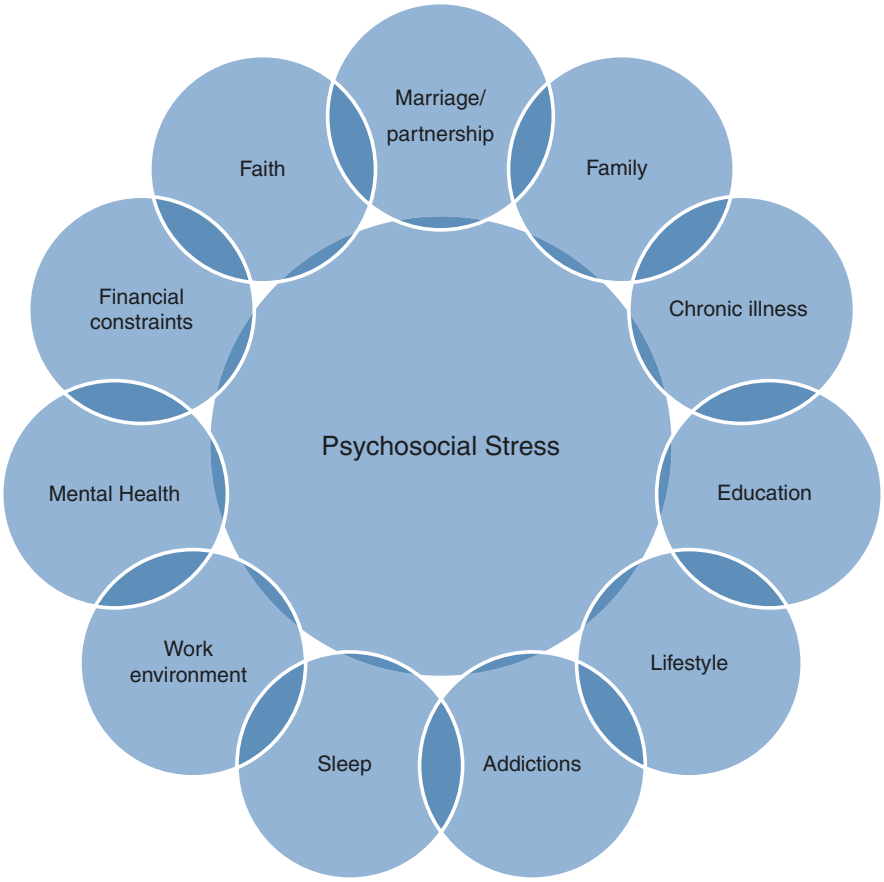

Fig. 20.1 Factors associated with psychosocial stress

The Effect of Stress on Heart Disease

In general, there is greater evidence for acute mental stress as a trigger for CVD events, including angina, acute myocardial infarction, arrhythmias, and sudden cardiac death (Smyth et al. 2017; Smeijers et al. 2017; Mostofsky et al. 2014; Dimsdale 2008). On the other hand, data for stress as a risk factor for developing CVD or influencing outcomes are less robust and gradually increasing.

The INTERHEART Study was a large case-control study that examined 11,119 patients with a first myocardial infarction to 13,648 age- and sex-matched controls in 52 countries (Rosengren et al. 2004). Compared to controls, individuals who sustained a myocardial infarction had a higher prevalence of stress at work, at home, financial stress, and major life events within the preceding year. Individuals who sustained a myocardial infarction reported a higher prevalence of all four stressors compared to controls in the preceding year ($p < 0.001$). Psychosocial stress carried

an odds ratio of 3.49 (99% CI 2.41–5.04) in women and 2.58 (95% CI 2.11–3.14) in men after adjustment for age, sex, and geographic region. In the presence of multiple risk factors such as active smoking status, hypertension, diabetes, ApoB/ApoA1 ratio, and abdominal obesity, the addition of psychosocial stress was associated with an odds ratio of 182.9 (99% CI 132.6–252.2) for an acute myocardial infarction (Fig. 20.2) (Yusuf et al. 2004).

In the Swedish National Patient Registry with a long-term follow-up of 27 years in 136,637 individuals, the hazard ratio for any cardiovascular disease was 1.64 (95% CI 1.45–1.84) during the first year after the diagnosis of a stress-related condition (Song et al. 2019).

In patients with stable coronary heart disease, persistent moderate or greater psychological stress is associated with significantly higher cardiovascular (HR 3.94, 95% CI 2.05–7.56, $p < 0.001$) and all-cause mortality (HR 2.85, 95% CI 1.74–4.66, $p < 0.001$) (Stewart et al. 2017). Mental stress-induced myocardial ischemia is associated with a doubling of the risk of total mortality (Wei et al. 2014).

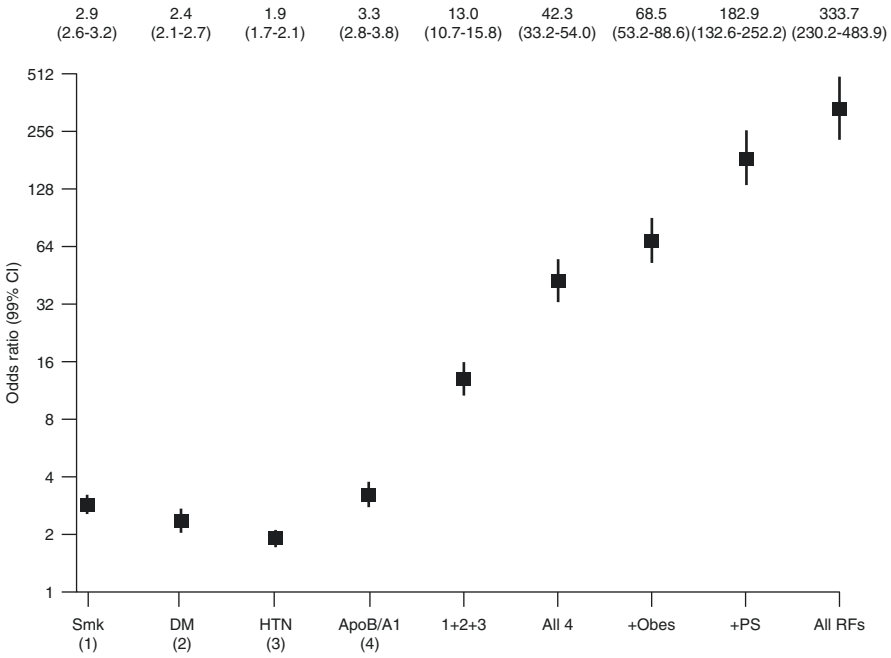

Fig. 20.2 Risk of acute myocardial infarction associated with exposure to multiple risk factors in the Interheart Study. (Reproduced with permission (Yusuf et al. 2004)). Smk smoking, DM diabetes mellitus, HTN hypertension, Obes abdominal obesity, PS psychosocial, RF risk factors. Note the doubling scale on the y axis. The odds ratios are based on current never smoking, top vs. lowest tertile for abdominal obesity, and top vs. lowest quintile for ApoB/ApoA1. If these three are substituted by current and former smoking, top two tertiles for abdominal obesity and top four quintiles for ApoB/ApoA1, then the odds ratio for the combined risk factor is 129·20 (99% CI 90·24–184·99)

Increasing levels and types of stress appear to contribute to worse CVD outcomes. In chronic coronary syndromes, a history of depression is associated with a twofold higher rate of mortality, higher major adverse cardiac events, and worse quality of life (De Luca et al. 2021).

Among cardiovascular disorders, the role of psychological stress appears to be more prominent in its association with arrhythmias such as atrial fibrillation and ventricular tachyarrhythmias. Atrial fibrillation is associated with negative emotions such as anxiety, anger, stress, and sadness (Lampert et al. 2014), whereas decreased anxiety and depression scores may be associated with a diminished AF burden in patients undergoing yoga training (Lakkireddy et al. 2013). Arrhythmias, including atrial fibrillation, supraventricular tachycardia, and nonsustained ventricular tachycardia, were significantly associated with stressful events such as the US Presidential Elections (Rosman et al. 2021).

In patients with implantable cardioverter-defibrillators, ventricular tachyarrhythmias are found to be significantly increased after terrorist attacks (Steinberg et al. 2004). Ventricular arrhythmias are associated with emotional distress and other events that increase the sympathetic tone, with an increase in sudden death related to watching stressful sporting matches (Katz et al. 2006).

In patients with heart failure, high perceived stress and anger were associated with poorer functional status (Endrighi et al. 2019). More than half of the patients presenting with stress cardiomyopathy have neurologic and psychiatric disorders compared to those with acute coronary syndromes (Templin et al. 2015). While no large-scale data are available on the correlation between psychosocial factors and heart failure, there appears to be a bidirectional association with depression. Individuals with depression had a significantly higher risk of developing new-onset heart failure (HR 2.08, 95% CI 1.89–2.28) and those with heart failure had an increased risk for new-onset depression (HR 1.34, CI 1.17–1.54) (Bobo et al. 2020).

Additionally, stress has indirect effects on CVD through the adoption of unfavorable lifestyles, lower self-care with delays in seeking care for symptoms of acute cardiac events, reduced compliance with medications, lower likelihood of adherence to favorable lifestyle changes, and successful participation in cardiac rehabilitation (Kivimäki and Steptoe 2018; Chinnaiyan 2019). Work stress is associated with greater physical inactivity and smoking (Griep et al. 2015), and in the British Whitehall II study, individuals with long-term stress were less likely to adhere to a healthy diet (Chandola et al. 2008).

Mental illness is also significantly associated with cardiovascular disease (De Hert et al. 2018). Schizophrenia, bipolar disorder, major depressive disorder, anxiety, persistent or intense stress, or post-traumatic stress disorders (PTSD) are independently associated with an increased risk for CVD. Conversely, these conditions are common in patients with CVD and may contribute to an increased risk of morbidity and mortality. Nearly 20% of patients with acute coronary syndromes have an associated acute stress disorder, which can evolve into post-traumatic stress disorder (Ginzburg et al. 2003; Edmondson et al. 2012).

Disorders such as anxiety and depression present an increased risk for CVD risk factors such as hypertension as well as higher cardiovascular disease mortality than hypertension alone (Ho et al. 2015). Additionally, mental disorders in conjunction

with hypertension result in increased healthcare resource utilization with a paradoxical contribution to more rapid blood pressure control. Moreover, depressive symptoms are associated with reduced cardiac output, cardiac index, stroke volume, and stroke volume index even after controlling for all associated factors (Vargas et al. 2021). Mental disorders have significant implications on return to work and quality of life. In one large systematic review, patients were more likely to return to work after myocardial infarction when they evaluated their general and mental health highly and had fewer mental health issues (Sun et al. 2021).

An important area of consideration is that of the cardiovascular implications of psychosocial stress resulting from chronic illness. In one study of 3267 adult survivors of childhood cancer, stress and distress were associated with hypertension, new-onset dysrhythmia, and metabolic syndrome independent of known cardiovascular risk factors (Lubas et al. 2021).

COVID-19 Pandemic, Isolation, Stress, and CVD

The COVID-19 pandemic has had many implications on CVD and CVD risk. Significantly worse cardiovascular risk factor control and outcomes have been associated with a combined effect of two phenomena (Lau and McAlister 2021). For one, more patients defer routine risk factor management as a result of a shift from in-person office visits. Second, the unprecedented curtailment of social and economic interaction has led to income loss, unemployment, social isolation, decreased physical activity, as well as increased frequency of depression and anxiety.

The pandemic in turn is associated with worsening of mental health in patients with CVD (Lim et al. 2020). Additionally, a significant increase in the incidence of Takotsubo syndrome or stress cardiomyopathy has been noted during the pandemic. In one systematic review, a 4.5-fold increase in the incidence of Takotsubo syndrome was noted during the COVID-19 pandemic even in individuals without severe acute respiratory syndrome coronavirus 2 infections (O'Keefe et al. 2020).

Long before the COVID-19 pandemic, increasing numbers of American elders were experiencing loneliness and social isolation (National Academies of Sciences E, Medicine 2020). Currently, 43% of US seniors are reporting feeling lonely (Cudjoe et al. 2020). Some US federal agencies have equated this to the risk imposed by smoking 15 cigarettes per day (HRSA.gov n.d.). In addition, social isolation increases the risk of mortality by 45% (Holt-Lunstad and Smith 2016). In a meta-analysis of 148 studies that included 308,849 participants, it was shown that the likelihood of survival goes up by 50% among individuals with strong social connections (Holt-Lunstad et al. 2010). In a recent analysis of the English Longitudinal Study of Ageing, it was shown that the highest levels of loneliness and social isolation were associated with a 30% increased risk of a new diagnosis of CVD and a 48% increased risk of CVD-related hospitalizations (Bu et al. 2020). Based on these and many other observations, screening for social isolation should be an integral part of the cardiovascular evaluation.

Pathophysiology of Stress and Resilience

The acute stress response is characterized by rapid activation of the sympathetic nervous system response. This includes the release of adrenaline and noradrenaline with a direct cardiostimulatory effect via β_1-adrenergic receptors, pressor effects via α_1-adrenergic receptors, stimulation of the pro-inflammatory cascade via release of IL-6, promotion of insulin resistance, and lipolysis. The hypothalamic–pituitary–adrenal (HPA) axis is activated in response to the acute stressor, with the release of cortisol that increases blood glucose levels. The autonomic nervous system and the HPA axis also result in increased platelet activation, fibrinogen levels, and coagulation factors (Kivimäki and Steptoe 2018). Circulating catecholamines stimulate an inflammatory response, particularly with exposure to repeated stress.

Chronic stress-related HPA axis and autonomic nervous system tone are associated with the acceleration of atherosclerosis as well as precipitation of acute CVD events (McEwen 1998). Emerging data demonstrate that there are sex differences in the biological stress response. In the REMIT (Responses of Mental Stress–Induced Myocardial Ischemia to Escitalopram) study among patients with stable ischemic heart disease, women had higher collagen-induced platelet aggregation in response to mental stress compared with men, who demonstrated changes in blood pressure and double product (Samad et al. 2014).

Tawakol et al. reported an inverse relationship between amygdalar activity and arterial inflammation and baseline income among 509 individuals followed over 4 years (Tawakol et al. 2019), suggesting that the relationship between income (low SES) and MACE proceeds through a pathway that includes higher amygdalar activity, bone marrow activity, and arterial inflammation. Accordingly, low income was associated with increased subsequent major adverse cardiac events (HR 0.67 CI 0.47–0.96, $p = 0.029$) presumably through the pathway of increased bone marrow activity.

The association of emotional states with heart disease and other chronic illnesses suggests that the underlying issue is one of low resilience. Resilience is defined as the ability to withstand or recover quickly from difficult conditions, or resistance to stress (Fletcher and Sarkar 2013). However, the adaptive mechanisms to stress depend on the stage of development (child or adult), specific socio-cultural influences, as well as the intensity of the external stressor. Some individuals are easily overwhelmed with day-to-day hassles, while some remain seemingly unscathed even in adversities such as war and terrorist attacks. Psychological resilience is known to play an important role in disease development as well as its prognosis. High resilience is associated with a slower progression of CVD and decreased inflammatory response related to stress (Arrebola-Moreno et al. 2014). Cultivating resilience as a primary and secondary prevention measure in CVD could be effective in promoting long-term health and wellness.

While resilience is commonly thought of as a personality trait, it can also be cultivated over time through various approaches, some of which are discussed

below. Major depressive disorders, PTSD, anxiety, and other stress-related conditions are thought to be the negative manifestations of resilience (Liu et al. 2018a). Emerging data in the biology of psychological resilience demonstrate the relationship between the medial prefrontal cortex and the hippocampus with the hypothalamus–pituitary–adrenal axis, and the roles of various neural pathways in the stress response (Liu et al. 2018b).

Numerous approaches have been used to improve psychological resilience, with nonuniform results. Psychological, behavioral, and pharmacological therapies can foster resilience. However, given the wide variability in the circumstances that lead to lack of resilience, the effect of any of these approaches in a given individual can differ. Further research is needed to understand the relationship between resilience, lifestyle choices that are associated with CVD, and resultant clinical outcomes (Fig. 20.3).

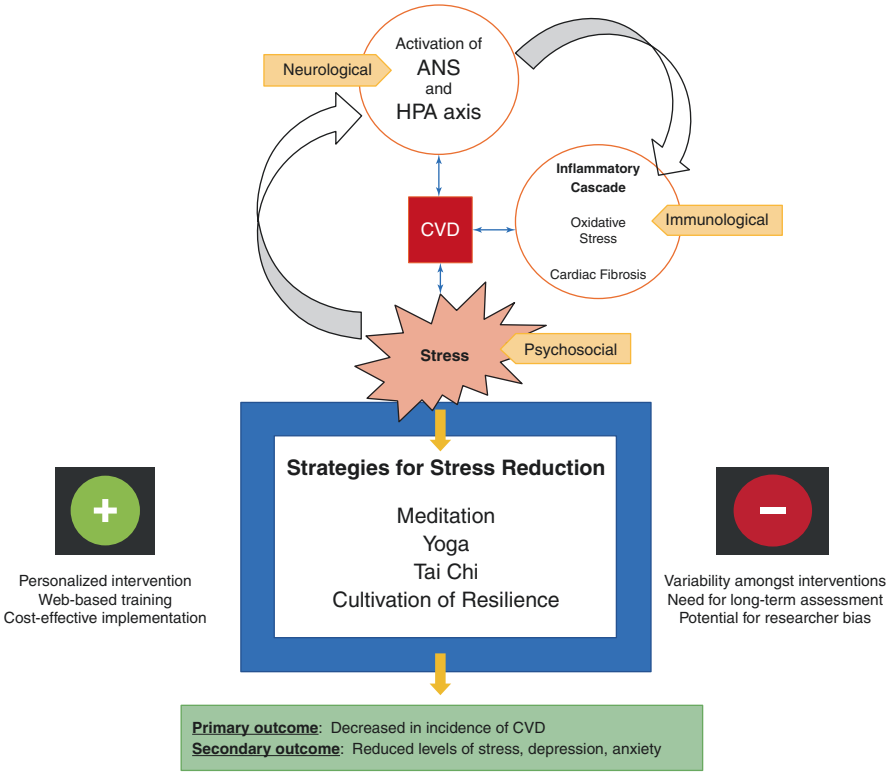

Fig. 20.3 Potential mechanisms of stress and its mitigation. Stress has a bidirectional relationship with cardiovascular disease, mediated by the autonomic nervous system (ANS) and the hypothalamic–pituitary–adrenal (HPA) axis resulting in an inflammatory cascade. Resilience through stress reduction may have implications for cardiovascular disease (CVD) outcomes

Stress Reduction and CVD Prevention

While CVD guidelines do not endorse the use of complementary and alternative medicine (CAM) therapies for secondary prevention, one study demonstrated that nearly one-third of patients report using a CAM modality for improving their quality of life after an acute MI. This list of modalities includes mind–body, biological, and manipulative therapies, although though no association was found between the different types of CAM and health status improvement (Katz et al. 2006).

Lack of uniformity is one of the most limiting factors in examining studies of stress reduction and their relationship with CVD prevention. Since psychosocial stress is multifaceted and largely subjective, it is particularly challenging to apply standard measures to reduce or manage it from the standpoint of improving cardiovascular health.

Not only are there data for numerous stress reduction strategies but also for specific situations and lifestyles. In general, a holistic approach that takes into account heart-healthy behaviors is associated with better CVD outcomes. One way of approaching stress reduction is to examine it from the standpoint of the various facets of life that contribute to stress or its alleviation (Fig. 20.4).

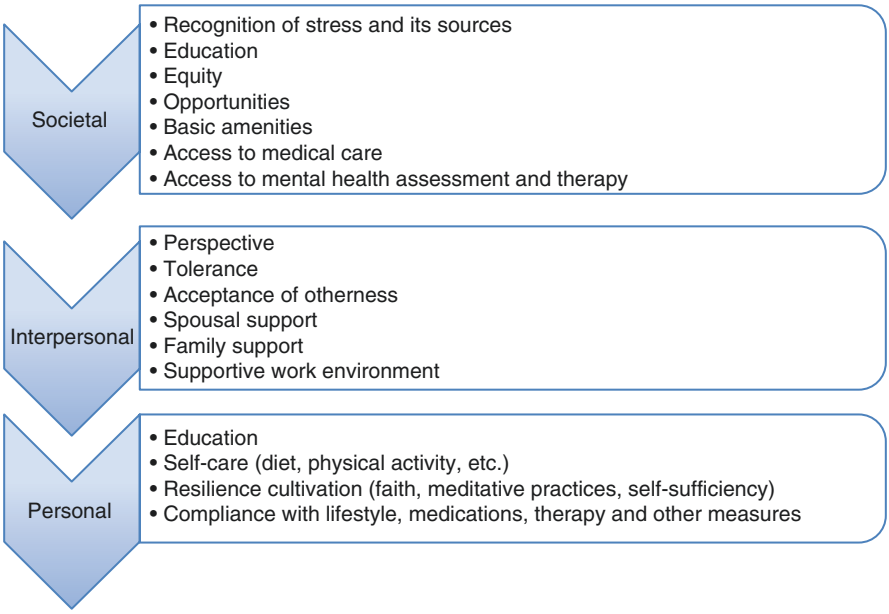

Fig. 20.4 Strategies for stress reduction. Stress reduction requires an examination of strategies applied at the societal, interpersonal, and personal levels

Societal

Two potential strategies are required for reducing stress: strategies that are population-based, and narrower targeted strategies in clinical practice. Population-based strategies can be considered only when stress is recognized as a universal risk factor (Kivimäki and Steptoe 2018). The importance of policies to improve education, job opportunities, basic amenities, social justice, and socioeconomic reform cannot be overstated.

Additionally, recognizing and managing stress must be regarded as a significant aspect of education. Managing stress begins in early childhood through the cultivation of a broad perspective, understanding differences, accepting otherness, cultivating tolerance, self-sufficiency and responsibility, early recognition, and treatment of mental disorders.

Interpersonal

Considering the value of spousal support, the Healing Hearts Together (HHT) intervention is an attachment-based relationship enhancement program that has been studied for couples in which one partner has CVD. It proved beneficial for patients' and partners' relationship quality, mental health, and QoL based on Dyadic Adjustment Scale (DAS), Couple Satisfaction Index (CSI), Hospital Anxiety and Depression Scale (HADS), and the SF-36 (QoL) (Tulloch et al. 2021).

Marital status has been shown to be an important indicator of cardiovascular outcomes, including emergency room readmissions, heart failure recurrence, and self-care (Senturk et al. 2021; Baptiste et al. 2021).

In clinical practice, it is commonly noted that patients with adequate familial support have a more positive outlook toward their own health, are motivated to engage in self-care, and are more compliant with medications and lifestyle prescriptions.

Personal

Education and Self-Care

Several studies have reported a regression in atherosclerotic disease with the use of a comprehensive mind–body program, where stress reduction through meditation is a significant component. Ornish et al. reported that, among 48 patients with moderate-to-severe CAD, those who were randomized to an intensive lifestyle intervention program had significant plaque regression at 5 years compared to those

in the standard of care arm (Ornish et al. 1990). The intensive lifestyle intervention program included a vegetarian diet, aerobic exercise, stress management training through meditation, smoking cessation, and group psychosocial support. This comprehensive lifestyle program (The Ornish Program) has demonstrated an improvement in symptoms, cardiac biomarkers, endothelial function and lower hospitalizations, costs and mortality, compared to standard of care.

Numerous studies have examined the usefulness of yoga in CVD. Yoga is a holistic ancient Eastern Indian practice that has evolved and expanded into several medical applications over the last three decades. Several studies have evaluated the positive effects of yoga on cardiovascular disease as well as risk factors for heart disease such as diabetes, hypertension, smoking, and sedentary lifestyle (Cramer et al. 2014; Desveaux et al. 2015; Yadav et al. 2015). Yoga is also shown to be associated with regression of atherosclerosis (Manchanda et al. 2000; Yogendra et al. 2004). Additionally, by facilitating a sense of awareness in daily activities, mindfulness as well as meditation and pranayama may play important roles in risk factor modification as well as promoting overall health and well-being.

Yoga-based cardiac rehabilitation (CR) has been studied primarily in India with mixed results. Among patients undergoing coronary artery bypass grafting, Raghuram et al. (2014) demonstrated a significant improvement in left ventricular ejection fraction, body mass index, blood glucose, perceived stress, anxiety, and depression over a period of 1 year in a yoga-based CR program compared to conventional CR. This yoga-based CR integrated the various limbs of traditional yoga. These constitute the eightfold path of moral or ethical injunctions (nonviolence, truth, nonstealing, celibacy, and nonclinging), virtues (purity, contentment, perseverance, self-reflection, and devotion), body postures, regulation of breath (known as pranayama), and meditation. At 5 years, there was a significant improvement in physical, mental and environmental health, perceived stress, and negative affect (Amaravathi et al. 2018).

Most recently, Prabhakaran et al. sought to evaluate the effects of yoga-based CR (Yoga-CaRe) on major cardiovascular events and self-rated health in a multicenter randomized controlled trial. The trial was conducted in 24 medical centers across India. This study recruited 3959 patients with acute myocardial infarction with a median and minimum follow-up of 22 and 6 months. Patients were individually randomized to receive either a Yoga-CaRe program (n = 1970) or enhanced standard care involving educational advice. Yoga-CaRe improved self-rated health and return to preinfarct activities after acute myocardial infarction, but the trial lacked statistical power to show a difference in MACE (Prabhakaran et al. 2020).

In general, an increase in vagal tone and reduction in autonomic fluctuation are thought to be the likely mechanisms of how yoga reduces arrhythmia burden, improves hemodynamic parameters (such as resting HR and BP), and reduces symptoms (Akella et al. 2020).

In one large study, 37 randomized controlled trials were included in a systematic review and 32 in a meta-analysis. Compared to nonexercise controls, yoga showed

significant improvement for body mass index, systolic and diastolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and heart rate but not fasting blood glucose nor glycosylated hemoglobin (Chu et al. 2016).

Decreased anxiety and depression scores noted with a 6-month yoga training among patients with atrial fibrillation were associated with a decreased arrhythmic burden (Lakkireddy et al. 2013).

Although numerous small studies have demonstrated benefits of yoga in the prevention and prognosis of CVD, the data are challenging to apply in large populations because of the diversity of practices and techniques included under the umbrella term of "yoga."

Similarly, numerous studies of Tai Chi have demonstrated a prognostic benefit in CVD such as an improvement in mindfulness (Salmoirago-Blotcher et al. 2021).

Resilience Cultivation

Numerous studies have demonstrated the benefits of meditation, with long-standing effects on neurophysiology and neuroanatomy (Levine et al. 2017). Meditation has been shown to be associated with neuroplasticity, with the development of novel neural circuits and alteration in the default mode network, which is thought to be responsible for the constant self-referencing rumination that is the hallmark of stressful states. Meditation is associated with lowered blood pressure, presumably related to lowered sympathetic activity and other autonomic nervous system-related activity resulting from neuroplasticity (Levine et al. 2017). A few small studies have demonstrated that meditation was more effective than group counseling for smoking cessation. In one randomized controlled trial among African American patients with established CVD, Transcendental Meditation (TM) was associated with a 48% risk reduction in all-cause mortality at 5.4 years compared to the control group (Schneider et al. 2012). While smaller nonrandomized studies demonstrated improved insulin sensitivity, endothelial function, and reversal of ischemia, data on the association between meditation and hard CVD end-points are lacking in large, randomized trials.

Many significant limitations must be acknowledged in the area of research on meditation. The first issue relates to the availability of a range of meditation techniques that differ in their effect on various psychological, neurophysiological, and neuroanatomical parameters. The second is that most studies are conducted by researchers who may have a strong belief in certain techniques and are avid meditators themselves, with inadvertent introduction of bias. The third limitation is that there appears to be a dose–response relationship with meditation, and the benefits are cumulative over the long term. Therefore, although it is a low-cost intervention, long-term adherence is better-aided through ongoing group support and concomitant coaching in other lifestyle changes such as diet and exercise; the establishment of such structured programs can be resource-intensive.

Chronic and unrelenting illness like CVD can result in a rearrangement of one's thinking and refocus attention on the meaning of life, purpose, and relationship to self, family, and community (Chinnaiyan et al. 2021). Illness can and does prompt the mending of relationships and reprioritizing life to align with what one holds to be most important. This shift of perspective can have unquantifiable effects on compliance, self-care, and indirectly on clinical outcomes.

There is a significant overlap in spiritual, religious, and meditative practices examined above. In the Nurses' Health Study featuring 74,534 women participants, attending a religious service more than once per week was associated with 33% lower all-cause mortality compared with those who had never attended religious services (HR = 0.67, 95% CI 0.62–0.71; $p < 0.001$) (Li et al. 2016).

Gratitude, spiritual well-being, and cultivation of psychological resilience have been associated with improved outcomes in heart failure and acute coronary syndromes (Arrebola-Moreno et al. 2014; Mills et al. 2015).

Clinical Implications

Despite the importance of its association with CVD, psychosocial stress is not included in risk scoring algorithms, with no widespread use of available measures in clinical cardiology practice. Moreover, there are no large or scalable interventions available in clinical practice.

With the growing evidence of its potentially significant and independent association with CVD, psychosocial stress must be included in clinical risk assessment and prevention counseling. Mitigating stress and cultivation of resilience should be considered routinely in CVD prevention since many of the risk factors are dependent on modifying behavior.

Targeted therapy in cardiology practice involves screening for stress, referral to psychological or behavioral therapy or to other interventions such as meditation, holistic self-care programs, yoga, Tai-chi, and other complementary approaches. Asking patients about stress, listening in a nonjudgmental fashion, not hurrying through clinic visits, and providing compassionate advice can be extremely helpful with downstream ramifications on adherence to lifestyle recommendations and medications, and overall clinical outcomes.

Web-based stress reduction programs can be effective and scalable, and easier to implement in the context of a busy clinical practice. In one meta-analysis, guided web-based interventions were effective for stress reduction over 6 months (Heber et al. 2017). Telephone-delivered positive psychology interventions can be useful, as demonstrated in one study of 164 post-ACS patients (Feig et al. 2021).

Larger studies with longer follow-up are needed to assess the effectiveness of easily implementable strategies for stress reduction.

Summary

Psychosocial stress is ubiquitous and multifaceted, with societal, interpersonal, and personal causes. There is growing evidence that psychosocial stress is both a significant risk factor for and a result of CVD. Recognition of stress and addressing it in clinical practice is crucial for improving clinical outcomes and quality of life. Despite an increasing body of data on stress and CVD, there are no large-scale data, especially for scalable interventions, which are as varied as its causes. Stress mitigation must occur at societal, interpersonal, and personal levels. Most available data for stress management fall in the personal category. Larger studies are required with the application of standardized approaches that can be easily adopted in clinical practice.

References

Akella K, Kanuri SH, Murtaza G, G Della Rocca D, Kodwani N, K Turagam M, et al. Impact of yoga on cardiac autonomic function and arrhythmias. J Atr Fibrillation. 2020;13(1):2408.

Amaravathi E, Ramarao NH, Raghuram N, Pradhan B. Yoga-based postoperative cardiac rehabilitation program for improving quality of life and stress levels: fifth-year follow-up through a randomized controlled trial. Int J Yoga. 2018;11(1):44–52.

Arrebola-Moreno A, Garcia-Retamero R, Catena A, Marfil-Alvarez R, Ramirez-Hernandez JA. On the protective effect of resilience in patients with acute coronary syndrome. Int J Clin Health Psychol. 2014;14(2):111–9.

Baptiste DL, Turkson-Ocran RA, Han HR, Himmelfarb CD, Commodore-Mensah Y. Social determinants of emergency department visits among persons diagnosed with coronary heart disease and stroke. Ethn Dis. 2021;31(1):41–6.

Bobo WV, Ryu E, Petterson TM, Lackore K, Cheng Y, Liu H, et al. Bi-directional association between depression and HF: an electronic health records-based cohort study. J Comorb. 2020;10:2235042X20984059.

Bu F, Zaninotto P, Fancourt D. Longitudinal associations between loneliness, social isolation and cardiovascular events. Heart. 2020;106(18):1394–9.

Chandola T, Britton A, Brunner E, Hemingway H, Malik M, Kumari M, et al. Work stress and coronary heart disease: what are the mechanisms? Eur Heart J. 2008;29(5):640–8.

Chinnaiyan KM. Role of stress management for cardiovascular disease prevention. Curr Opin Cardiol. 2019;34(5):531–5.

Chinnaiyan KM, Revankar R, Shapiro MD, Kalra A. Heart, mind, and soul: spirituality in cardiovascular medicine. Eur Heart J. 2021;42(31):2965–8.

Chu P, Gotink RA, Yeh GY, Goldie SJ, Hunink MG. The effectiveness of yoga in modifying risk factors for cardiovascular disease and metabolic syndrome: a systematic review and meta-analysis of randomized controlled trials. Eur J Prev Cardiol. 2016;23(3):291–307.

Cramer H, Lauche R, Haller H, Steckhan N, Michalsen A, Dobos G. Effects of yoga on cardiovascular disease risk factors: a systematic review and meta-analysis. Int J Cardiol. 2014;173(2):170–83.

Cudjoe TKM, Roth DL, Szanton SL, Wolff JL, Boyd CM, Thorpe RJ. The epidemiology of social isolation: national health and aging trends study. J Gerontol B Psychol Sci Soc Sci. 2020;75(1):107–13.

De Hert M, Detraux J, Vancampfort D. The intriguing relationship between coronary heart disease and mental disorders. Dialogues Clin Neurosci. 2018;20(1):31–40.

De Luca L, Temporelli PL, Amico AF, Gonzini L, Uguccioni M, Varani E, et al. Impact of history of depression on 1-year outcomes in patients with chronic coronary syndromes: an analysis of a contemporary, prospective, nationwide registry. Int J Cardiol. 2021;331:273–80.
Desveaux L, Lee A, Goldstein R, Brooks D. Yoga in the management of chronic disease: a systematic review and meta-analysis. Med Care. 2015;53(7):653–61.
Dimsdale JE. Psychological stress and cardiovascular disease. J Am Coll Cardiol. 2008;51(13):1237–46.
Edmondson D, Richardson S, Falzon L, Davidson KW, Mills MA, Neria Y. Posttraumatic stress disorder prevalence and risk of recurrence in acute coronary syndrome patients: a meta-analytic review. PLoS One. 2012;7(6):e38915.
Endrighi R, Dimond AJ, Waters AJ, Dimond CC, Harris KM, Gottlieb SS, et al. Associations of perceived stress and state anger with symptom burden and functional status in patients with heart failure. Psychol Health. 2019;34(10):1250–66.
Feig EH, Celano CM, Massey CN, Chung WJ, Romero P, Harnedy LE, et al. Association of midlife status with response to a positive psychology intervention in patients with acute coronary syndrome. J Acad Consult Liaison Psychiatry. 2021;62(2):220–7.
Fletcher D, Sarkar M. Psychological resilience: a review and critique of definitions, concepts, and theory. Eur Psychol. 2013;18:12–23.
Ginzburg K, Solomon Z, Koifman B, Keren G, Roth A, Kriwisky M, et al. Trajectories of posttraumatic stress disorder following myocardial infarction: a prospective study. J Clin Psychiatry. 2003;64(10):1217–23.
Griep RH, Nobre AA, Alves MG, da Fonseca Mde J, Cardoso Lde O, Giatti L, et al. Job strain and unhealthy lifestyle: results from the baseline cohort study, Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). BMC Public Health. 2015;15:309.
Hatch SL, Dohrenwend BP. Distribution of traumatic and other stressful life events by race/ethnicity, gender, SES and age: a review of the research. Am J Community Psychol. 2007;40(3–4):313–32.
Heber E, Ebert DD, Lehr D, Cuijpers P, Berking M, Nobis S, et al. The benefit of web- and computer-based interventions for stress: a systematic review and meta-analysis. J Med Internet Res. 2017;19(2):e32.
Ho AK, Thorpe CT, Pandhi N, Palta M, Smith MA, Johnson HM. Association of anxiety and depression with hypertension control: a US multidisciplinary group practice observational study. J Hypertens. 2015;33(11):2215–22.
Holt-Lunstad J, Smith TB. Loneliness and social isolation as risk factors for CVD: implications for evidence-based patient care and scientific inquiry. Heart. 2016;102(13):987–9.
Holt-Lunstad J, Smith TB, Layton JB. Social relationships and mortality risk: a meta-analytic review. PLoS Med. 2010;7(7):e1000316.
HRSA.gov. The loneliness epidemic. n.d. Available from: https://www.hrsa.gov/enews/past-issues/2019/january-17/loneliness-epidemic.
Katz E, Metzger JT, Marazzi A, Kappenberger L. Increase of sudden cardiac deaths in Switzerland during the 2002 FIFA World Cup. Int J Cardiol. 2006;107(1):132–3.
Kivimäki M, Steptoe A. Effects of stress on the development and progression of cardiovascular disease. Nat Rev Cardiol. 2018;15(4):215–29.
Lakkireddy D, Atkins D, Pillarisetti J, Ryschon K, Bommana S, Drisko J, et al. Effect of yoga on arrhythmia burden, anxiety, depression, and quality of life in paroxysmal atrial fibrillation: the YOGA My Heart Study. J Am Coll Cardiol. 2013;61(11):1177–82.
Lampert R, Jamner L, Burg M, Dziura J, Brandt C, Liu H, et al. Triggering of symptomatic atrial fibrillation by negative emotion. J Am Coll Cardiol. 2014;64(14):1533–4.
Lau D, McAlister FA. Implications of the COVID-19 pandemic for cardiovascular disease and risk factor management. Can J Cardiol. 2021;37(5):722–32.
Levine GN, Lange RA, Bairey-Merz CN, Davidson RJ, Jamerson K, Mehta PK, et al. Meditation and cardiovascular risk reduction: a scientific statement from the American Heart Association. J Am Heart Assoc. 2017;6(10):e002218.

Li S, Stampfer MJ, Williams DR, VanderWeele TJ. Association of religious service attendance with mortality among women. JAMA Intern Med. 2016;176(6):777–85.
Lim SL, Woo KL, Lim E, Ng F, Chan MY, Gandhi M. Impact of COVID-19 on health-related quality of life in patients with cardiovascular disease: a multi-ethnic Asian study. Health Qual Life Outcomes. 2020;18(1):387.
Liu N, Liu S, Yu N, Peng Y, Wen Y, Tang J, et al. Correlations among psychological resilience, self-efficacy, and negative emotion in acute myocardial infarction patients after percutaneous coronary intervention. Front Psych. 2018a;9:1.
Liu H, Zhang C, Ji Y, Yang L. Biological and psychological perspectives of resilience: is it possible to improve stress resistance? Front Hum Neurosci. 2018b;12:326.
Lubas MM, Wang M, Jefferies JL, Ness KK, Ehrhardt MJ, Krull KR, et al. The contribution of stress and distress to cardiovascular health in adult survivors of childhood cancer. Cancer Epidemiol Biomark Prev. 2021;30(2):286–94.
Manchanda SC, Narang R, Reddy KS, Sachdeva U, Prabhakaran D, Dharmanand S, et al. Retardation of coronary atherosclerosis with yoga lifestyle intervention. J Assoc Physicians India. 2000;48(7):687–94.
McEwen BS. Protective and damaging effects of stress mediators. N Engl J Med. 1998;338(3):171–9.
Mills PJ, Redwine L, Wilson K, Pung MA, Chinh K, Greenberg BH, et al. The role of gratitude in spiritual well-being in asymptomatic heart failure patients. Spiritual Clin Pract (Wash D C). 2015;2(1):5–17.
Mostofsky E, Penner EA, Mittleman MA. Outbursts of anger as a trigger of acute cardiovascular events: a systematic review and meta-analysis. Eur Heart J. 2014;35(21):1404–10.
National Academies of Sciences E, Medicine. Social isolation and loneliness in older adults: opportunities for the health care system. Washington, DC: The National Academies Press; 2020. 316 p.
O'Keefe EL, Torres-Acosta N, O'Keefe JH, Sturgess JE, Lavie CJ, Bybee KA. Takotsubo syndrome: cardiotoxic stress in the COVID era. Mayo Clin Proc Innov Qual Outcomes. 2020;4(6):775–85.
Ornish D, Brown SE, Scherwitz LW, Billings JH, Armstrong WT, Ports TA, et al. Can lifestyle changes reverse coronary heart disease? The Lifestyle Heart Trial. Lancet. 1990;336(8708):129–33.
Prabhakaran D, Chandrasekaran AM, Singh K, Mohan B, Chattopadhyay K, Chadha DS, et al. Yoga-based cardiac rehabilitation after acute myocardial infarction: a randomized trial. J Am Coll Cardiol. 2020;75(13):1551–61.
Raghuram N, Parachuri VR, Swarnagowri MV, Babu S, Chaku R, Kulkarni R, et al. Yoga based cardiac rehabilitation after coronary artery bypass surgery: one-year results on LVEF, lipid profile and psychological states – a randomized controlled study. Indian Heart J. 2014;66(5):490–502.
Rosengren A, Hawken S, Ounpuu S, Sliwa K, Zubaid M, Almahmeed WA, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364(9438):953–62.
Rosman L, Salmoirago-Blotcher E, Mahmood R, Yang H, Li Q, Mazzella AJ, et al. Arrhythmia risk during the 2016 US presidential election: the cost of stressful politics. J Am Heart Assoc. 2021;10:e020559.
Salmoirago-Blotcher E, Trivedi D, Dunsiger S. Tai Chi practice and change in exercise habits in survivors of acute coronary syndromes: is mindfulness a possible mechanism? Explore (NY). 2021;17(5):475–8.
Samad Z, Boyle S, Ersboll M, Vora AN, Zhang Y, Becker RC, et al. Sex differences in platelet reactivity and cardiovascular and psychological response to mental stress in patients with stable ischemic heart disease: insights from the REMIT study. J Am Coll Cardiol. 2014;64(16):1669–78.
Schneider RH, Grim CE, Rainforth MV, Kotchen T, Nidich SI, Gaylord-King C, et al. Stress reduction in the secondary prevention of cardiovascular disease: randomized, controlled trial

of transcendental meditation and health education in Blacks. Circ Cardiovasc Qual Outcomes. 2012;5(6):750–8.
Senturk B, Kaya H, Celik A, Bekar L, Gungor H, Zoghi M, et al. Marital status and outcomes in chronic heart failure: does it make a difference of being married, widow or widower? North Clin Istanb. 2021;8(1):63–70.
Smeijers L, Mostofsky E, Tofler GH, Muller JE, Kop WJ, Mittleman MA. Anxiety and anger immediately prior to myocardial infarction and long-term mortality: characteristics of high-risk patients. J Psychosom Res. 2017;93:19–27.
Smyth A, O'Donnell M, Yusuf S, Investigators I. Response by Smyth et al to letters regarding article, "Physical activity and anger or emotional upset as triggers of acute myocardial infarction: the INTERHEART study". Circulation. 2017;135(10):e644–e5.
Song H, Fang F, Arnberg FK, Mataix-Cols D, Fernández de la Cruz L, Almqvist C, et al. Stress related disorders and risk of cardiovascular disease: population based, sibling controlled cohort study. BMJ. 2019;365:l1255.
Steinberg JS, Arshad A, Kowalski M, Kukar A, Suma V, Vloka M, et al. Increased incidence of life-threatening ventricular arrhythmias in implantable defibrillator patients after the World Trade Center attack. J Am Coll Cardiol. 2004;44(6):1261–4.
Sternthal MJ, Slopen N, Williams DR. Racial Disparities in Health: how much does stress really matter? Du Bois Rev. 2011;8(1):95–113.
Stewart RAH, Colquhoun DM, Marschner SL, Kirby AC, Simes J, Nestel PJ, et al. Persistent psychological distress and mortality in patients with stable coronary artery disease. Heart. 2017;103(23):1860–6.
Sun W, Gholizadeh L, Perry L, Kang K, Heydari M. Factors associated with return to work following myocardial infarction: a systematic review of observational studies. J Clin Nurs. 2021;30(3–4):323–40.
Tawakol A, Osborne MT, Wang Y, Hammed B, Tung B, Patrich T, et al. Stress-associated neurobiological pathway linking socioeconomic disparities to cardiovascular disease. J Am Coll Cardiol. 2019;73(25):3243–55.
Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, et al. Clinical features and outcomes of takotsubo (stress) cardiomyopathy. N Engl J Med. 2015;373(10):929–38.
Tulloch H, Johnson S, Demidenko N, Clyde M, Bouchard K, Greenman PS. An attachment-based intervention for patients with cardiovascular disease and their partners: a proof-of-concept study. Health Psychol. 2021;40(12):909–19.
Vargas EA, Patel RB, Medina-Lezama J, Chirinos DA. Depressive symptoms are associated with reduced cardiac function among hispanics: results from the PREVENCION study. Int J Behav Med. 2021;28(5):531–9.
Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, et al. Heart disease and stroke statistics-2021 update: a report from the American Heart Association. Circulation. 2021;143(8):e254–743.
Wei J, Rooks C, Ramadan R, Shah AJ, Bremner JD, Quyyumi AA, et al. Meta-analysis of mental stress-induced myocardial ischemia and subsequent cardiac events in patients with coronary artery disease. Am J Cardiol. 2014;114(2):187–92.
Yadav A, Singh S, Singh K, Pai P. Effect of yoga regimen on lung functions including diffusion capacity in coronary artery disease patients: a randomized controlled study. Int J Yoga. 2015;8(1):62–7.
Yogendra J, Yogendra HJ, Ambardekar S, Lele RD, Shetty S, Dave M, et al. Beneficial effects of yoga lifestyle on reversibility of ischaemic heart disease: caring heart project of International Board of Yoga. J Assoc Physicians India. 2004;52:283–9.
Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364(9438):937–52.

Chapter 21
Polygenic Risk Scores

Mette Christoffersen and Anne Tybjærg-Hansen

Introduction to Polygenic Risk Scores

Atherosclerosis and coronary artery disease (CAD) are caused by the cumulative effects of a variety of risk factors and their interactions. Some risk factors (e.g., smoking status and physical inactivity) are acquired, while others are partly or completely genetically determined (e.g., gender and plasma lipoprotein(a)). Since CAD is highly heritable (Zdravkovic et al. 2002), genetically determined risk factors have long been known to play a significant role for the development and clinical manifestations of atherosclerosis. The genetic basis for atherosclerosis and CAD has however until recently been limited to the classical monogenic understanding, which is characterized by the presence of rare genetic variants with large effects and a strong correlation to the risk phenotype. The technological advances over the past decade have enabled faster and more comprehensive genetic analysis with a simultaneous lowering of costs. This has resulted in a better understanding of the genetic determinants of atherosclerosis and CAD – thus increasing the interest in and demands for polygenic risk scores (PRSs) to evaluate the genetic susceptibility for developing these diseases.

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Rationale for Using Polygenic Risk Scores

In addition to the classical monogenic determinants of atherosclerosis and CAD, polygenic inheritance has also been shown to play a role – as it is shown for a wide spectrum of common diseases. Polygenic inheritance is characterized by the simultaneous presence of numerous common genetic variants, each with a smaller effect size and a weaker correlation to the risk phenotype compared to the classical monogenic variants. These variants can then be combined into a PRS to identify individuals with a high polygenic risk (Fig. 21.1).

Recent studies have demonstrated the potential impact of polygenic inheritance in CAD. First, the risk of having extreme LDL cholesterol levels was roughly similar in individuals with a high polygenic risk or a monogenic mutation known to cause familial hypercholesterolemia, but individuals with high polygenic risk were 10 times more common. Second, polygenic inheritance accounts for an up to 20-fold larger proportion of individuals with CAD compared to classical monogenic variants known to cause familial hypercholesterolemia (Natarajan et al. 2018; Khera

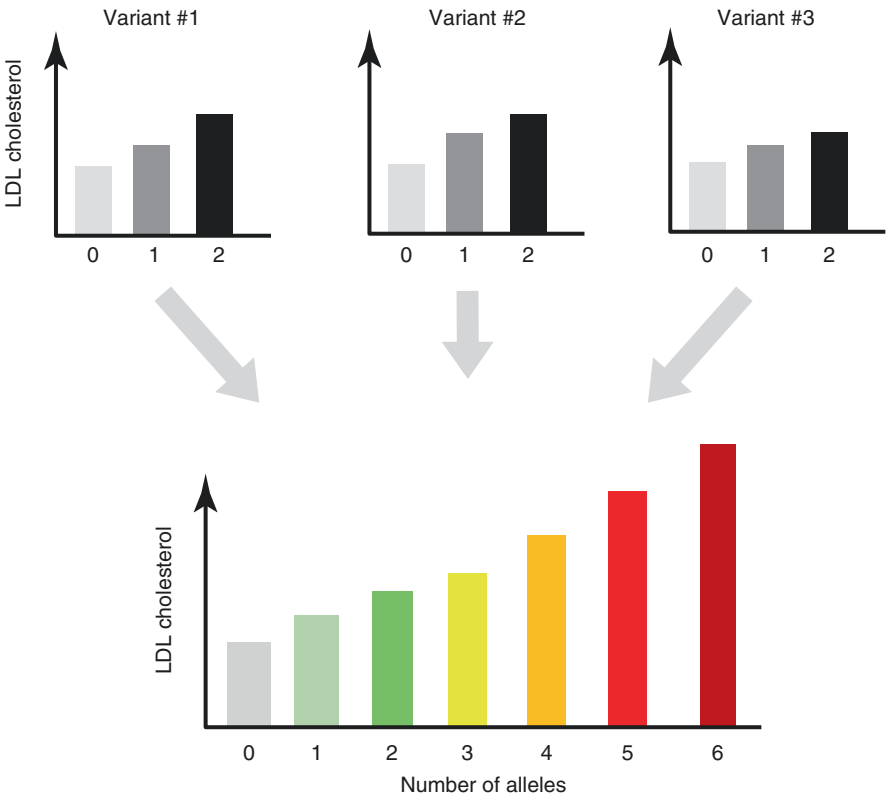

Fig. 21.1 Schematic overview of the combination of variant alleles into a simple polygenic risk score

et al. 2018). These observations suggest that the polygenic risk outweighs the monogenic risk for atherosclerosis and CAD on the population level. Finally, polygenic risk additionally augments the risk conferred by classical monogenic risk variants (Fahed et al. 2020).

On the individual level, it is important to notice that individuals with a high polygenic risk for CAD will typically not be caught by the classical risk assessment algorithms for primary prevention of CAD. A recent study found that current guideline-based clinical risk assessment algorithms for primary prevention of CAD did not optimally predict risk in young people at high polygenic risk (Aragam et al. 2020). This is mainly due to age being the primary risk factor for CAD, leading to an inherent estimation of low risk in young individuals with the current risk algorithms.

To sum up, the development and implementation of PRSs in clinical practice has several advantages. First, PRSs can identify more individuals at high risk of CAD compared to the classical monogenic variants (Natarajan et al. 2018; Khera et al. 2018). Second, PRSs may capture individuals with a high PRS who are typically not captured by classical risk assessment algorithms used to identify individuals eligible for primary prevention (Aragam et al. 2020). This is especially important since individuals at high genetic risk, due to the lifetime exposure, usually have a more severe phenotype compared to individuals at low genetic risk with similar risk factors (Khera et al. 2016a). Third, high polygenic risk contributes independently to the risk of CAD conferred by lifestyle risk factors (Khera et al. 2016b). Finally, PRSs have recently been shown to identify subgroups of patients who are likely to benefit more from lipid-lowering therapy (Khera et al. 2018; Marston et al. 2020; Damask et al. 2020). These findings may impact the treatment strategy for individuals at high polygenic risk for CAD, who may specifically benefit from earlier onset of lifestyle changes and pharmaceutical treatment, intensive treatment, and a comprehensive approach targeting several modifiable risk factors simultaneously (summarized in Table 21.1).

Table 21.1 Treatment strategy for individuals at high polygenic risk for CAD (Khera et al. 2016a, b; Lechner et al. 2020; Christoffersen and Tybjærg-Hansen 2021)

Treatment strategy	Argument
The earlier the better Lifestyle changes Pharmaceutical treatment	Earlier onset of disease manifestations due to lifelong exposure to risk Classical risk assessment algorithms will not capture young individuals at high polygenic risk
The lower the better Narrower treatment targets	The phenotype is more severe compared to individuals at low genetic risk with the same risk profile due to lifetime exposure of genetic risk
The broader the better Targeting several risk factors	Genetic risk contributes independently to the risk conferred by lifestyle risk factors Targeting several lifestyle risk factors at once reduces the risk of CAD substantially regardless of the individuals genetic risk profile – however the absolute risk reduction is strongest in individuals at high genetic risk.

While most PRSs have focused on predicting disease risk, examples of risk scores directed toward prediction of disease prognosis also exist. Furthermore, PRSs have recently been investigated as a tool to guide therapeutic treatment toward high-respondent groups of patients (Marston et al. 2020; Damask et al. 2020; Natarajan et al. 2017).

Construction of Polygenic Risk Scores

The evolution of genome-wide association studies (GWAS) has been the major driver for development of PRSs. GWAS are observational studies of millions of common genetic variants across the entire genome in cases and controls for a specific trait or disease. GWAS are therefore able to identify genetic variants which differ by their frequency in cases and controls, thus marking an association to the trait or disease being investigated. The major advantage of a GWAS is the unbiased nature regarding prior biological knowledge of the investigated disease and genomic loci of interest. Since the publication of the first GWAS in 2005, the development has been massive with a continuous increase in sample sizes, number of genetic variants included in the studies, and the number of novel risk loci identified belonging to either known and unknown biological pathways (Klein et al. 2005; Buniello et al. 2019). Usually, these novel risk loci are individually characterized by small effect sizes with correspondingly low predictive power for the trait of interest. These findings however substantiated the concept of polygenic inheritance of most common traits and diseases and furthermore paved the way for the development of PRSs to assess the potentially large and clinically relevant combined effects of all risk loci.

PRSs are usually constructed from GWAS summary statistics data which are publicly available. These data consist of a beta coefficient for quantitative traits such as LDL cholesterol levels or an odds ratio for disease endpoints such as CAD, which describes the magnitude and direction of the association for each effect allele. The strength of the association is described by an associated P-value. A PRS counts the number of effect alleles (either 0, 1, or 2 at each risk locus) for each individual and multiplies the count by the corresponding effect size derived from GWAS summary statistics data. A higher PRS indicates a greater accumulation of risk-associated genetic variants in an individual. On the population level, a distribution of the sums of the weighted effect alleles is observed. In situations where there is a significant polygenic contribution to the phenotype, the cases will on average have a higher PRS compared to healthy controls, thus the distribution for the cases is shifted to the right compared to the distribution for the controls. A relevant threshold cutoff can subsequently be used to identify individuals at high polygenic risk (Fig. 21.2).

Despite this overall simple approach, there are many things to consider when constructing a PRS (Table 21.2). First, the study populations must be selected and described in detail. This should include the study design, participant demographics, ancestral background, the phenotype of interest, and the degree of missing data. Second, the development of the PRS requires a comprehensive description

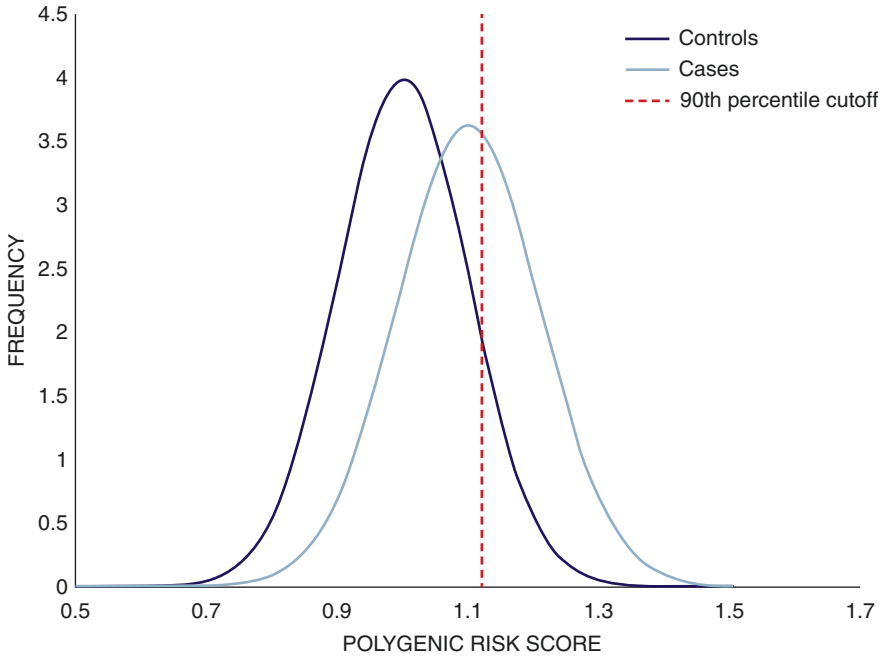

Fig. 21.2 Polygenic risk score distributions in cases (light blue) and controls (dark blue). The distribution of the polygenic risk score is shifted toward the right in cases. The dashed red line indicates a cutoff indicative of high polygenic risk set at the 90th percentile in the controls. A larger proportion of cases exceed this threshold

Table 21.2 Relevant considerations for polygenic risk scores (Wand et al. 2021; Choi et al. 2020; Dron and Hegele 2019)

Choice and characteristics of the study populations
Training sample for the construction of the polygenic risk score
Independent validation sample to confirm the validity of the polygenic risk score
Development of polygenic risk score models
Choice and characteristics of discovery GWAS
Criteria for selection of genetic variants to include in score
Statistical methods for weighing effect sizes of genetic variants
Statistical methods for evaluating the effect on risk of the phenotype
Definition of threshold for a high polygenic risk score
Evaluation of polygenic risk score performance
Methods used for risk score validation
Predictive ability of the score
Limitations and clinical applicability
Generalizability of the score
Incremental performance compared to conventional risk prediction algorithms
Intended use of the score in a clinical setting

including the characteristics of the discovery GWAS, the selection criteria for the included variants, and the statistical methods used for constructing and evaluating the risk score performance. Finally, the framework for the intended use of the PRS should be explained including the clinical applicability and limitations of the PRS. At present, this discipline is characterized by lack of consensus on both the methods used when constructing PRSs, the accompanying reporting of these methods as well as of the results. This currently complicates the interpretation and replication of published scores and limits their clinical utility (Wand et al. 2021; Choi et al. 2020).

Over the past decade, PRSs for atherosclerosis and CAD have evolved from small-scale scores based on relatively few significant genetic variants from distinct genomic regions to large-scale (often termed "omnigenic") scores based on several thousand or even millions of genetic variants spanning the entire genome. The main driver for this development has been the increasing sizes of emerging GWAS', revealing novel genetic variants associated with the disease which did not previously reach genome-wide significance. An extrapolation of this trend suggested the relevance of including additional genetic variants that are incrementally associated with the disease regardless of the nominal significance (Boyle et al. 2017).

Polygenic Risk Scores in Dyslipidemia

Several studies have investigated the polygenic contribution to dyslipidemia using PRSs constructed from genetic variants associated with lipid traits. The main lipid phenotypes studied are increased levels of LDL cholesterol or triglycerides. Key findings for each lipid trait are summarized in the following sections.

LDL Cholesterol

Familial hypercholesterolemia (FH) is an autosomal dominant genetic disorder caused by rare mutations in one of the 3 FH genes, i.e., *LDLR*, *APOB,* and *PCSK9*. With an estimated prevalence of approximately 1/250 in the general population, FH is the most common monogenic disorder in humans (Beheshti et al. 2020). The disease is characterized by lifelong exposure to high plasma levels of LDL cholesterol and a substantially increased risk of premature CAD in heterozygotes, and by CAD before the age of 20 in untreated homozygotes. The clinical diagnosis of FH is based on a set of diagnostic criteria including information on LDL cholesterol levels and premature CAD in the patient, family history of hypercholesterolemia or premature CAD combined with genetic testing for causative mutations in the 3 FH genes (Nordestgaard et al. 2013; National Institute for Health and Clinical Excellence TNCC for PC 2008). Genetic testing however only detects FH-causing mutations in approximately 40–70% of patients with a clinical diagnosis of FH

depending on the referral criteria used (Trinder et al. 2019; Reeskamp et al. 2021; Dron et al. 2020a; Pirillo et al. 2017). A polygenic cause for the FH-phenotype in a fraction of the remaining 30–60% has therefore been anticipated. On the other hand, some individuals carry an FH-causing monogenic mutation without a clinical diagnosis of FH. The variable penetrance of FH-causing mutations may in part be due to a concomitant polygenic background modifying the effects of the monogenic variants (Fig. 21.3).

The landmark study from 2013 by Talmud et al. was the first study to introduce the term "polygenic familial hypercholesterolemia" (Talmud et al. 2013). In this study, the authors constructed a PRS based on 12 common genetic variants known to increase LDL cholesterol levels and applied this score to 321 mutation-negative FH patients, 319 mutation-positive FH patients, and 3020 healthy controls from the UK Whitehall II Study. The primary conclusion was that the higher LDL cholesterol concentration in a considerable proportion of patients with a clinical diagnosis of FH but without a known causative monogenic mutation could be explained by a high PRS. Furthermore, even in patients with a known causative FH mutation, a substantial polygenic contribution might add to the variable penetrance of the disease. Following this first study, further refinement revealed that a score consisting of only 6 genetic variants performed as well as the initial score based on 12 genetic variants. The authors of this study further concluded that a polygenic origin is a

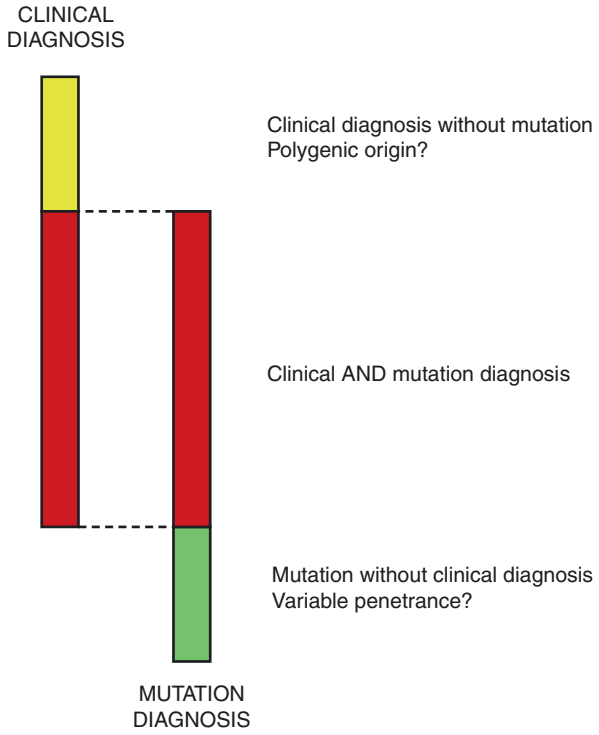

Fig. 21.3 Overlap and discrepancy between mutation diagnosis and clinical diagnosis in patients with familial hypercholesterolemia. The clinical diagnosis is based on a set of diagnostic criteria. The mutation diagnosis is based on disease-causing mutations in one of the 3 FH genes, i.e., *LDLR*, *APOB,* and *PCSK9*. (Modified from Nordestgaard et al. 2013)

likely explanation for up to 90% of mutation negative patients with a clinical diagnosis of FH (Futema et al. 2015). Since these initial studies, these PRSs have been applied in numerous populations of increasing size. Most studies investigated smaller cohorts of patients with a clinical diagnosis of FH without any causative monogenic variants and confirmed that mutation-negative FH patients on average had a higher PRS compared to both monogenic FH patients and healthy controls (Sharifi et al. 2016; Durst et al. 2017; Rabès et al. 2018; Balder et al. 2018; Wang et al. 2016; Lamiquiz-Moneo et al. 2018; Rieck et al. 2020). However, some studies further concluded that the PRSs only explained a small fraction of the variation in LDL cholesterol levels, could not discriminate between phenotypically unaffected and affected individuals and, therefore, could not be used as a diagnostic tool in clinical practice (Lamiquiz-Moneo et al. 2018; Rieck et al. 2020; Sjouke et al. 2017; Ghaleb et al. 2018). While PRSs are clearly associated with LDL cholesterol levels, it was unclear until recently whether a high PRS was associated with increased risk of CAD. However, a recent large study of a PRS based on 223 genetic variants confirmed that a high PRS (≥80th percentile) was associated with a higher risk of CAD compared to hypercholesterolemia without a genetic cause, but a lower risk compared to monogenic FH patients when adjusting for LDL cholesterol levels (Trinder et al. 2020a). Moreover, a high polygenic risk increased the risk of CAD in patients with monogenic FH, and therefore could partly explain the variability of the phenotype observed between patients carrying the same monogenic mutation (Trinder et al. 2019, 2020b). Finally, the largest studies to date using the UK Biobank and more sophisticated methods for developing polygenic scores have shown that PRSs including 8367 SNPs could explain as much as 21% of the variance in LDL cholesterol in a white British population. The risk of incident ischemic heart disease was correspondingly increased independently of LDL cholesterol and other risk factors, supporting that PRSs may partly cause a (life-long) higher risk of IHD through LDL-independent pathways (Wu et al. 2021). Additionally, using a PRS including 1.9 mill SNPs from the UK Biobank, the risk of CAD conferred by LDL cholesterol was shown to be modified by the polygenic background. In individuals in the upper decile of the PRS, the risk of CAD increased with increasing LDL cholesterol concentration, whereas the risk of CAD was similar across increasing LDL cholesterol strata in the lowest decile of the PRS (Bolli et al. 2021). These findings also indirectly support previous studies reporting greater risk reduction from LDL cholesterol-lowering drugs in European individuals with a high PRS (Marston et al. 2020; Damask et al. 2020; Natarajan et al. 2017).

In summary, current data suggest that extreme LDL cholesterol levels or extreme diagnostic scores for FH increase the likelihood of detecting a monogenic variant, while a larger fraction of patients have a polygenic or nongenetic origin of the phenotype, when LDL cholesterol levels or clinical diagnostic criteria are less extreme (Trinder et al. 2019; Wang et al. 2016). For the same baseline level of LDL cholesterol, genetically determined hypercholesterolemia is associated with a higher risk of premature CAD compared to hypercholesterolemia without a known genetic background, with monogenic FH associated with the highest risk. These findings suggest that in individuals with hypercholesterolemia in the general population,

knowledge of the underlying genetic cause may provide relevant prognostic information. The higher risk associated with genetically determined hypercholesterolemia is explained by the lifelong exposure to high LDL cholesterol levels leading to a greater cumulative LDL cholesterol exposure to the arterial wall. The reasons for the higher risk in monogenic hypercholesterolemia compared with polygenic hypercholesterolemia are still unknown. However, while the mechanism of LDL elevation in genetic hypercholesterolemia is primarily due to lower LDL receptor activity in monogenic FH, the pathways perturbed in polygenic FH are unknown and most likely pleiotropic. In comparison with monogenic hypercholesterolemia, this could result in a slower cumulative LDL exposure or an improved response to as lipid-lowering therapy, leading to a more beneficial risk profile in polygenic hypercholesterolemia (Trinder et al. 2019, 2020b; Sharifi et al. 2017).

Triglycerides

Hypertriglyceridemia is defined as fasting plasma triglyceride levels above 2 mmol/L. The phenotype is often further divided into "mild-to-moderate" and "severe" hypertriglyceridemia, when plasma triglyceride levels are within the range 2.0–9.9 mmol/L and above 10 mmol/L, respectively. Mild-to-moderate hypertriglyceridemia is a common phenotype affecting 25% of the adult population, while severe hypertriglyceridemia or chylomicronemia only affects approximately 1 in 1000 individuals in the general population (Dron and Hegele 2020; Retterstøl et al. 2017).

The genetic contribution to hypertriglyceridemia is complex and largely polygenic. One exception is familial chylomicronemia syndrome (FCS), an extremely rare autosomal recessive form of severe hypertriglyceridemia affecting 1 in 200,000 to 1,000,000. FCS is caused by mutations in the 5 canonical genes for FCS, i.e., *LPL, APOC2, APOA5, LMF1,* and *GPIHBP1,* leading to impaired function of lipoprotein lipase and thus affecting triglyceride metabolism (Dron and Hegele 2020). A highly penetrant autosomal dominant hypertriglyceridemia, as a counterpart to familial hypercholesterolemia, does not exist. Instead the genetic contribution to hypertriglyceridemia consists of either heterozygous large effect rare variants mainly in the five canonical genes for FCS, or an increased burden of common variants each with small effects on plasma triglyceride levels. The presence of these variants increases the probability that an individual will develop hypertriglyceridemia, but they do not per se cause hypertriglyceridemia. Instead, secondary factors are usually required before the hypertriglyceridemia becomes manifest, which causes the penetrance of polygenic hypertriglyceridemia to be highly variable. These secondary factors are not completely known, but gene–gene interactions, gene–environment interaction, and epigenetic factors have been suggested to be of importance for triggering the phenotype. The most important environmental triggers include obesity, diabetes or insulin resistance, excessive alcohol consumption, hormonal treatment, and pregnancy (Dron and Hegele 2020).

While mild-to-moderate hypertriglyceridemia is associated with an increased risk of ischemic heart disease and stroke, severe hypertriglyceridemia ≥10 mmol/L is primarily associated with an increased risk of acute pancreatitis. The likely explanation for this difference is that the smaller triglyceride rich lipoproteins, remnant lipoproteins, and small very low-density lipoproteins (VLDLs), in mild-to- moderate hypertriglyceridemia can enter into the arterial wall and cause atherosclerosis due to their cholesterol content. In contrast, chylomicrons and large VLDLs are too large to enter into the arterial wall, but can cause inflammation in the pancreas possibly by triggering autodigestion since high triglycerides are toxic and cause inflammation.

Although the polygenic and complex inheritance of hypertriglyceridemia has been known for several decades, the value of PRSs in hypertriglyceridemia has not been studied to the same extent as in hypercholesterolemia. Most studies used small cohorts of individuals and the risk scores were comprised of relatively few genetic variants. These studies all found a strong association between high PRS and hypertriglyceridemia. However, only a small fraction of the variance in plasma triglyceride levels was explained by the PRSs leading to poor discrimination between phenotypically unaffected and affected individuals (Justesen et al. 2015; Lutsey et al. 2012; Latsuzbaia et al. 2016; Buscot et al. 2016). Recent studies concluded that the genetic determinants of both mild-to-moderate and severe hypertriglyceridemia comprise both rare large-effect variants and an extreme accumulation of common small-effect variants included in a PRS. However, the polygenic risk accounts for an up to threefold larger fraction of individuals with hypertriglyceridemia compared with rare large-effect variants, and therefore has a larger contribution on the population level (Dron et al. 2019, 2020b). Finally, an omnigenic risk score including 6 million genetic variants was applied in a cohort of approximately 135,000 participants from the FinnGen project, an aggregation of Finnish prospective epidemiological and disease-based cohorts and hospital biobank samples. This study found that a high PRS was associated with increased triglyceride concentrations and a corresponding increased risk of prevalent CAD (Ripatti et al. 2021).

Several aspects of the genetic determinants of hypertriglyceridemia need further study. First, whether a high PRS was associated with increased risk of acute pancreatitis remains unknown. Second, whether the choice of treatment should be differentiated according to the underlying genetic predisposition for hypertriglyceridemia also needs further investigation. Finally, the interplay between genetic predisposition for hypertriglyceridemia and potential nongenetic triggers should be studied to improve our understanding of the variable penetrance observed in individuals with similar genetic susceptibility for hypertriglyceridemia.

Polygenic Risk Scores in Coronary Artery Disease

The PRSs based on genetic variants associated with lipid phenotypes predict the specific fraction of CAD caused by dyslipidemia. Additional PRSs have been developed focusing on all genetic variants associated with CAD. As such, these risk

scores consider the entire genetic component of CAD regardless of the underlying mechanisms and pathways involved.

Risk Prediction and Conventional Risk Factors

Similarly to the PRSs in dyslipidemia, the initial studies on PRSs in CAD were based on relatively few genetic variants with confirmed effects on risk of CAD. One of the first studies tested 2 PRSs for CAD of 12 and 101 SNPs, respectively, in almost 20,000 female health professionals. Both scores associated with incident CAD after adjustment for age, but the effect was not evident after adjustment for traditional risk factors. Also, the PRSs did not improve risk prediction beyond traditional risk factors (Paynter et al. 2010). Subsequent studies based on known GWAS significant SNPs confirmed the association with CAD and also found either no (De Vries et al. 2015; Morris et al. 2016) or modest (Antiochos et al. 2016; Beaney et al. 2017; Iribarren et al. 2016) improvements in risk prediction, when added to traditional risk prediction algorithms. An explanation for the modest effects of these initial PRSs was most likely the low fraction of CAD heritability explained by the genetic variants included. However, one study suggested a better performance in younger individuals, most likely because traditional clinical risk factors are usually not evident at young age (Tada et al. 2016).

In 2018, the landmark study by Khera et al. for the first time used an omnigenic risk score for CAD comprising 6.6 million genetic variants across the entire human genome. Using this score, the study found that 8% of the population had inherited a PRS conferring more than threefold increased risk of CAD. A threefold increased risk of CAD corresponded to the risk conferred by mutations causing familial hypercholesterolemia. However, the PRS identified 20-fold more individuals at high risk for CAD, suggesting that PRS contributed significantly to risk of CAD on the population level. Furthermore, the PRS had a stronger association to prevalent CAD compared to previously published smaller PRSs (Khera et al. 2018). Whether the PRS improved risk prediction on top of already existing clinical risk factors was not investigated. Also in 2018, Inouye et al. developed a risk score consisting of 1.7 million variants which was tested and validated in the approximately 500,000 participants in the UK Biobank (Inouye et al. 2018). This study showed that a meta-analysis of several independent PRSs had a stronger association with CAD than any single conventional risk factor. The meta-analyzed risk score further improved risk prediction when added to all conventional risk factors.

The omnigenic risk scores developed by Khera et al. and Inouye et al. have been repeatedly evaluated in several studies and are therefore regarded as benchmarks in CAD risk prediction. Most studies confirm the predictive superiority of the omnigenic scores over the smaller PRSs. Some studies further confirm that the omnigenic scores improve risk prediction when added to current guideline-based algorithms (Aragam et al. 2020; Hindy et al. 2020; Dikilitas et al. 2020), while others were not able to validate these findings (Wünnemann et al. 2019; Mosley et al. 2020; Bauer

et al. 2021). Furthermore, validation studies find a lower performance for incident and recurrent CAD compared to prevalent events (Wünnemann et al. 2019; Mosley et al. 2020) as well as a lower performance in non-European ethnicities (Dikilitas et al. 2020). This is not surprising, since current PRSs are mainly based on variants selected from cross-sectional studies of prevalent CAD in individuals from European populations. Variant effect sizes may therefore not be valid for other ethnicities or for the prediction of incident events of CAD.

Risk Stratification and Response to Treatment

A key question is whether polygenic risk impacts on other genetic and environmental risk factors as well as on pharmacological treatment for CAD and thus, if PRSs can aid in identifying strata of individuals which may benefit from early onset and more intensive lifestyle and pharmacological interventions.

Fahed and coworkers explored whether disease risk conferred by a monogenic variant can be modified by polygenic risk factors that involve small perturbations to a wide range of cellular pathways. The study included 80,000 individuals from three different populations and showed that among carriers of monogenic FH mutations, the probability of CAD by age 75 ranged from 13% to 76% depending on the polygenic background (Fahed et al. 2020). These findings suggest that accounting for polygenic risk is likely to increase the accuracy of risk estimation for individuals who inherit a monogenic risk variant, and therefore may have implications for the timing and intensity of pharmacological therapy in carriers of these mutations. Furthermore, the polygenic background may explain part of the variable penetrance observed for most monogenic disease-causing mutations. Several studies have further shown that PRSs for CAD may identify subsets of the population more likely to benefit from lifestyle modifications and statin therapy (Khera et al. 2016b; Natarajan et al. 2017; Inouye et al. 2018; Abdullah Said et al. 2018; Mega et al. 2015).

The future implications may be that PRSs should be incorporated into guideline-based primary prevention algorithms as risk-enhancing factors in line with traditional clinical risk factors, and, for example, used to guide statin eligibility in patients at borderline to intermediate risk.

Clinical Utility and Unresolved Issues

The growing interest in the development of PRSs and the corresponding accumulation of scientific publications over the past years have highlighted several potential benefits of introducing PRSs into clinical practice. First, PRSs will increase the likelihood of identifying patients at high risk of CAD at an earlier age before traditional clinical risk factors become evident (Aragam et al. 2020). This enables early onset of lifestyle changes and pharmacological treatment, thus slowing the

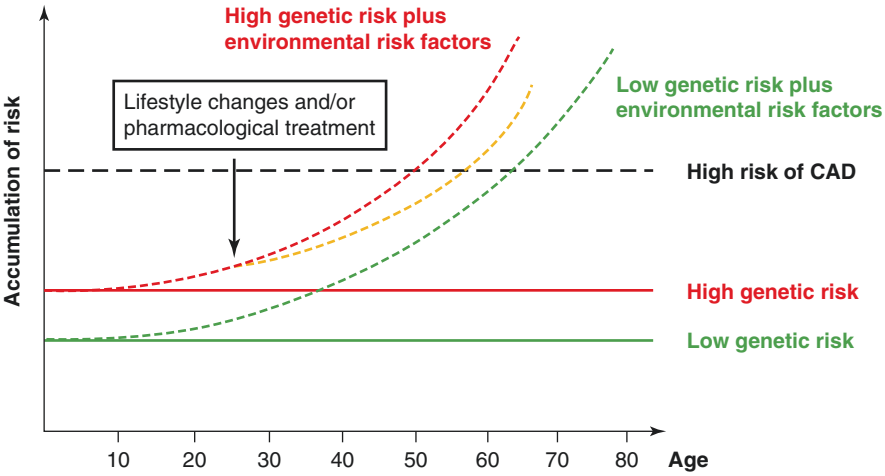

Fig. 21.4 Theoretical accumulation of risk of coronary artery disease (CAD) with increasing age in individuals with low (green) or high (red) polygenic risk. Genetic risk is constant through life, while environmental risk factors accumulate with increasing age. Individuals at high polygenic risk will reach the threshold for CAD much earlier (red dotted line) compared to individuals at low polygenic risk (green dotted line), when exposed to similar environmental risk factors through life. Early interventions, i.e., lifestyle changes and/or pharmacological treatment (arrow), slow the accumulation of risk, thus postponing the age at which the threshold for (symptomatic) CAD is reached (yellow dotted line)

accumulation of risk and most likely reducing the lifetime risk of CAD for this subgroup (Fig. 21.4).

Second, PRSs add to current guideline-based clinical risk algorithms. This enables reclassification of individuals at borderline to intermediate risk into either low or high risk, which in turn can be used to encourage lifestyle changes or guide pharmacological treatment in this subgroup. Third, PRSs can identify subsets of the population already in early life, which are more likely to benefit from intensive lifestyle modifications (Khera et al. 2016b; Inouye et al. 2018; Abdullah Said et al. 2018). The disclosure of high genetic risk has therefore been suggested to be effective in the patient's motivation for and adherence to lifestyle changes. Finally, PRSs have a potential impact on the choice of pharmaceutical treatment strategy, since patients with a high polygenic risk for CAD are more likely to benefit from earlier and more intensive treatment with lipid-lowering therapy (Marston et al. 2020; Damask et al. 2020; Natarajan et al. 2017; Mega et al. 2015).

Nevertheless, the introduction of PRSs into clinical practice is not without challenges. The clinical utility and applications of PRSs are still debated, and the implementation into clinical settings therefore remains premature. Some of the current limitations and unresolved issues regarding the clinical utility of the PRSs are discussed below. First, PRSs are ancestry specific. Since most GWAS' only include individuals of European descent, this limits the applicability of currently developed PRSs to populations of European ancestry. Second, even across populations of European ancestry the performance of PRSs may vary. Different large-scale PRSs may predict

differently when applied to the same cohort. Likewise, the same PRS may predict differently across similar cohorts. Slight changes in the methods applied for the development and application of PRSs as well as small differences between populations may be responsible for these discrepancies. This highlights the urgent need for establishing both analytical and clinical reporting standards for PRSs (Wand et al. 2021; Choi et al. 2020). Third, PRSs are normally distributed and only few individuals are at the extremes of the distribution. A threshold for intervention therefore needs to be established and integrated into an overall risk assessment. Fourth, variant selection and effect sizes for PRSs are based on GWAS studies. While GWAS sizes have increased and the effects of the individual genetic variants therefore are determined with a higher precision, most GWAS' use a cross-sectional study design comparing prevalent cases and controls. The clinical utility of PRSs however relies on the ability to predict incident or recurrent CAD, and current studies find a much lower performance for incident and recurrent CAD compared to prevalent events for similar scores. Using large prospective studies for variant selection would most likely improve the predictive performance for incident CAD. Fifth, it will be necessary to establish training programs for medical staff to understand PRSs and how they are developed, to communicate polygenic risk in a comprehensive way to the patient, and to acquire knowledge about risk modification via lifestyle modification or pharmacotherapy. Finally, there are several ethical and legal issues that also need to be considered.

Conclusion

PRSs can identify 10–20 times as many individuals at high polygenic risk compared to monogenic mutations, and PRSs can modulate the effect of a monogenic variant on risk. Polygenic risk can be quantified already at birth, long before other risk factors used to predict risk of CAD, and before clinical manifestations of disease, and PRSs for CAD add more predictive information to a baseline model including age and sex, than any of a number of traditional risk factors. In addition, current guideline-based risk prediction tools for cardiovascular prevention incompletely capture polygenic susceptibility to CAD. Consequently, now is an opportunity to integrate both genetic and clinical risk into personalized prevention of CAD provided that PRSs become sufficiently accurate to justify lifestyle and pharmacological interventions.

References

Abdullah Said M, Verweij N, Van Der Harst P. Associations of combined genetic and lifestyle risks with incident cardiovascular disease and diabetes in the UK biobank study. JAMA Cardiol. 2018;3:693–702.

Antiochos P, Marques-Vidal P, McDaid A, Waeber G, Vollenweider P. Association between parental history and genetic risk scores for coronary heart disease prediction: the population-based

CoLaus study. Atherosclerosis [Internet]. Elsevier Ltd. 2016;244:59–65. Available from: https://doi.org/10.1016/j.atherosclerosis.2015.10.104.

Aragam KG, Dobbyn A, Judy R, Chaffin M, Chaudhary K, Hindy G, et al. Limitations of contemporary guidelines for managing patients at high genetic risk of coronary artery disease. J Am Coll Cardiol. 2020;75:2769–80.

Balder J-W, Rimbert A, Zhang X, Viel M, Kanninga R, van Dijk F, et al. Genetics, lifestyle, and low-density lipoprotein cholesterol in young and apparently healthy women. Circulation [Internet]. 2018;137:820–31. Available from: http://circ.ahajournals.org/lookup/doi/10.1161/CIRCULATIONAHA.117.032479.

Bauer A, Zierer A, Gieger C, Büyüközkan M, Müller-Nurasyid M, Grallert H, et al. Comparison of genetic risk prediction models to improve prediction of coronary heart disease in two large cohorts of the MONICA/KORA study. Genet Epidemiol. 2021;45:633–50.

Beaney KE, Cooper JA, Drenos F, Humphries SE. Assessment of the clinical utility of adding common single nucleotide polymorphism genetic scores to classical risk factor algorithms in coronary heart disease risk prediction in UK men. Clin Chem Lab Med. 2017;55:1605–13.

Beheshti SO, Madsen CM, Varbo A, Nordestgaard BG. Worldwide prevalence of familial hypercholesterolemia: meta-analyses of 11 million subjects. J Am Coll Cardiol. 2020;75:2553–66.

Bolli A, Di Domenico P, Pastorino R, Busby GB, Bottà G. Risk of coronary artery disease conferred by low-density lipoprotein cholesterol depends on polygenic background. Circulation. 2021;143:1452–4.

Boyle EA, Li YI, Pritchard JK. An expanded view of complex traits: from polygenic to omnigenic. Cell [Internet]. Elsevier. 2017;169:1177–1186. Available from: https://doi.org/10.1016/j.cell.2017.05.038.

Buniello A, Macarthur JAL, Cerezo M, Harris LW, Hayhurst J, Malangone C, et al. The NHGRI-EBI GWAS catalog of published genome-wide association studies, targeted arrays and summary statistics 2019. Nucleic Acids Res. Oxford University Press. 2019;47:D1005–12.

Buscot MJ, Magnussen CG, Juonala M, Pitkänen N, Lehtimäki T, Viikari JSA, et al. The combined effect of common genetic risk variants on circulating lipoproteins is evident in childhood: a longitudinal analysis of the cardiovascular risk in Young Finns study. PLoS One. 2016;11:1–21.

Choi SW, Mak TSH, O'Reilly PF. Tutorial: a guide to performing polygenic risk score analyses. Nat Protoc [Internet]. Springer US. 2020;15:2759–72. Available from: https://doi.org/10.1038/s41596-020-0353-1.

Christoffersen M, Tybjærg-Hansen A. Polygenic risk scores: how much do they add? Curr Opin Lipidol. 2021;32:157–62.

Damask A, Steg PG, Schwartz GG, Szarek M, Hagström E, Badimon L, et al. Patients with high genome-wide polygenic risk scores for coronary artery disease may receive greater clinical benefit from alirocumab treatment in the ODYSSEY OUTCOMES trial. Circulation. 2020;141:624–36.

De Vries PS, Kavousi M, Ligthart S, Uitterlinden AG, Hofman A, Franco OH, et al. Incremental predictive value of 152 single nucleotide polymorphisms in the 10-year risk prediction of incident coronary heart disease: the Rotterdam study. Int J Epidemiol. 2015;44:682–8.

Dikilitas O, Schaid DJ, Kosel ML, Carroll RJ, Chute CG, Denny JA, et al. Predictive utility of polygenic risk scores for coronary heart disease in three major racial and ethnic groups. Am J Hum Genet. Elsevier Company. 2020;106:707–16.

Dron JS, Hegele RA. The evolution of genetic-based risk scores for lipids and cardiovascular disease. Curr Opin Lipidol. 2019;30:71–81.

Dron JS, Hegele RA. Genetics of hypertriglyceridemia. Front Endocrinol (Lausanne). 2020;11:455.

Dron JS, Wang J, Cao H, McIntyre AD, Iacocca MA, Menard JR, et al. Severe hypertriglyceridemia is primarily polygenic. J Clin Lipidol [Internet]. Elsevier Inc. 2019;13:80–8. Available from: https://doi.org/10.1016/j.jacl.2018.10.006.

Dron JS, Wang J, McIntyre AD, Iacocca MA, Robinson JF, Ban MR, et al. Six years' experience with LipidSeq: clinical and research learnings from a hybrid, targeted sequencing panel for dyslipidemias. BMC Med Genomics. 2020a;13:1–15.

Dron JS, Wang J, McIntyre AD, Cao H, Hegele RA. The polygenic nature of mild-to-moderate hypertriglyceridemia. J Clin Lipidol [Internet]. Elsevier Inc. 2020b;14:28–34.e2. Available from: https://doi.org/10.1016/j.jacl.2020.01.003.

Durst R, Ibe UK, Shpitzen S, Schurr D, Eliav O, Futema M, et al. Molecular genetics of familial hypercholesterolemia in Israel–revisited. Atherosclerosis [Internet]. Elsevier Ltd. 2017;257:55–63. Available from: https://doi.org/10.1016/j.atherosclerosis.2016.12.021.

Fahed AC, Wang M, Homburger JR, Patel AP, Bick AG, Neben CL, et al. Polygenic background modifies penetrance of monogenic variants for tier 1 genomic conditions. Nat Commun [Internet]. Springer US. 2020;11:1–9. Available from: https://doi.org/10.1038/s41467-020-17374-3.

Futema M, Shah S, Cooper JA, Li K, Whittall RA, Sharifi M, et al. Refinement of variant selection for the LDL cholesterol genetic risk score in the diagnosis of the polygenic form of clinical familial hypercholesterolemia and replication in samples from 6 countries. Clin Chem. 2015;61:231–8.

Ghaleb Y, Elbitar S, El Khoury P, Bruckert E, Carreau V, Carrié A, et al. Usefulness of the genetic risk score to identify phenocopies in families with familial hypercholesterolemia? Eur J Hum Genet. Springer US. 2018;26:570–8.

Hindy G, Aragam KG, Ng K, Chaffin M, Lotta LA, Baras A, et al. Genome-wide polygenic score, clinical risk factors, and long-term trajectories of coronary artery disease. Arterioscler Thromb Vasc Biol. 2020:2738–46.

Inouye M, Abraham G, Nelson CP, Wood AM, Sweeting MJ, Dudbridge F, et al. Genomic risk prediction of coronary artery disease in 480,000 adults: implications for primary prevention. J Am Coll Cardiol. 2018;72:1883–93.

Iribarren C, Lu M, Jorgenson E, Martínez M, Lluis-Ganella C, Subirana I, et al. Clinical utility of multimarker genetic risk scores for prediction of incident coronary heart disease: a cohort study among over 51 thousand individuals of European ancestry. Circ Cardiovasc Genet. 2016;9:531–40.

Justesen JM, Allin KH, Sandholt CH, Borglykke A, Krarup NT, Grarup N, et al. Interactions of lipid genetic risk scores with estimates of metabolic health in a Danish population. Circ Cardiovasc Genet. 2015;8:465–72.

Khera AV, Won HH, Peloso GM, Lawson KS, Bartz TM, Deng X, et al. Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. J Am Coll Cardiol. 2016a;67:2578–89.

Khera AV, Emdin CA, Drake I, Natarajan P, Bick AG, Cook NR, et al. Genetic risk, adherence to a healthy lifestyle, and coronary disease. N Engl J Med. 2016b;375:2349–58.

Khera AV., Chaffin M, Aragam KG, Haas ME, Roselli C, Choi SH, et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. Nat Genet [Internet]. Springer US. 2018;50:1219–24. Available from: https://doi.org/10.1038/s41588-018-0183-z.

Klein RJ, Zeiss C, Chew EY, Tsai J-Y, Sackler RS, Haynes C, et al. Complement factor H polymorphism in age-related macular degeneration. Science. 2005;308:385–9.

Lamiquiz-Moneo I, Pérez-Ruiz MR, Jarauta E, Tejedor MT, Bea AM, Mateo-Gallego R, et al. Single nucleotide variants associated with polygenic hypercholesterolemia in families diagnosed clinically with familial hypercholesterolemia. Rev Española Cardiol (English Ed). 2018;71:351–6.

Latsuzbaia A, Jaddoe VWV, Hofman A, Franco OH, Felix JF. Associations of genetic variants for adult lipid levels with lipid levels in children. The Generation R study. J Lipid Res. 2016;57:2185–92.

Lechner K, Kessler T, Schunkert H. Should we use genetic scores in the determination of treatment strategies to control dyslipidemias? Curr Cardiol Rep. 2020;22:1–9.

Lutsey PL, Rasmussen-Torvik LJ, Pankow JS, Alonso A, Smolenski DJ, Tang W, et al. Relation of lipid gene scores to longitudinal trends in lipid levels and incidence of abnormal lipid levels among individuals of European ancestry the atherosclerosis risk in communities (ARIC) study. Circ Cardiovasc Genet. 2012;5:73–80.

Marston NA, Kamanu FK, Nordio F, Gurmu Y, Roselli C, Sever PS, et al. Predicting benefit from evolocumab therapy in patients with atherosclerotic disease using a genetic risk score. Circulation. 2020;141:616–23.

Mega JL, Stitziel NO, Smith JG, Chasman DI, Caulfield MJ, Devlin JJ, et al. Genetic risk, coronary heart disease events, and the clinical benefit of statin therapy: an analysis of primary and secondary prevention trials. Lancet. 2015;385:2264–71.

Morris RW, Cooper JA, Shah T, Wong A, Drenos F, Engmann J, et al. Marginal role for 53 common genetic variants in cardiovascular disease prediction. Heart. 2016;102:1640–7.

Mosley JD, Gupta DK, Tan J, Yao J, Wells QS, Shaffer CM, et al. Predictive accuracy of a polygenic risk score compared with a clinical risk score for incident coronary heart disease. JAMA J Am Med Assoc. 2020;323:627–35.

Natarajan P, Young R, Stitziel NO, Padmanabhan S, Baber U, Mehran R, et al. Polygenic risk score identifies subgroup with higher burden of atherosclerosis and greater relative benefit from statin therapy in the primary prevention setting. Circulation. 2017;135:2091–101.

Natarajan P, Peloso GM, Zekavat SM, Montasser M, Ganna A, Chaffin M, et al. Deep-coverage whole genome sequences and blood lipids among 16,324 individuals. Nat Commun. 2018;9:1–12.

National Institute for Health and Clinical Excellence TNCC for PC. NICE Clinical Guideline 71: Identification and management of familial hypercholesterolaemia [Internet]. UK Natl Inst Heal Care Excell. 2008. Available from: http://www.nice.org.uk/nicemedia/pdf/FHConsFullGuideline.pdf.

Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. Eur Heart J. 2013;34:3478–90.

Paynter NP, Chasman DI, Paré G, Buring JE, Cook NR, Miletich JP, et al. Association between a literature-based genetic risk score and cardiovascular events in women. JAMA J Am Med Assoc. 2010;303:631–7.

Pirillo A, Garlaschelli K, Arca M, Averna M, Bertolini S, Calandra S, et al. Spectrum of mutations in Italian patients with familial hypercholesterolemia: new results from the LIPIGEN study. Atheroscler Suppl. 2017;29:17–24.

Rabès JP, Béliard S, Carrié A. Familial hypercholesterolemia: experience from France. Curr Opin Lipidol. 2018;29:65–71.

Reeskamp LF, Tromp TR, Defesche JC, Grefhorst A, Stroes ESG, Hovingh GK, et al. Next-generation sequencing to confirm clinical familial hypercholesterolemia. Eur J Prev Cardiol. 2021;28:875–83.

Retterstøl K, Narverud I, Selmer R, Berge KE, Osnes IV, Ulven SM, et al. Severe hypertriglyceridemia in Norway: prevalence, clinical and genetic characteristics. Lipids Health Dis Lipids in Health and Disease. 2017;16:1–8.

Rieck L, Bardey F, Grenkowitz T, Bertram L, Helmuth J, Mischung C, et al. Mutation spectrum and polygenic score in German patients with familial hypercholesterolemia. Clin Genet. 2020;98:457–67.

Ripatti P, Rämö JT, Mars NJ, Fu Y, Lin J, Söderlund S, et al. Polygenic hyperlipidemias and coronary artery disease risk. Circ Genomic Precis Med. 2021;13:59–65.

Sharifi M, Walus-Miarka M, Idzior-Waluś B, Malecki MT, Sanak M, Whittall R, et al. The genetic spectrum of familial hypercholesterolemia in south-eastern Poland. Metabolism. 2016;65:48–53.

Sharifi M, Higginson E, Bos S, Gallivan A, Harvey D, Li KW, et al. Greater preclinical atherosclerosis in treated monogenic familial hypercholesterolemia vs polygenic hypercholesterolemia. Atherosclerosis. 2017;263:405–11.

Sjouke B, Tanck MWT, Fouchier SW, Defesche JC, Hutten BA, Wiegman A, et al. Children with hypercholesterolemia of unknown cause : value of genetic risk scores. J Clin Lipidol [Internet]. Elsevier Inc. 2017;10:851–9. Available from: https://doi.org/10.1016/j.jacl.2016.02.017.

Tada H, Melander O, Louie JZ, Catanese JJ, Rowland CM, Devlin JJ, et al. Risk prediction by genetic risk scores for coronary heart disease is independent of self-reported family history. Eur Heart J. 2016;37:561–7.

Talmud PJ, Shah S, Whittall R, Futema M, Howard P, Cooper JA, et al. Use of low-density lipoprotein cholesterol gene score to distinguish patients with polygenic and monogenic familial hypercholesterolaemia : a case-control study. Lancet [Internet]. Elsevier Ltd; 2013;381:1293–301. Available from: https://doi.org/10.1016/S0140-6736(12)62127-8.

Trinder M, Li X, DeCastro ML, Cermakova L, Sadananda S, Jackson LM, et al. Risk of premature atherosclerotic disease in patients with monogenic versus polygenic familial hypercholesterolemia. J Am Coll Cardiol. 2019;74:512–22.

Trinder M, Francis GA, Brunham LR. Association of monogenic vs polygenic hypercholesterolemia with risk of atherosclerotic cardiovascular disease. JAMA Cardiol. 2020a;5:390–9.

Trinder M, Paquette M, Cermakova L, Ban MR, Hegele RA, Baass A, et al. Polygenic contribution to low-density lipoprotein cholesterol levels and cardiovascular risk in monogenic familial hypercholesterolemia. Circ Genomic Precis Med. 2020b;13:515–23.

Wand H, Lambert SA, Tamburro C, Iacocca MA, O'Sullivan JW, Sillari C, et al. Improving reporting standards for polygenic scores in risk prediction studies. Nature [Internet]. Springer US. 2021;591:211–9. Available from: https://doi.org/10.1038/s41586-021-03243-6

Wang J, Dron JS, Ban MR, Robinson JF, McIntyre AD, Alazzam M, et al. Polygenic versus monogenic causes of hypercholesterolemia ascertained clinically. Arterioscler Thromb Vasc Biol. 2016;36:2439–45.

Wu H, Forgetta V, Zhou S, Bhatnagar SR, Paré G, Richards BJ. Polygenic risk score for low-density lipoprotein cholesterol is associated with risk of ischemic heart disease and enriches for individuals with familial hypercholesterolemia. Circ Genomic Precis Med. 2021;14:88–96.

Wünnemann F, Sin Lo K, Langford-Avelar A, Busseuil D, Dubé MP, Tardif JC, et al. Validation of genome-wide polygenic risk scores for coronary artery disease in French Canadians. Circ Genomic Precis Med. 2019;12:e002481.

Zdravkovic S, Wienke A, Pedersen NL, Marenberg ME, Yashin AI, De Faire U. Heritability of death from coronary heart disease: a 36-year follow-up of 20 966 Swedish twins. J Intern Med. 2002;252:247–54.

Part V
Atherosclerosis Imaging as a Tool to Refine Risk Estimates

Chapter 22
Coronary Artery Calcium

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Introduction

Atherosclerotic cardiovascular disease (ASCVD), inclusive of coronary heart disease (CHD) and stroke events, remains a leading cause of morbidity and mortality in the United States and globally (Virani et al. 2021). Traditional risk scoring tools provide a quantitative estimation of the absolute risk of having an ASCVD event within a given timeframe. These risk estimators use demographic variables and other traditional risk factors to inform the allocation and intensity of primary prevention interventions and represent a guideline-endorsed first step for ASCVD risk assessment in the United States and Europe (Arnett et al. 2019; Grundy et al. 2019; Visseren et al. 2021). Clinical risk scores, however, use epidemiological data of ASCVD event rates observed in large populations to inform an individual's risk of having an event over time, which results in important challenges when providing meaningful, personalized estimations of risk at the patient level. Moreover, these scores tend to underestimate risk among higher-risk younger individuals who would benefit from early preventive therapies; and to overestimate risk in many middle-aged and older individuals, allowing for little individualization of risk management in these groups and raising concerns of overtreatment (Lloyd-Jones et al. 2019). In this context, tools that can help further improve risk stratification and guide a more personalized allocation of preventive interventions can significantly enrich shared

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decision-making conversations with patients in primary prevention, resulting in a more "precise" allocation of lifelong preventive interventions.

Coronary artery calcium (CAC) scoring allows visualization of calcifications in the coronary walls, a finding that is a highly specific marker of coronary atherosclerosis. Coronary atherosclerotic plaque is the primary underlying substrate for coronary atherosclerotic events, and among individuals with no prior clinical ASCVD, multiple studies have consistently shown that the presence, extent, and severity of coronary atherosclerosis provide additional prognostic information and improve risk stratification beyond clinical risk scores (Nasir and Cainzos-Achirica 2021; Greenland et al. 2018). While the performance of the Pooled Cohort Equations (PCE) is reasonably good at the extremes of risk (<5% and >20% estimated 10-year ASCVD risk), there is significant room for nuance in the borderline (5–<7.5%) and intermediate (7.5–<20%) risk groups. In those individuals, current guidelines around the world acknowledge that other features, from race/ethnicity and advanced lipid measurements to the burden of coronary plaque, can enhance and further personalize risk assessment and management, matching the intensity of interventions to a most accurate estimation of absolute ASCVD risk. Among available tools, US and European guidelines acknowledge the CAC score as the best-established imaging technique to enhance risk assessment (Arnett et al. 2019; Grundy et al. 2019; Visseren et al. 2021).

This chapter focuses on the clinical role of CAC and its utility for shared decision-making, enhanced risk stratification, and guiding a more personalized management in the primary prevention of ASCVD. We also discuss implications for cost-effectiveness and long-term adherence to preventive interventions using CAC to inform the allocation of preventive therapies.

Pathophysiology of Coronary Artery Calcifications

Coronary artery calcification accompanies the development of atherosclerosis, and the extent of calcification reflects the progression of atherosclerosis. Coronary calcification occurs predominantly within the intima layer (intimal calcification) of the coronary artery as opposed to peripheral arteries, where calcification occurs mostly within the media layer (medial calcification). The process of coronary calcification appears to start within the atheromatous components of vascular plaque (lipid pools) and progresses with inflammatory and metabolic mediators, such as lipoproteins and cytokines, leading to the development of a necrotic core (Demer and Tintut 2008). Coronary artery calcification is initially seen within a thickened intima that contains microcalcifications with a size ranging from 0.5 to 15.0 μm. Early microcalcification is thought to originate from the apoptosis of smooth muscle cells resulting in fine microcalcification; this is followed by infiltration of macrophages into the lipid pool, which also undergoes apoptosis and release of matrix vesicles producing a relatively larger microcalcification appearance. These microcalcified deposits are commonly seen in the deeper areas of necrotic core close to the internal

elastic lamina, which eventually coalesce to form more prominent speckles and fragments of calcifications, and further progression leads to a plaque with calcified sheet-like deposits more than 3 mm in size (Mori et al. 2018). Coronary artery calcification leads to arterial stiffness, decreased compliance, impaired vasomotor response, and compromised myocardial perfusion.

Coronary calcification is heavily influenced by demographic factors such as age, gender, and race/ethnicity. Age is a strong (albeit imperfect) predictor of CAC burden, and for a given age, men tend to have higher CAC scores than women, the development of coronary calcification in women is delayed by 10–15 years compared to men, which is likely due to the protective effects of estrogens in the premenopausal years. For racial/ethnic groups, coronary calcification is highest among non-Hispanic Whites and South Asians, followed by Chinese, Hispanics, and non-Hispanic Blacks (Mori et al. 2018; Kanaya et al. 2014; McClelland et al. 2006).

Measurement and Quantification of CAC and Clinically Relevant Cutpoints

The presence and extent of CAC can be seen using various imaging modalities, including radiography, computed tomography (CT), and intravascular imaging. Nevertheless, non-contrast-enhanced cardiac CT is the test of choice for the quantification of CAC scores in 2022. Specifically, multidetector CT (MDCT) has largely superseded the use of prior imaging modalities, such as electron-beam CT, and its clinical use is backed by a compelling body of international studies confirming the correlation between CAC scores and incident ASCVD outcomes across multiple cohorts. MDCT is safe, highly sensitive for detecting calcium-dense lesions, and an effective imaging tool producing 128–320 sections of the heart using a low radiation dose. Based on the method described by Dr. Arthur Agatston, each lesion detected with an area ≥ 1 mm^2 and radiological attenuation >130 Hounsfield units is assigned a score that measures both the area and the radiological density of the lesion. Then, the overall score is calculated based on the sum of the individual lesions, and the final score ranges from zero (indicates no detectable calcified plaque) to thousands of Agatston units (higher score indicates higher calcified plaque burden).

CAC scores can be interpreted either as an absolute value with fixed cutoff points that are the same for all demographic groups or using age-, sex-, and race/ethnicity-specific thresholds. Absolute CAC scores are more commonly used in risk assessment, simpler, and easier to communicate. Absolute CAC scores are typically classified into four broad categories that signal increased risk of CHD/ASCVD event: 0, 1 to 99, 100 to 399, and ≥400 (Fig. 22.1). Of note, a CAC score ≥400 identifies individuals with event rates similar to those of secondary prevention populations, while CAC = 0 is associated with low event rates, particularly for CHD. In contrast, age-, sex-, and race/ethnicity-specific CAC cutpoints allow providers to examine whether an individual has a high CAC score relative to others

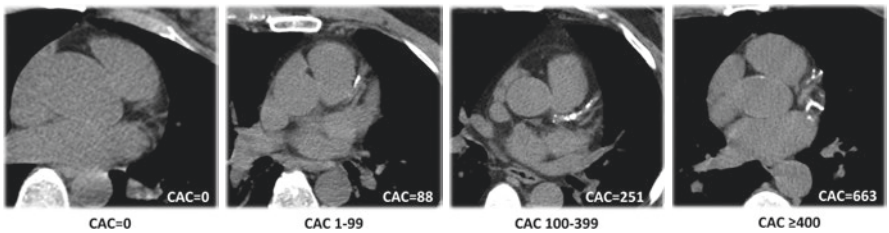

Fig. 22.1 Axial tomographic images of the heart using noncontrast multidetector computed tomography scanning in four patients with increasingly higher CAC scores

with similar demographic characteristics, and may allow for more personalized risk management decisions in women, individuals at the extremes of age, and racial/ethnic minorities. These cutpoints should be derived based on diverse population-based cohort data obtained in the same country where the patient is being evaluated, and in the United States, data from the Multi-Ethnic Study of Atherosclerosis (MESA) is typically used for this purpose (https://www.mesa-nhlbi.org/Calcium/input.aspx).

CAC Burden as a Predictor of Future ASCVD Events

A wealth of epidemiological studies has demonstrated a strong association between baseline burden of CAC and the risk of incident ASCVD events, with studies such as MESA now confirming these associations at up to 18 years of follow-up (Al Rifai et al. 2021). CAC provides robust prognostic information in both men and women, across age strata, in multiple racial/ethnic groups, and in populations with varying burdens of traditional risk factors. Moreover, CAC provides prognostic information that is independent of and substantially incremental to traditional ASCVD risk factors, with several studies reporting statistically significant improvements in risk discrimination for the prediction of CHD/ASCVD events (Detrano et al. 2009; Erbel et al. 2010).

Compared with individuals with CAC = 0, individuals with CAC 1 to 99, CAC 100 to 399, and CAC ≥ 400 have 2- to 3-fold, 4- to 7-fold, and 9- to 16-fold higher risk of cardiovascular events and mortality, respectively (Detrano et al. 2009; Erbel et al. 2010; Hecht et al. 2017). Table 22.1 illustrates the strong correlation between CAC scores and 10-year ASCVD event rates in MESA. Of note, multiple studies have demonstrated that the absence of CAC is associated with a very low risk of CHD events, low risk of ASCVD events, and of cardiovascular death, in asymptomatic individuals from the general primary prevention population (Blaha et al. 2016; Nasir et al. 2015). Results of these studies have led to the concept of "*power of*

Table 22.1 Ten-year rates of atherosclerotic cardiovascular disease (ASCVD) events by baseline CAC score strata in the Multi-Ethnic Study of Atherosclerosis (MESA)

CAC score	Plaque burden	10-year risk of ASCVD
0	No plaque	3.2%
1–99	Mild	8.0%
100–399	Moderate	13.4%
≥400	Severe	17.5%

Atherosclerotic cardiovascular disease (ASCVD) events in MESA included fatal and nonfatal myocardial infarction, fatal and nonfatal stroke, resuscitated cardiac arrest, other fatal CHD, and other cardiovascular death (Budoff et al. 2018).

zero," highlighting the fact that asymptomatic individuals with CAC = 0 have a low risk of cardiovascular events, or at least the lowest risk within populations at increased average risk (e.g., populations with diabetes or familial hypercholesterolemia). Moreover, studies have also shown that individuals without traditional ASCVD risk factors such as cigarette smoking, dyslipidemia, diabetes mellitus, hypertension, or family history of CHD, but who have elevated CAC have significantly higher cardiovascular events and mortality rates than individuals with multiple traditional ASCVD risk factors but CAC = 0 (Lakoski et al. 2007; Nasir et al. 2012).

Below we summarize the evidence of CAC providing prognostic value across key groups.

Younger and Older Adults

Although CAC burden correlates with age, several other various factors also contribute to an individual's CAC burden, including genetics, lifetime exposure to traditional and novel risk factors, individual susceptibility vs. resilience to atherosclerosis, and other factors. In this context, CAC accurately stratifies ASCVD risk across age strata, including among individuals at the extremes of the age continuum. This is important, as the PCE perform poorly in these groups, usually resulting in low-risk estimations in younger adults and high-risk estimations in the elderly. Specifically, young individuals with any CAC had a 4-fold higher risk of major ASCVD events, and a 10-fold higher risk when CAC > 100 compared with individuals of the same age with a CAC score of 0 (Miedema et al. 2019). For individuals over 75 years of age, CAC also independently predicts CHD/ASCVD events and mortality (Tota-Maharaj et al. 2014). Interestingly, young and elderly adults with CAC = 0 have a similar 5-year survival rate, and elderly adults with CAC = 0 have a lower mortality rate than younger adults with high CAC (Tota-Maharaj et al. 2012).

Men and Women

Biological sex affects the development of atherosclerosis. For the same age, women tend to have lower CAC scores, and CAC is detected on average 10 years after than in men. When sex-specific presence and pattern of CAC is examined, women and men with CAC = 0 have similar long-term CVD mortality, whereas if CAC > 0, women (in whom this finding is less frequent) have a 1.3-fold higher risk of CVD mortality when compared with men. Regarding calcification patterns, women tend to have more dense plaques but fewer calcified lesions and vessels and less volume of calcifications (Shaw et al. 2018). Using sex-specific CAC cutpoints can help improve ASCVD risk stratification and management in women.

Racial/Ethnic Groups

Given the fact that the PCE is limited to non-Hispanic White and non-Hispanic Black individuals, the ACC/AHA guideline recommended using the PCE version for non-Hispanic White individuals as an initial approximation to ASCVD risk in other racial/ethnic groups. However, the guidelines acknowledged that this approach could result in overestimating risk in certain racial/ethnic groups with lower ASCVD risk than their non-Hispanic White counterparts, such as East Asian individuals (e.g., Chinese, Koreans, or Japanese) (Lloyd-Jones et al. 2019), and underestimating risk in other racial/ethnic groups with higher ASCVD risk than their non-Hispanic White counterparts, such as South Asian individuals (e.g., Indian, Pakistani, or Bangladeshi) (Volgman et al. 2018). Therefore, measuring CAC score may be particularly helpful in refining initial risk estimates in these groups. In the CAC Consortium, a large prospective cohort of individuals undergoing self- or clinically referred CAC scores, CAC has shown predictive value independent of traditional CVD risk factors for both all-cause and CVD-specific mortality in non-Hispanic White, non-Hispanic Black, non-Hispanic Asian, and Hispanic individuals (Orimoloye et al. 2018). The same is true in the population-based MESA cohort. Also, a recent study has suggested that CAC may also have value in personalizing risk management in US Asian Indian adults free of diabetes and at borderline estimated risk (Haque et al. 2021).

Individuals with a Family History of Premature CHD/ASCVD

Family history of premature CHD/ASCVD is an established risk factor of future ASCVD events independent of traditional risk factors (Patel et al. 2018). Physicians are constantly challenged with assessing ASCVD risk among individuals who report a family history but with no clearly abnormal traditional risk factors. Future risk among those individuals will not be captured using the PCE, and in this context,

multiple studies have demonstrated that CAC testing is effective in stratifying ASCVD risk (Patel 2015; Cohen et al. 2014). In MESA, approximately half of individuals with family history of premature CHD/ASCVD had CAC = 0 and were at low absolute risk for events over a median follow-up of 10 years, whereas those with CAC ≥ 400 had a 4-fold future risk compared with CAC = 0 (Patel 2015). Several guidelines recommend a selective use of CAC in low estimated-risk individuals (<5% 10-year ASCVD risk with the PCE) with a family history of premature CHD/ASCVD. The absence of CAC (CAC = 0) would confirm their low-risk status, while the presence of CAC (CAC >0) would identify a group who might benefit from greater intensity of lifestyle modification and preventive therapies (Hecht et al. 2017).

The Evolving Role of CAC for Statin Therapy Allocation in Primary Prevention

In the late 1990s and early 2000s, CAC was seen as a tool that could help identify apparently healthy individuals with subclinical atherosclerosis who could benefit from more aggressive preventive interventions, typically statins. However, in the last decade, with the broadening of eligibility of statins to reduce ASCVD risk and background of risk overestimation with the PCE (Karmali et al. 2014; DeFilippis et al. 2015), after 2013, a substantial proportion of adult individuals in the United States became potential candidates for statin therapy (Nasir et al. 2015). In this context, the CAC score gained popularity in identifying statin-eligible individuals expected to derive small absolute benefit from treatment (Nasir and Cainzos-Achirica 2021; Greenland et al. 2018; Nasir et al. 2015). As discussed above, many studies have shown that the absence of CAC (CAC = 0) indicates low risk for future ASCVD events, particularly CHD events (Nasir et al. 2015; Blaha et al. 2009; Sarwar et al. 2009). Analyses in MESA showed that among statin-eligible candidates according to the AHA/ACC guidelines for cholesterol management, approximately one-half had CAC = 0 and had a lower 10-year ASCVD risk than the threshold recommended for treatment. Specifically, the absence of CAC reclassified risk below the threshold for statin consideration in almost 50% of those with borderline to intermediate 10-year ASCVD risk (5–20%; Fig. 22.2). Moreover, over a

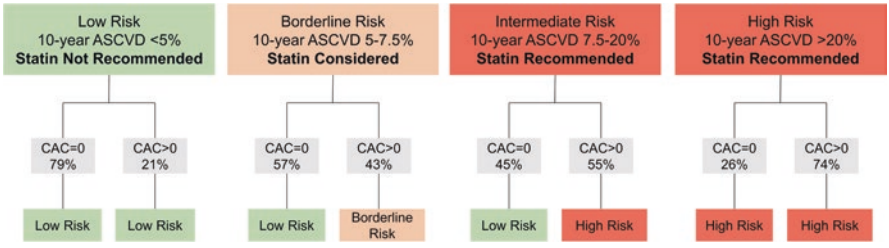

Fig. 22.2 Utility of the absence of CAC in reclassifying 10-year ASCVD risk below the risk threshold for statin consideration in the borderline- and intermediate-risk groups. (Reprinted from Nasir et al. 2015 with permission)

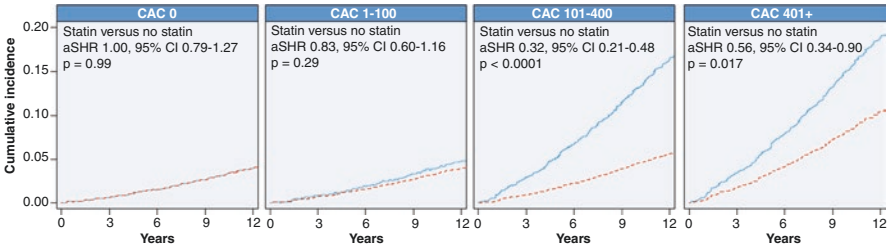

Fig. 22.3 Cumulative incidence of major adverse cardiovascular events stratified by statin treatment and CAC severity. Blue line; no statin; dashed red line, statin therapy. (Reprinted from Mitchell et al. 2018 with permission)

median follow-up of about 10 years, most ASCVD events occurred among those with detectable CAC, consistent with 10-year risk levels suggested by guidelines for statin therapy (Nasir et al. 2015). These findings have been replicated in other prospective cohorts from the United States and elsewhere.

Large observational studies with baseline CAC data and including users and nonusers of statins also suggest that the presence and severity of CAC is associated with the benefit that can be derived from statin therapy for the primary prevention of CHD/ASCVD, at least on a 10-year timeframe (Mitchell et al. 2018). Specifically, among individuals with detected CAC (CAC > 0), statin therapy is associated with significant reductions in CHD/ASCVD events, and these are larger the higher the baseline CAC score. Conversely, in patients with baseline CAC = 0, these observational analyses suggest a very modest benefit, if any at all. Analysis from the Walter Reed Cohort Study showed that the number of individuals needed to be treated with statin to prevent one initial CHD/ASCVD event over 10 years ranged from 100 for CAC 1–100 to 12 for CAC >100 (Fig. 22.3).

CAC Compared to Other Biomarkers

Several studies have compared the value of CAC and of other various markers, such as serum biomarkers, carotid plaque, carotid intima-media thickness, and ankle-brachial index, among others, for ASCVD risk assessment and prediction of ASCVD events. Of note, studies have consistently shown minimal to no improvement in risk reclassification beyond traditional risk factors with those other markers, as opposed to CAC (Blaha et al. 2016). Importantly, the reliability of absence of CAC score as a marker of low ASCVD risk is superior to absence of risk-enhancing factors, low levels of biomarkers, or absence of carotid plaque (Peters et al. 2012).

CAC for Shared Decision-Making in the Allocation of Statin Therapy and Implications for Adherence

Shared decision-making refers to the process by which clinicians learn about, consider, and incorporate patients' values, goals, and preferences and jointly discuss risk stratification and therapeutic options and potential benefits/harms of available therapeutic options. Shared decision-making means involving the patient at the core of the risk assessment and therapeutic process, engaging them in selecting meaningful risk assessment strategies and interventions. This can enhance adherence to recommendations, as patients have a better understanding of the rationale of the decisions being made and are directly involved in those, actively engaging in such decisions (Montori et al. 2013). In addition, patients who have higher insight into their disease and risk factors are regularly engaged in self-monitoring and are more motivated to control their risk factors more than their peers who do not (Bodenheimer et al. 2002).

In this context, CAC testing can provide additional relevant information among patients who are uncertain about their management after clinical risk scoring and are willing to use the burden of coronary plaque to inform their decisions about preventive statin therapy. On the contrary, for patients unlikely to change their management based on this information, CAC scoring would be of low value and is not recommended. This represents an important conceptual departure from the notion of CAC as a "screening" tool, rather, it serves as a decision aid in specific patients willing to consider additional information to make a final decision. Figure 22.4

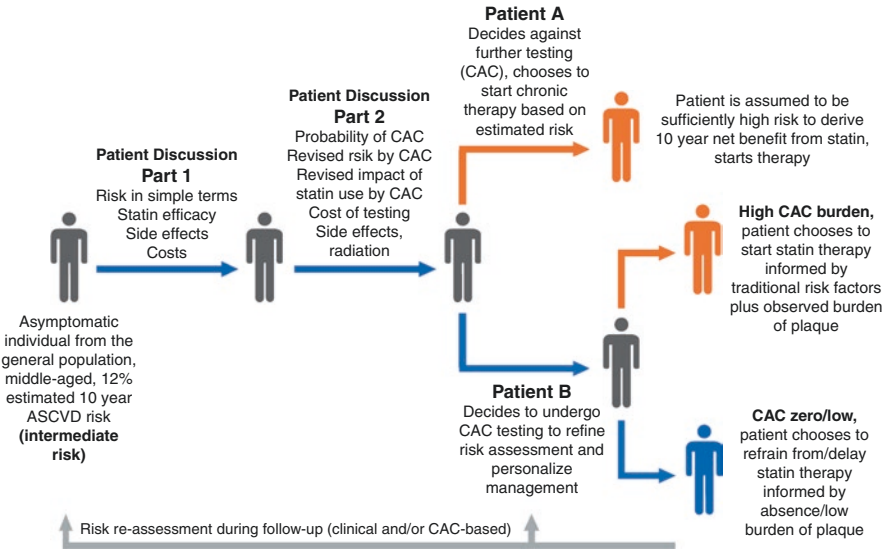

Fig. 22.4 CAC score as a decision aid in shared decision-making in risk assessment and management for primary ASCVD prevention. (Reprinted from Nasir and Cainzos-Achirica 2021 with permission)

describes the proposed role of CAC scoring in shared decision-making in the allocation of statin therapy in primary prevention.

Long-term adherence to preventive interventions is a critical unmet need in the primary prevention of ASCVD, and this is an area where CAC can have a very important impact on improving preventive care and potential outcomes. Indeed, several studies suggest improved adherence to preventive care (lifestyle modifications and medications) following CAC scoring (Mamudu et al. 2014). Interestingly, a randomized trial (CorCal) was conducted and compared CAC-based vs. PCE risk score-based strategy for initiation of statin therapy for primary ASCVD prevention. After 1 year, CAC-based strategy resulted in superior statin adherence rate, lower low-density lipoprotein cholesterol (LDL-C) levels, similar or reduced estimated costs, and fewer ASCVD events occurred compared to PCE risk score-based strategy (Muhlestein et al. 2021). In order to communicate with patients even more effectively, physicians may consider providing visual graphics and resources to patients to help them understand their risk, as visualization of CAC images may improve patient understanding and compliance (Kalia et al. 2006).

CAC in Current Primary Prevention Guidelines

Current guidelines around the world recommend considering CAC as part of the evaluation among individuals with borderline and intermediate-risk for ASCVD in case of uncertainty regarding decisions for initiation of preventive therapies. Table 22.2 summarizes major guidelines and expert consensus on use of CAC for risk assessment in primary prevention.

In the United States, the 2018 American College of Cardiology/American Heart Association (ACC/AHA) / Multisociety guideline authors concluded that it is appropriate to consider CAC testing in the context of shared decision-making for asymptomatic individuals without underling clinical ASCVD who are 40–75 years of age, have a 10-year ASCVD risk between 5% and 20%, and are uncertain about their risk management after clinical risk estimation (class of recommendation IIa) (Grundy et al. 2019). Also, the guideline endorsed the selective consideration of CAC testing among individuals with estimated risk <5% with a family history of premature CHD/ASCVD (class of recommendation IIa). Similar recommendations were included in the 2019 ACC/AHA Primary Prevention Guideline. Both guidelines emphasized the ability of CAC = 0 to de-risk individuals at borderline/intermediate risk who are not active smokers and do not have diabetes as a group where statins can be avoided given an expected small absolute risk reduction and the interventions focus on lifestyle modification. Similarly, for adults 75 years of age or older, guidelines highlight the role of measuring CAC to reclassify those with CAC = 0 to avoid statin therapy (class of recommendation IIa) (Arnett et al. 2019).

In contrast, the ACC/AHA guideline authors concluded that CAC testing has limited impact on decisions regarding preventive therapy utilization among individuals with low (<5%) and no family history, as well as in those with high (>20%)

Table 22.2 Guidelines and expert consensus on the use of CAC for risk assessment in primary prevention

Guideline/Consensus	Summary of recommendations
2018/2019 ACC/AHA guidelines on the management of blood cholesterol & primary cardiovascular prevention (Arnett et al. 2019; Grundy et al. 2019)	CAC score is reasonable to measure if uncertainty of decision prevails in intermediate (7.5 to >20%) and select borderline (5 to <7.5%) 10-year ASCVD risk groups for the purpose of clinician–patient discussion. (*class of recommendation IIa*)
2017 Expert consensus statement from SCCT (Hecht et al. 2017)	It is appropriate to measure CAC as a part of shared decision making in adults of 40–75 years of age who have 10 -year estimated ASCVD risk of 5–20% and selective individuals having <5% (i.e., family history of premature CHD/ASCVD).
2018 USPSTF guideline on nontraditional risk factors (Lin et al. 2018)	In asymptomatic individuals, the current level of evidence is insufficient to assess the balance of benefits and harms of adding CAC score to traditional risk assessment for CVD prevention, and the clinical meaning of improvements in measures of calibration, discrimination, and reclassification risk prediction studies is uncertain
2021 ESC guidelines on cardiovascular disease prevention (Visseren et al. 2021)	CAC scoring is the best-established imaging modality to improve CVD risk stratification, and is considered as a risk modifier. CAC scoring may be considered to improve classification around treatment decision thresholds (*class of recommendation IIb*).
2021 CCS Guidelines for the management of dyslipidemia (Pearson et al. 2021)	CAC might be considered for asymptomatic adults 40 years of age or older and at intermediate risk (FRS 10%–20%) for whom treatment decisions are uncertain (strong recommendation). CAC might be considered for a subset of low-risk individuals 40 years of age or older with a family history of premature ASCVD (weak recommendation)

ACC American College of Cardiology, *AHA* American Heart Association, *ASCVD* atherosclerotic cardiovascular disease, *CCS* Canadian Cardiovascular Society, *ESC* European Society of Cardiology, *FRS* Framingham Risk Score, *USPSTF* United States Preventive Services Task Force, *SCCT* Society of Cardiovascular Computed Tomography

10-year calculated ASCVD risk. Among the low-risk group, the majority of individuals have CAC = 0 and have an extremely low 10-year ASCVD event rate of 1.6%, and <5% of individuals have CAC > 100 (Nasir et al. 2015). At the other end of the risk spectrum, the majority of high-risk individuals (estimated risk >20%) have detectable CAC, and despite the fact that high-risk individuals with CAC = 0 have a lower observed event rate than the calculated risk (<20%), CAC is unlikely to have an impact on the decision to initiate preventive statin therapy, as the risk remains above the >7.5% threshold suggested for treatment (Nasir et al. 2015).

In Europe, the 2021 European Society of Cardiology (ESC) guidelines recommended the use of CAC as a risk modifier that can reclassify CVD risk upward and downward in addition to conventional risk factors, and may thus be considered in men and women with calculated risks around decision thresholds and uncertain about their management (Visseren et al. 2021).

CAC for the Allocation of Other Preventive Pharmacotherapies Beyond Statins

The primary aim of ASCVD risk assessment is to identify individuals who would benefit the most (i.e., largest absolute risk reduction) from available preventive pharmacotherapies that are proven to reduce risk. Similarly, accurate risk stratification can help identify individuals expected to derive the smallest benefit from an intervention, which is an important consideration when therapeutic decisions involve treatments that are expensive or have potential side effects. In this context, using CAC to inform not only statin allocation but the use of multiple other preventive treatments is an active area of research. Below we discuss studies on the prognostic value of CAC in several special populations where despite increased average ASCVD risk, CAC can help further stratify risk and thereby inform a more personalized use of specific add-on therapies. Some of these uses of CAC are now discussed in recent expert consensus documents by the National Lipid Association and the Endocrine Society (Orringer et al. 2021; Newman et al. 2020), but they have not yet been incorporated into ACC/AHA or the ESC guidelines. Based on those novel studies, in Table 22.3, we present a summary of the proposed role of CAC in guiding treatment decisions for multiple preventive therapies in primary prevention.

Table 22.3 CAC score-based treatment recommendations proposed by the authors based on guidelines from scientific societies, expert consensus, and most recent research findings from observational CAC research

CAC score	Preventive therapies considerations
0	Statin may result in very modest/no absolute benefit and may be safely delayed, unless (1) estimated 10-year risk >20%, (2) diabetes, (3) severe hypercholesterolemia, or (4) patients who continue to smoke (Grundy et al. 2019)
1–99	Moderate-to-high intensity statin if <75th percentile for a patient's age and sex (Grundy et al. 2019) High intensity if >75th percentile for a patient's age and sex (Grundy et al. 2019)
100–399	High-intensity statin (Grundy et al. 2019) Aspirin 81 mg (class IIb), if not at increased bleeding risk, weaker recommendation than of CAC > 400 (Ajufo et al. 2021; Cainzos-Achirica et al. 2020) Intensification of antihypertensive treatment if hypertension (Parcha et al. 2021; McEvoy et al. 2017) GLP-1RA for patients with diabetes (Cainzos-Achirica et al. 2021a) Icosepant ethyl for patients with hypertriglyceridemia (Cainzos-Achirica et al. 2021b)
≥400	High-intensity statin (Grundy et al. 2019) Aspirin 81 mg (class IIb), if not at increased bleeding risk, stronger recommendation (even rates very similar to secondary prevention) (Ajufo et al. 2021; Cainzos-Achirica et al. 2020) Intensification of antihypertensive treatment if hypertension (Parcha et al. 2021; McEvoy et al. 2017) GLP-1RA for patients with diabetes (Cainzos-Achirica et al. 2021a) Icosepant ethyl for patients with hypertriglyceridemia (Cainzos-Achirica et al. 2021b)

CAC coronary artery calcium, *GLP-1RA* glucagon-like peptide-1 receptor agonists

Aspirin

ACC/AHA guidelines recommend considering low-dose aspirin therapy for adults at very high ASCVD risk and not at high bleeding risk (class of recommendation IIa). However, the optimal approach for identifying appropriate, very high-risk candidates for therapy is unclear. Analyses from two cohorts (MESA and the Dallas Heart Study) suggest that among individuals at low bleeding risk, CAC ≥ 100, and particularly a CAC score ≥ 400, identifies individuals who would likely derive net benefit from aspirin. In contrast, CAC = 0 identifies individuals who would likely derive net harm from aspirin, even among those at low bleeding risk. Conversely, the PCE failed to identify subgroups expected to derive net benefit, not even among those at estimated ASCVD risk >20%. CAC can thus provide a valuable tool for a selective, most personalized allocation of low-dose aspirin in primary prevention (Ajufo et al. 2021; Cainzos-Achirica et al. 2020).

Blood Pressure (BP) Goals

The ACC/AHA guidelines for the management of high BP recommend using the PCE to estimate 10-year ASCVD risk to establish BP treatment goals. Analysis from multiple prospective cohorts showed that among individuals with elevated BP as well as among strata defined by increasing hypertension severity, those with CAC > 0 had a significantly higher incidence of CVD events as opposed to those with CAC = 0, and the number needed to be treated to prevent one future CVD event was lower if CAC > 0 than CAC = 0, in all groups. These results were consistent across racial/ethnic subgroups (Parcha et al. 2021). Furthermore, among individuals with systolic BP <160 mm Hg and 10-year ASCVD risk estimates between 5% and 15%, CAC > 100 can identify those who would likely benefit from initiation or intensification of systolic BP goal compared with CAC = 0 (McEvoy et al. 2017).

Diabetes

Individuals with diabetes are more likely to have ASCVD events, and guidelines recommend at least a moderate-intensity statin in all adults 40–75 years of age with diabetes; and high-intensity statin in those at higher ASCVD risk. Studies have shown that CAC can be useful in stratifying risk among individuals with diabetes (Jensen et al. 2020; Malik et al. 2017), as the risk for CHD and ASCVD events increases progressively with higher CAC scores. Moreover, CAC augments the prognostic information provided by diabetes duration, glycemic control, and insulin use. Thus, CAC may be used to personalize the intensity of statin therapy in patients with diabetes, and may help inform the allocation of novel, costly ASCVD

risk-reduction pharmacotherapies in diabetes such as glucagon-like peptide-1 receptor agonists (GLP-1RAs) (Cainzos-Achirica et al. 2021a).

Hypertriglyceridemia

With a prevalence of 25% of hypertriglyceridemia in the general United States population, and evidence of an independent association between levels of triglyceride-rich particles and risk of ASCVD events, there is great interest in the identification of specific pharmacological interventions that can help further reduce ASCVD risk in these individuals. Icosapent ethyl (IPE) is currently the only omega-3-based therapy approved by the Food and Drug Administration (FDA) for ASCVD risk reduction in primary prevention patients with hypertriglyceridemia, and other fatty acids have and are being evaluated for this purpose. In this contest, a recent analysis pooling MESA and three other population-based cohorts suggested that CAC can have a role in identifying high-risk candidates for IPE in primary prevention, and this was true among individuals with and without diabetes (Cainzos-Achirica et al. 2021b).

Severe Hypercholesterolemia and Genetically Confirmed Familial Hypercholesterolemia

There is substantial heterogeneity in long-term ASCVD risk among individuals with severe hypercholesterolemia. Although individuals with high LDL-C (>190 mg/dL) and individuals with familial hypercholesterolemia (FH) are at increased risk for ASCVD compared to the general population, a considerable proportion of these individuals do not experience ASCVD events despite having lifelong elevated LDL-C levels. In this context, multiple studies have shown that CAC has the ability to accurately stratify ASCVD risk in these individuals. For instance, in MESA, among those with LDL-C $\geq$ 190 mg/dL and CAC = 0, 10-year ASCVD event rates were 3.7%, compared with 20% in individuals with LDL-C $\geq$ 190 mg/dL and CAC > 0 (Sandesara et al. 2020).

Similarly, among individuals with genetically confirmed FH, CAC has the ability to shed light on ASCVD risk heterogeneity and inform a more personalized management. During a 10-year follow-up of patients with heterozygous FH from Brazil, higher CAC scores were strongly associated with ASCVD, while events were remarkably lower among those with CAC = 0 (Miname et al. 2019). Of note, according to a meta-analysis of 9 small FH clinical cohorts, the prevalence of CAC = 0 in individuals with FH is 45% (Mszar et al. 2020). While guidelines are consistent in their recommendation of statin therapy in all individuals with genetically confirmed FH as well as in those with LDL-C > 190 mg/dL, these studies suggest that CAC may help individualize the allocation of more costly add-on interventions, such as

PCSK9 inhibitors or inclisiran. Risk stratification using CAC tailored to patients with FH may further enhance the cost-effectiveness and resource utilization of these novel lipid-lowering treatments.

Follow-Up on Initial CAC Scan

Given the predictive and prognostic power of CAC, particularly the power of CAC = 0, there is an overall interest in knowing the "warranty period" during which individuals with CAC = 0 remain at low or lower risk of events, and when a repeat scan will most likely detect conversion to CAC > 0. The time for conversion to CAC > 0 varies according to baseline estimated ASCVD risk, age, sex, race/ethnicity, and diabetes status. Studies have shown that for individuals with CAC = 0 undergoing yearly CAC scans, conversion to CAC > 0 occurred in 15% of individuals between 3 and 7 years after the initial scan. Repeat CAC scanning can be considered in 5–7 years for patients at low 10-year ASCVD risk (<5%), 3–5 years in those at intermediate risk for ASCVD (5%–10%), and three years in those with diabetes (Dzaye et al. 2021).

The value of repeating the scan in individuals with CAC = 0 relies on the potential for changing preventive treatment recommendations, which will be more intensive if the CAC score increases, and therefore, absolute risk increases. On the other hand, in patients with CAC > 0, particularly those with CAC > 100, repeating the scan will unlikely change established management. In addition, serial CAC testing to assess the efficacy of preventive therapies is not recommended.

Conclusions

The CAC score is a marker of coronary atherosclerosis, is strongly and independently associated with incident CHD/ASCVD events, and is a powerful tool for risk assessment in primary prevention. Among patients uncertain about their risk management after initial clinical risk assessment, CAC can be used to reclassify risk by identifying individuals at higher risk (CAC > 0, and particularly CAC > 100), and de-risk individuals who are expected to derive modest absolute benefit from certain pharmacological interventions (CAC = 0). This is true across age groups, in both men and women, and across a wide range of clinical risk management scenarios. CAC helps further personalize the allocation of statins in primary prevention, a role that is currently endorsed across international cardiovascular prevention guidelines, with studies suggesting that this use of CAC may enhance physician prescription of statins and long-term adherence by patients. In the near future, CAC may also help personalize the allocation of multiple other preventive interventions among individuals free of clinical ASCVD, a very active area of research and innovation in this space.

References

Ajufo E, Ayers CR, Vigen R, Joshi PH, Rohatgi A, de Lemos JA, Khera A. Value of coronary artery calcium scanning in association with the net benefit of aspirin in primary prevention of atherosclerotic cardiovascular disease. JAMA Cardiol. 2021;6:179–87.

Al Rifai M, Blaha MJ, Nambi V, et al. Determinants of incident atherosclerotic cardiovascular disease events among those with absent coronary artery calcium: multi-ethnic study of atherosclerosis. Circulation. 2021. https://doi.org/10.1161/CIRCULATIONAHA.121.056705.

Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Circulation. 2019;140:e596–646.

Blaha M, Budoff MJ, Shaw LJ, Khosa F, Rumberger JA, Berman D, Callister T, Raggi P, Blumenthal RS, Nasir K. Absence of coronary artery calcification and all-cause mortality. JACC Cardiovasc Imaging. 2009;2:692–700.

Blaha MJ, Cainzos-Achirica M, Greenland P, et al. Role of coronary artery calcium score of zero and other negative risk markers for cardiovascular disease : the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation. 2016;133:849–58.

Bodenheimer T, Lorig K, Holman H, Grumbach K. Patient self-management of chronic disease in primary care. JAMA. 2002;288:2469–75.

Budoff MJ, Young R, Burke G, et al. Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD) events: the multi-ethnic study of atherosclerosis (MESA). Eur Heart J. 2018;39:2401–8.

Cainzos-Achirica M, Miedema MD, McEvoy JW, et al. Coronary artery calcium for personalized allocation of aspirin in primary prevention of cardiovascular disease in 2019: the MESA study (Multi-Ethnic Study of Atherosclerosis). Circulation. 2020;141:1541–53.

Cainzos-Achirica M, Patel KV, Quispe R, et al. Coronary artery calcium for the allocation of GLP-1RA for primary prevention of atherosclerotic cardiovascular disease. JACC Cardiovasc Imaging. 2021a;14:1470–2.

Cainzos-Achirica M, Quispe R, Dudum R, et al. CAC for risk stratification among individuals with hypertriglyceridemia free of clinical atherosclerotic cardiovascular disease. JACC Cardiovasc Imaging. 2021b. https://doi.org/10.1016/J.JCMG.2021.10.017.

Cohen R, Budoff M, McClelland RL, Sillau S, Burke G, Blaha M, Szklo M, Uretsky S, Rozanski A, Shea S. Significance of a positive family history for coronary heart disease in patients with a zero coronary artery calcium score (from the Multi-Ethnic Study of Atherosclerosis). Am J Cardiol. 2014;114:1210–4.

DeFilippis AP, Young R, Carrubba CJ, McEvoy JW, Budoff MJ, Blumenthal RS, Kronmal RA, McClelland RL, Nasir K, Blaha MJ. An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. Ann Intern Med. 2015;162:266–75.

Demer LL, Tintut Y. Vascular calcification: pathobiology of a multifaceted disease. Circulation. 2008;117:2938–48.

Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med. 2009;358:1336–45.

Dzaye O, Dardari ZA, Cainzos-Achirica M, et al. Warranty period of a calcium score of zero: comprehensive analysis from MESA. JACC Cardiovasc Imaging. 2021;14:990–1002.

Erbel R, Mhlenkamp S, Moebus S, et al. Coronary risk stratification, discrimination, and reclassification improvement based on quantification of subclinical coronary atherosclerosis: the Heinz Nixdorf Recall study. J Am Coll Cardiol. 2010;56:1397–406.

Greenland P, Blaha MJ, Budoff MJ, Erbel R, Watson KE. Coronary calcium score and cardiovascular risk. J Am Coll Cardiol. 2018;72:434–47.

Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of

the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Circulation. 2019;139:E1082–143.

Haque W, Grandhi GR, Kanaya AM, et al. Implications of the 2019 American College of Cardiology/American Heart Association primary prevention guidelines and potential value of the coronary artery calcium score among south Asians in the US: the Mediators of Atherosclerosis in South Asians Living in America (MASALA) study. Atherosclerosis. 2021;334:48–56.

Hecht H, Blaha MJ, Berman DS, Nasir K, Budoff M, Leipsic J, Blankstein R, Narula J, Rumberger J, Shaw LJ. Clinical indications for coronary artery calcium scoring in asymptomatic patients: expert consensus statement from the Society of Cardiovascular Computed Tomography. J Cardiovasc Comput Tomogr. 2017;11:157–68.

Jensen JC, Dardari ZA, Blaha MJ, et al. Association of body mass index with coronary artery calcium and subsequent cardiovascular mortality: the coronary artery calcium consortium. Circ Cardiovasc Imaging. 2020;13:9495.

Kalia NK, Miller LG, Nasir K, Blumenthal RS, Agrawal N, Budoff MJ. Visualizing coronary calcium is associated with improvements in adherence to statin therapy. Atherosclerosis. 2006;185:394–9.

Kanaya AM, Kandula NR, Ewing SK, Herrington D, Liu K, Blaha MJ, Srivastava S, Dave SS, Budoff MJ. Comparing coronary artery calcium among US South Asians with four racial/ethnic groups: the MASALA and MESA studies. Atherosclerosis. 2014;234:102–7.

Karmali KN, Goff DC, Ning H, Lloyd-Jones DM. A systematic examination of the 2013 ACC/AHA pooled cohort risk assessment tool for atherosclerotic cardiovascular disease. J Am Coll Cardiol. 2014;64:959–68.

Lakoski SG, Greenland P, Wong ND, Schreiner PJ, Herrington DM, Kronmal RA, Liu K, Blumenthal RS. Coronary artery calcium scores and risk for cardiovascular events in women classified as "low risk" based on Framingham risk score: the Multi-Ethnic Study of Atherosclerosis (MESA). Arch Intern Med. 2007;167:2437–42.

Lin JS, Evans CV, Johnson E, Redmond N, Coppola EL, Smith N. Nontraditional risk factors in cardiovascular disease risk assessment: updated evidence report and systematic review for the US preventive services task force. JAMA. 2018;320:281–97.

Lloyd-Jones DM, Braun LT, Ndumele CE, Smith SC, Sperling LS, Virani SS, Blumenthal RS. Use of risk assessment tools to guide decision-making in the primary prevention of atherosclerotic cardiovascular disease: a special report from the American Heart Association and American College of Cardiology. Circulation. 2019;139:E1162–77.

Malik S, Zhao Y, Budoff M, Nasir K, Blumenthal RS, Bertoni AG, Wong ND. Coronary artery calcium score for long-term risk classification in individuals with type 2 diabetes and metabolic syndrome from the multi-ethnic study of atherosclerosis. JAMA Cardiol. 2017;2:1332–40.

Mamudu HM, Paul TK, Veeranki SP, Budoff M. The effects of coronary artery calcium screening on behavioral modification, risk perception, and medication adherence among asymptomatic adults: a systematic review. Atherosclerosis. 2014;236:338–50.

McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. Distribution of coronary artery calcium by race, gender, and age: results from the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation. 2006;113:30–7.

McEvoy JW, Martin SS, Dardari ZA, et al. Coronary artery calcium to guide a personalized risk-based approach to initiation and intensification of antihypertensive therapy. Circulation. 2017;135:153–65.

Miedema MD, Dardari ZA, Nasir K, et al. Association of coronary artery calcium with long-term, cause-specific mortality among young adults. JAMA Netw Open. 2019;2:e197440.

Miname MH, Bittencourt MS, Moraes SR, Alves RIM, Silva PRS, Jannes CE, Pereira AC, Krieger JE, Nasir K, Santos RD. Coronary artery calcium and cardiovascular events in patients with familial hypercholesterolemia receiving standard lipid-lowering therapy. JACC Cardiovasc Imaging. 2019;12:1797–804.

Mitchell JD, Fergestrom N, Gage BF, Paisley R, Moon P, Novak E, Cheezum M, Shaw LJ, Villines TC. Impact of statins on cardiovascular outcomes following coronary artery calcium scoring. J Am Coll Cardiol. 2018;72:3233–42.

Montori VM, Brito JP, Murad MH. The optimal practice of evidence-based medicine: incorporating patient preferences in practice guidelines. JAMA. 2013;310:2503–4.

Mori H, Torii S, Kutyna M, Sakamoto A, Finn AV, Virmani R. Coronary artery calcification and its progression: what does it really mean? JACC Cardiovasc Imaging. 2018;11:127–42.

Mszar R, Grandhi GR, Valero-Elizondo J, et al. Absence of coronary artery calcification in middle-aged familial hypercholesterolemia patients without atherosclerotic cardiovascular disease. JACC Cardiovasc Imaging. 2020;13:1090–2.

Muhlestein JB, Knowlton KU, Le VT, et al. Coronary artery calcium versus pooled cohort equations score for primary prevention guidance. JACC Cardiovasc Imaging. 2021. https://doi.org/10.1016/J.JCMG.2021.11.006.

Nasir K, Cainzos-Achirica M. Role of coronary artery calcium score in the primary prevention of cardiovascular disease. BMJ. 2021. https://doi.org/10.1136/BMJ.N776.

Nasir K, Rubin J, Blaha MJ, et al. Interplay of coronary artery calcification and traditional risk factors for the prediction of all-cause mortality in asymptomatic individuals. Circ Cardiovasc Imaging. 2012;5:467–73.

Nasir K, Bittencourt MS, Blaha MJ, et al. Implications of coronary artery calcium testing among statin candidates according to American College of Cardiology/American Heart Association cholesterol management guidelines: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol. 2015;66:1657–68.

Newman CB, Blaha MJ, Boord JB, et al. Lipid management in patients with endocrine disorders: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2020;105:3613–82.

Orimoloye OA, Budoff MJ, Dardari ZA, et al. Race/ethnicity and the prognostic implications of coronary artery calcium for all-cause and cardiovascular disease mortality: the coronary artery calcium consortium. 2018. J Am Heart Assoc. https://doi.org/10.1161/JAHA.118.010471.

Orringer CE, Blaha MJ, Blankstein R, Budoff MJ, Goldberg RB, Gill EA, Maki KC, Mehta L, Jacobson TA. The National Lipid Association scientific statement on coronary artery calcium scoring to guide preventive strategies for ASCVD risk reduction. J Clin Lipidol. 2021;15:33–60.

Parcha V, Malla G, Kalra R, Li P, Pandey A, Nasir K, Arora G, Arora P. Coronary artery calcium score for personalization of antihypertensive therapy: a pooled cohort analysis. Hypertension. 2021;77:1106–18.

Patel J, Al Rifai M, Blaha MJ, et al. Coronary artery calcium improves risk assessment in adults with a family history of premature coronary heart disease: results from multiethnic study of atherosclerosis. Circ Cardiovasc Imaging. 2015. https://doi.org/10.1161/CIRCIMAGING.115.003186.

Patel J, Al Rifai M, Scheuner MT, Shea S, Blumenthal RS, Nasir K, Blaha MJ, McEvoy JW. Basic vs more complex definitions of family history in the prediction of coronary heart disease: the multi-ethnic study of atherosclerosis. Mayo Clin Proc. 2018;93:1213–23.

Pearson GJ, Thanassoulis G, Anderson TJ, et al. 2021 Canadian cardiovascular society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in adults. Can J Cardiol. 2021;37:1129–50.

Peters SAE, den Ruijter HM, Bots ML, Moons KGM. Improvements in risk stratification for the occurrence of cardiovascular disease by imaging subclinical atherosclerosis: a systematic review. Heart. 2012;98:177–84.

Sandesara PB, Mehta A, O'Neal WT, Kelli HM, Sathiyakumar V, Martin SS, Blaha MJ, Blumenthal RS, Sperling LS. Clinical significance of zero coronary artery calcium in individuals with LDL cholesterol ≥190 mg/dL: the Multi-Ethnic Study of Atherosclerosis. Atherosclerosis. 2020;292:224–9.

Sarwar A, Shaw LJ, Shapiro MD, et al. Diagnostic and prognostic value of absence of coronary artery calcification. JACC Cardiovasc Imaging. 2009;2:675–88.

Shaw LJ, Min JK, Nasir K, et al. Sex differences in calcified plaque and long-term cardiovascular mortality: observations from the CAC consortium. Eur Heart J. 2018;39:3727–35.

Tota-Maharaj R, Blaha MJ, McEvoy JW, et al. Coronary artery calcium for the prediction of mortality in young adults <45 years old and elderly adults >75 years old. Eur Heart J. 2012;33:2955–62.

Tota-Maharaj R, Blaha MJ, Blankstein R, Silverman MG, Eng J, Shaw LJ, Blumenthal RS, Budoff MJ, Nasir K. Association of coronary artery calcium and coronary heart disease events in young and elderly participants in the multi-ethnic study of atherosclerosis: a secondary analysis of a prospective, population-based cohort. Mayo Clin Proc. 2014;89:1350–9.

Virani SS, Alonso A, Aparicio HJ, et al. Heart disease and stroke statistics—2021 update. Circulation. 2021;143:E254–743.

Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice developed by the task force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies with the special contribution of the European Association of Preventive Cardiology (EAPC). Eur Heart J. 2021;42:3227–337.

Volgman AS, Palaniappan LS, Aggarwal NT, et al. Atherosclerotic cardiovascular disease in South Asians in the United States: epidemiology, risk factors, and treatments: a scientific statement from the American Heart Association. Circulation. 2018;138:e1–e34.

Chapter 23
Cardiac Computed Tomography Angiography for Prevention of Cardiovascular Events

Rhanderson Cardoso and Ron Blankstein

Abbreviations

ASCVD	Atherosclerotic cardiovascular disease
CAC	Coronary artery calcium
CAD	Coronary artery disease
CCTA	Coronary computed tomography angiography
CIN	Contrast-induced nephropathy
CT	Computed tomography
FAI	Fat attenuation index
HU	Hounsfield Units

Introduction

Coronary CT angiography (CCTA) is a well-established technique for a noninvasive evaluation of the coronary anatomy in selected patients with stable chest pain syndromes or low to intermediate risk acute chest pain. When compared with functional tests which are designed to detect ischemia CCTA has two major advantages. First, CCTA has a high negative predictive value to exclude the presence of either obstructive or nonobstructive coronary artery disease (CAD). Thus, a normal CCTA (i.e., having no coronary plaque or stenosis) is associated with a very low rate of incident cardiovascular events. Second, CCTA has a unique ability to identify subclinical coronary artery disease, which has immediate implications for the initiation

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or intensification of preventive therapies, both behavioral and pharmacologic. This capability is particularly relevant given the recent expansion of preventive pharmacotherapy options, which now span antiplatelet agents, statin and nonstatin lipid-lowering therapies, cardiometabolic agents in patients with diabetes, and more. Herein, we highlight the power of CCTA as an adjunct tool for the diagnosis of CAD and its downstream effect in the prevention of atherosclerotic cardiovascular disease (ASCVD) outcomes.

Imaging Technique

Computed tomography (CT) imaging is based on the attenuation of X-rays in tissues. An electrical current in the X-ray tube (source) causes electrons to migrate from a cathode to an anode, generating X-rays, which in turn travel through the patient, where they are attenuated to different extents based on the types of tissue encountered. Residual X-rays that are not attenuated reach the image detector, where they are converted to light and then to an electric signal. Each pixel in the CT image is a representation of X-ray attenuation in that volume of tissue, expressed numerically in Hounsfield Units (HU).

This technology has been used in cardiovascular imaging for nearly 40 years (Lipton et al. 1984). Imaging of the coronary arteries, however, was initially challenging due to the small caliber and highly mobile nature of these vessels. Over the last few decades, technological advances in the field have resulted in sufficient spatial and temporal resolution to enable imaging of the coronary arteries. Specifically, faster gantry rotation and an increasing number of detector rows have been paramount to improve the quality of coronary imaging allowing higher resolution images while "freezing" the motion of the heart.

Modern CT scanners have a rotation time of 240–280 msec. Typically, the temporal resolution of the scanner equals to half the gantry rotation time, because a 180° rotation is sufficient to acquire data on all of the volume of interest. Therefore, the temporal resolution is approximately 120–140 msec on most modern scanners. This can be improved further by dual-source technology, in which two separate X-ray sources and detectors are hosted within the same gantry. Only one-quarter of the full gantry rotation in dual-source scanners is needed for 360° coverage, which can improve the temporal resolution to as low as 66 msec. Another significant improvement with modern cardiac CT scanners is the number of detector rows, which ranges from 64 to 320, allowing for increased patient coverage with a single rotation (up to 16-cm with 320-detector row CT systems). The narrow width of each detector now ranges from 0.5 to 0.625 mm, leading to high spatial-resolution imaging.

Parallel to improvements in temporal and spatial resolution, there has been a substantial reduction in the overall radiation dose with CCTA. The reasons are multifactorial. First, the use of lower tube voltage in appropriate candidates. The tube voltage describes the peak energy of the emitted X-rays. While 120-kVp imaging

may be needed for patients who are obese, the use lower of tube voltage, when feasible, lowers the radiation dose significantly as there is an exponential association between kVp and dose. Other techniques for reducing radiation dose include current modulation, axial acquisition using prospective ECG-triggering, iterative reconstruction, and high-pitch helical CT (Hausleiter et al. 2012; Deseive et al. 2015). The randomized PROTECTION III trial found a 69% reduction in radiation exposure with prospective ECG-triggered axial scanning compared with retrospective helical scanning, with similar image quality (Hausleiter et al. 2012). Altogether, these techniques allow for CCTA imaging with very low radiation doses with modern scanners (<2 mSv) (Kosmala et al. 2019).

Despite these major advances, there are still technical challenges in certain patient groups that limit CT imaging of the coronaries with low radiation dose and high temporal and spatial resolution. Notably, patients who are obese still require higher tube voltage, which increases radiation dose. Also, individuals with fast or irregular heart rates may require a helical acquisition using retrospective gating or a wider acquisition window within the RR interval, both techniques which increase radiation exposure. Even with increased radiation exposure, image quality may still be limited in these patients. Patients who are unable to hold their breath are also unsuitable for CCTA imaging. Therefore, many of the attributes of CCTA described in this chapter and elsewhere can only be fully achieved when scanner technology and patient factors allow for good image quality. Furthermore, because the main applications of CCTA in this chapter relate to plaque identification for optimizing preventive therapies, it is noteworthy that in challenging situations (e.g., obesity, irregular heart rate), a coronary artery calcium scan (see Chap. 22) may be technically easier to perform and less susceptible to some of the technical limitations of CCTA.

Safety of Contrast Administration

Unlike CAC scans, CCTA requires the administration of iodine contrast to opacify the coronary arteries. Patients require an intravenous access capable of flows of 5–7 mL/s for a total contrast volume of 50–90 mL. Adverse reactions to contrast media are infrequent. They can be divided into anaphylactoid (or hypersensitivity) and nonanaphylactoid reactions. Serious hypersensitivity reactions are quite rare. In a study with 29,508 patients undergoing contrast-enhanced CT with a low osmolar, nonionic contrast agent, moderate or severe reactions occurred in 23 patients (0.08%) (Mortele et al. 2005). Pretreatment with corticosteroids and antihistamines is routinely administered for patients with a history of mild reactions to iodinated contrast. Those with a history of severe or breakthrough reactions should be considered for alternative imaging or undergo evaluation by an allergist/immunologist.

Whereas anaphylactoid reactions are idiosyncratic and independent of dose, nonanaphylactoid reactions are dependent on dose and concentration of contrast media. These reactions are also infrequent and include gastrointestinal symptoms,

pulmonary edema, vasovagal reactions, and contrast-induced nephropathy (CIN). CIN is characterized by an increase in serum creatinine of at least 0.5 mg/dL within 24–72 hours. Recovery of renal function typically occurs in 7–10 days. The major risk factors for CIN include baseline renal dysfunction, diabetes, volume of contrast, and high osmolality agents (Tao et al. 2016). Intravenous administration of iodinated contrast, such as for CCTA, carries a lower risk of CIN than intra-arterial administration of contrast for coronary and other arterial interventions. Indeed, several observational studies have shown that the incidence of acute kidney injury may be no different in those who receive contrast media for CT scans compared with controls who do not (McDonald et al. 2013, 2014; Davenport et al. 2013).

CCTA Use in Symptomatic Patients

The aforementioned advances in CCTA technology, together with a robust evidence base supporting the accuracy and efficacy of CCTA testing, have established CCTA as a first-line noninvasive testing option for patients with acute or stable chest patients who do not have known CAD (Marwick et al. 2015; Knuuti et al. 2020; Moss et al. 2017; Gulati et al. 2021). Accordingly, the most recent guidelines from the United States, United Kingdom, and Europe have assigned a prominent role for CCTA for the evaluation of symptomatic patients (Knuuti et al. 2020; Moss et al. 2017; Gulati et al. 2021). CCTA has an outstanding negative predictive value for obstructive epicardial atherosclerotic plaque, exceeding that of functional studies aimed at detecting ischemia (Stein et al. 2008). In a systematic review, the negative predictive value for excluding significant (≥50%) coronary stenosis with CCTA was approximately 96% compared with invasive angiography in studies with an average CAD prevalence of 61% (Stein et al. 2008). The negative likelihood ratio of CCTA is less than 0.1 (Stein et al. 2008; Budoff et al. 2008).

Absence of Plaque on CCTA

The prognosis of patients without any CAD by CCTA is excellent. In a study with 1304 patients who underwent CCTA for suspected CAD, 46% of whom had moderate or high pretest probability, there were no major cardiovascular events over a mean follow-up of 52 months among the 503 (42%) patients who had no CAD (Andreini et al. 2012). In a meta-analysis including 9592 symptomatic patients with a median follow-up of 20 months, the annualized rate of major adverse cardiovascular events was 0.17% per year in patients without CAD on CCTA, compared with 8.8% per year in those with obstructive epicardial disease (>50% luminal stenosis) (Hulten et al. 2011).

Patients with no CAD (i.e., no plaque or stenosis) on CCTA, as shown in Fig. 23.1, have a very low event rate and benefit from preventive pharmacotherapies

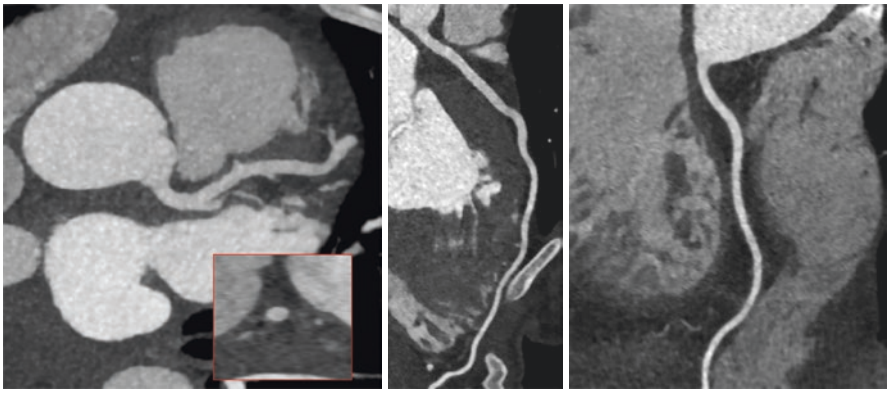

Fig. 23.1 Example of normal coronary CTA with no plaque or stenosis. The insert (red box) shows an en-face view of the LAD showing no plaque or stenosis

may be more limited. Although data on CCTA-guided preventive care for asymptomatic patients are limited, CAC data may be considered in this regard. In a cohort of 13,644 individuals from a military population who underwent CAC testing, statin therapy in patients without plaque (i.e., CAC = 0) was not associated with a significant reduction in adverse cardiovascular events over a median follow-up of 9.4 years (Mitchell Joshua et al. 2018). Although a negative CCTA should be even more reassuring than a CAC of zero (as it denotes the absence of both calcified and noncalcified plaque), this data should be considered with caution due to its observational nature. Moreover, it is conceivable that despite the very low risk of patients who do not have any plaque on CCTA, there could be long-term benefits to some preventive therapies, albeit the magnitude of such a benefit would be expected to be lower in patient who do not have any plaque when compared with individuals who have significant plaque. Another caveat is that outcomes data in asymptomatic individuals may be less applicable to symptomatic populations.

Prognostic Implications of Plaque Burden by CCTA

In addition to its role in ruling out disease and identifying patients without CAD who are at low risk of cardiovascular events, CCTA has a major advantage over ischemic testing with functional imaging: its ability to identify subclinical coronary atherosclerosis. Approximately 1 in 3 patients with suspected CAD who undergo CCTA are found to have nonobstructive CAD (Shaw et al. 2021). Visualization of CAD on anatomical imaging, even if nonobstructive, identifies patients at increased risk for future events despite the absence of obstructive disease, who may benefit from more intense preventive therapy (Bittencourt et al. 2014; Hulten et al. 2014).

A comprehensive meta-analysis of nearly 50,000 patients over a median follow-up of 2.5 years found an 8-fold higher annual event rate in those with nonobstructive

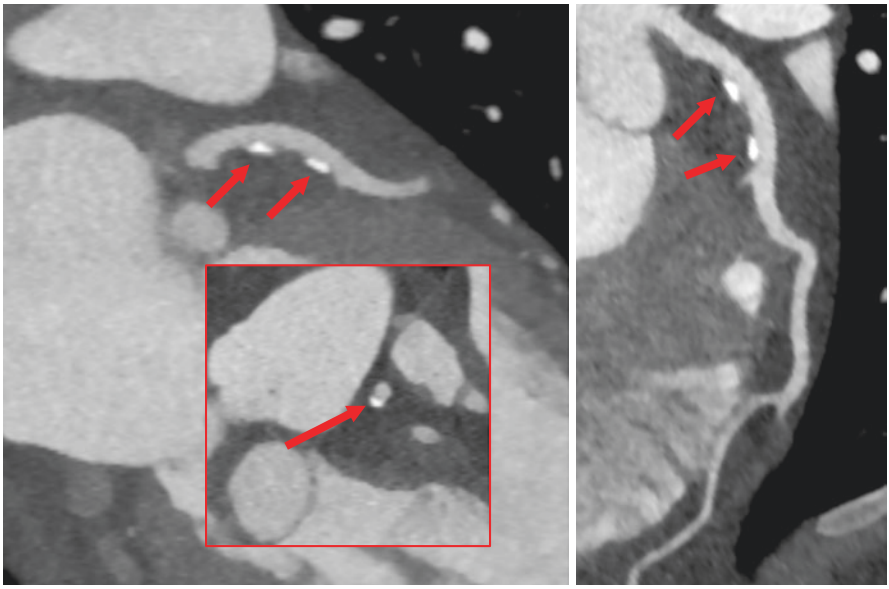

Fig. 23.2 Example of coronary CTA showing a small amount of predominantly calcified plaque involving the LAD (red arrows point to areas of plaque). The segment involvement score is 2

CAD (1.6%) compared with those with no CAD (0.2%) (Shaw et al. 2021). Patients with a small burden of atherosclerotic plaque, as shown in Fig. 23.2, may benefit from intensification of medical therapy for prevention of atherosclerotic events, even without obstructive plaque.

The importance of overall plaque burden was demonstrated in the Western Denmark Heart Registry. Among 23,759 symptomatic participants who underwent CCTA and were followed for a median of 4.3 years, the presence of obstructive CAD was not associated with a higher risk than nonobstructive disease when stratified by five groups of CAC score. In other words, patients with a similar plaque burden, as measured by the CAC score, had similar event rates regardless of whether there was obstructive plaque or not (Mortensen et al. 2020).

High-Risk Plaque Features

Certain high-risk plaque features may also add to the risk prediction of CCTA imaging. Specifically, the presence of low-attenuation plaque (typically defined as plaque that has a noncalcified component with <30 HU), positive remodeling, spotty calcifications, and the napkin-ring sign (central area of low-attenuation plaque with a peripheral rim of high attenuation) are all associated with a high risk of downstream events (Shaw et al. 2021; Cury et al. 2016). These plaque attributes can be identified during routine CCTA interpretation and do not require the need of any specific

software. However, similar to the identification of high-risk plaque features using invasive techniques, the positive predictive value of CCTA high-risk plaque to identify the site of a future acute coronary syndrome event is low.

In the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) study, 676 (15%) of 4415 patients who underwent CCTA for suspicion of CAD had high-risk plaques, which was associated with a higher risk of major adverse cardiac events even after adjustment for the ASCVD risk score and the presence of significant stenosis (aHR 1.72; 95% CI 1.3–2.62) (Ferencik et al. 2018). Similarly, in the Scottish Computed Tomography of the Heart (SCOT-HEART) trial, the presence of positive remodeling or low attenuation plaque had a threefold higher incidence of coronary heart disease death or nonfatal myocardial infarction relative to those without high-risk plaque features (Williams et al. 2019). However, high-risk plaque was not associated with a higher event rate once adjusted for coronary artery calcium (CAC), which is a surrogate measure of total coronary plaque burden.

Estimating Plaque Burden

Given the increased evidence supporting the prognostic value of plaque burden, a recent Expert Consensus Document on Coronary CT Imaging of Atherosclerotic Plaque from the Society of Cardiovascular Computed Tomography and the North American Society of Cardiovascular Imaging emphasized the importance of adding an assessment of the total burden of atherosclerotic plaque on CCTA reports, as well as whether high-risk plaque features are present (Shaw et al. 2021). Although fully quantitative and automated measurements of plaque burden are not widely available, there are several methods that can be used to estimate overall plaque burden: (a) Quantify CAC score – this requires performing an additional noncontrast CT scan during the CCTA acquisition, which is associated with a small increase in radiation dose; (b) Determine the segment involvement score (SIS) – a semi-quantitative assessment which represents the number of coronary artery segments which have plaque, using a 16-segment model (left main and proximal, mid, and distal segments of left anterior descending artery, diagonal or ramus branch, left circumflex, obtuse marginal, and right coronary artery); (c) Provide a visual estimation of overall plaque burden which incorporate an estimate of the overall amount of calcified and noncalcified plaque.

Supporting the role of measuring the SIS, a study of 3243 patients found that those with nonobstructive, but extensive CAD (defined as a segment involvement score > 4) had a similar risk of cardiovascular death or myocardial infarction over a median follow-up of 3.6 years compared with those with obstructive, but nonextensive CAD (14.5 vs. 13.6/1000 patient-years, respectively) (see Figs. 23.3 and 23.4 for examples of moderate and extensive amount plaque on CCTA) (Bittencourt et al. 2014).

Using the above methods to estimate overall plaque burden on CCTA, extensive plaque is often defined when the CAC score is greater than 300 (if quantified, or

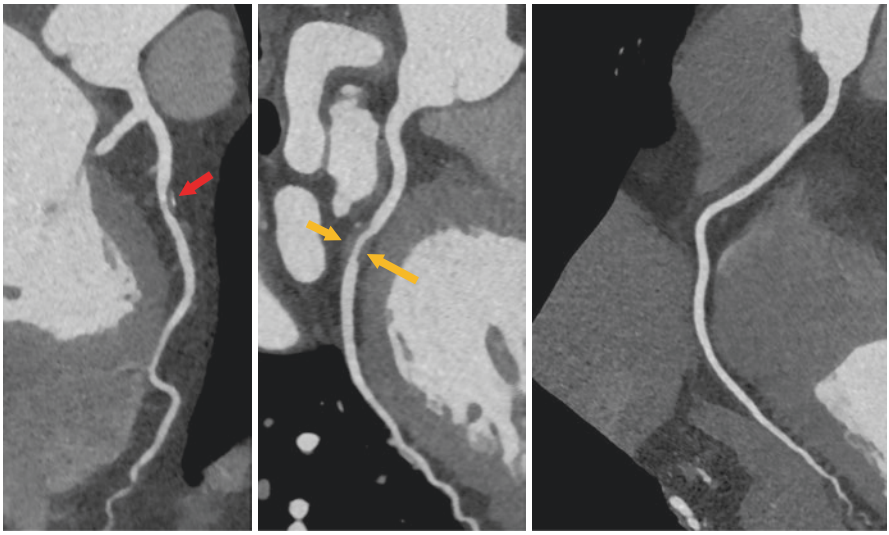

Fig. 23.3 Example of coronary CTA showing a moderate amount of predominantly noncalcified plaque involving the LAD (red arrows; mild stenosis: 25–49%) and left circumflex (orange arrows; moderate stenosis: 50–69%). The segment involvement score is 3

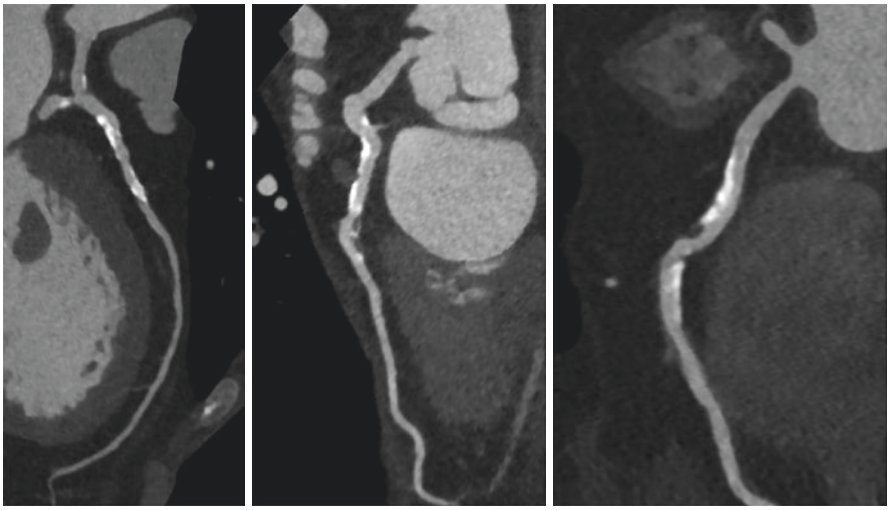

Fig. 23.4 Example of coronary CTA showing extensive plaque burden in a multivessel distribution, including both calcified and noncalcified plaque. The segment involvement score is 9

visually assessed), or if the segment involvement score is 5 or greater. Individuals with extensive plaque will often have plaque involving all three coronary arteries, with at least one vessel demonstrating plaque which involves most of the vessel. When the CAC score exceeds 1000 (if quantified or visually assessed), the overall

amount of plaque can be categorized as very extensive, a finding which corresponds to a very high risk of future cardiovascular events (Peng et al. 2020).

CCTA and Cardiovascular Outcomes

Whether the prognostic implications of CCTA findings can ultimately improve patient outcomes was the subject of two large randomized controlled trials: SCOT-HEART and PROMISE (Newby et al. 2018; Douglas et al. 2015). In the SCOT-HEART trial, 4146 individuals with stable chest pain were randomized to standard care with or without CCTA. Standard care included a stress ECG study in 85% of the patients. Preventive therapies, such as aspirin and statin therapy, were recommended to patients with nonobstructive disease on CCTA or those with a high cardiovascular risk score (Newby et al. 2018). The rate of invasive coronary angiography (24%) or coronary revascularization (13%) was not significantly different between groups (Newby et al. 2018; Investigators S-H 2015). During a median follow-up of 4.8 years, more patients in the CCTA group were started on preventive therapies (19.4%) as compared with patients on standard care alone (14.7%). In addition to a higher rate of initiation of preventive therapies, it is likely that preventive therapies in the CCTA group were allocated to higher-risk patients, more likely to benefit from these therapies, as guided by anatomic evidence of atherosclerosis. Approximately two-thirds of patients in the CCTA group were found to have an abnormal test, either nonobstructive or obstructive CAD, whereas only 15% of patients had an abnormal stress ECG study (Investigators S-H 2015).

The primary endpoint of death from coronary heart disease or nonfatal myocardial infarction was significantly lower among patients who underwent CCTA (2.3%) relative to those who received standard-care alone (3.9%) (HR 0.59; 95% CI 0.41–0.84; $p = 0.004$), driven primarily by a lower incidence of nonfatal myocardial infarction in the CCTA group (HR 0.60; 95% CI 0.41–0.87) (Newby et al. 2018). Results were consistent among subgroups of age, sex, and baseline cardiovascular risk (Newby et al. 2018).

Important limitations of the SCOT-HEART trial include the nonblinded adjudication of clinical endpoints and the paucity of ischemic imaging in the standard of care group. This was not the case in the PROMISE study, in which 10,003 symptomatic patients were randomized to CCTA or functional testing, with blinded adjudication of outcomes (Douglas et al. 2015). In the functional-testing group, approximately two-thirds of patients underwent nuclear stress imaging, 22% had an exercise echocardiogram, and 10% had an exercise ECG. Over a follow-up of 2 years, the primary composite endpoint of death, myocardial infarction, hospitalizations for unstable angina, or major procedural complications was not significantly different between groups (3.3% CTA vs. 3.0% functional testing; HR 1.04; 95% CI 0.83–1.29) (Douglas et al. 2015).

So how does one reconcile the discrepant results between PROMISE and SCOT-HEART? The answer may lie in the differences in the endpoints used by each trial

as well as the differences in study population. In the PROMISE study, there was an excess of hospitalizations for unstable angina – which is a softer endpoint – among patients who were randomized to CCTA, possibly reflecting the consequences of informing patients that they have significant plaque in their coronary arteries. With respect to the different patient populations, the PROMISE study enrolled a lower risk group: only 12% of patients had typical angina and 25% had no chest pain (Douglas et al. 2015). In contrast, all patients in SCOT-HEART had chest pain, including 35% with typical angina, and it is likely that such patients were more likely to benefit from downstream preventive therapies (Newby et al. 2018).

In the PROMISE study, the proportion of patients taking statin therapy at 60 days was higher in the CCTA group for patients with diabetes (71.4% CCTA vs. 64.3% functional testing; OR 1.40; 95% CI 1.14–1.72; $p = 0.001$) and without diabetes (53% CCTA vs. 46% functional testing; OR 1.36; 95% CI 1.23–1.50; $p < 0.001$) (Sharma et al. 2019). The same was noted for aspirin in patients with diabetes (62.1% vs. 57.3%; $p = 0.04$) or without diabetes (52.4% vs. 47.5%; $p < 0.001$). Overall, results from SCOT-HEART and PROMISE indicate that CCTA-mediated knowledge of the coronary anatomy and global atherosclerotic burden leads to an intensification of preventive therapies. Nevertheless, the intensification of preventive therapies in both the SCOTH-HEART and PROMISE trials were suboptimal, likely reflecting the pragmatic nature of these trials, and the lack of strict guidance to treating physicians on how use CCTA results to optimize preventive therapies.

The impact of atherosclerosis imaging on patient management has also been observed in patients who are found to have a CAC > 0. A systematic review and meta-analysis including more than 11,000 participants who underwent CAC testing showed that identifying coronary atherosclerosis significantly improves the likelihood of initiating or continuing preventive therapies for cardiovascular disease – both pharmacological and lifestyle-related (Gupta et al. 2017).

CCTA Use in Symptomatic Patients with Diabetes

In the subgroup of patients with diabetes, both the SCOT-HEART and PROMISE trials showed favorable outcomes with CCTA relative to standard care or functional imaging. In the SCOT-HEART study, among 444 patients with diabetes, the absolute risk reduction in the composite endpoint of death from coronary heart disease or nonfatal myocardial infarction with CCTA was 4.6% (3.1% CCTA vs. 7.7% in standard care; HR 0.36; 95% CI 0.15–0.87) (Newby et al. 2018).

Similarly, among patients with diabetes in the PROMISE study ($n = 1908$), the outcome of cardiovascular death or myocardial infarction was significantly lower with CCTA (1.1%) relative to stress testing (2.6%) over a period of 2 years (HR 0.38; 95% CI 0.18–0.79; $p = 0.01$) (Sharma et al. 2019). Altogether, these data suggest that patients with diabetes and stable chest pain syndromes without known CAD may benefit from a testing strategy of CCTA over functional testing. This anatomical approach with identification of clinical or subclinical atherosclerosis

can lead to an intensification of prevention therapies and ultimately to the reduction in atherosclerotic cardiovascular events.

CCTA Use in Asymptomatic Patients

CAC is well established as an imaging technique for advanced risk stratification and guidance of preventive therapies in patients at intermediate-risk for atherosclerotic events who have no symptoms of CAD. A CAC score of zero indicates a low risk of events in the next 10 years, more so than several other "negative" risk markers, such as absence of carotid plaque, low C-reactive protein, absence of family history, and others (Blaha et al. 2016). Even among patients with risk factors or risk-enhancing conditions, such as diabetes, HIV, or a positive family history of premature ASCVD, CAC can provide valuable risk stratification beyond risk factors to guide personalized patient management (Cardoso et al. 2020; Pereira et al. 2020; Patel et al. 2015). Table 23.1 outlines a summary comparison of CAC vs. CCTA.

Whether CCTA has an incremental value over CAC for risk stratification and guidance of preventive therapies, with an impact on hard endpoints, is unclear. In the CONFIRM registry, 7590 participants without chest pain or known CAD from 6 countries underwent CCTA and CAC testing. After a median follow-up of 24 months, both CAC and CCTA improved the performance of risk factor-based prediction models, but the improvement in net risk reclassification from adding CCTA to a model with the CAC score was trivial (Cho et al. 2012). A subanalysis of the CONFIRM registry focused on 400 asymptomatic individuals with diabetes showed an improvement in the C-statistic from 0.64 to 0.77 by adding CCTA to a model of age, gender, and CAC score (Min et al. 2014).

Other single-center studies have shown incremental value of CCTA over CAC score in select populations of asymptomatic patients. Among 591 asymptomatic individuals with type 2 diabetes from South Korea, followed for a median of 5.3 years, CCTA parameters, such as number of obstructive lesions and severity of CAD (obstructive, nonobstructive, or no CAD), had incremental value in risk

Table 23.1 Comparison of CAC vs. CCTA

	CAC	CCTA
Intravenous contrast	No	Yes
Low heart rate required	No	Yes
Nitroglycerin for coronary vasodilation	No	Yes
Slice thickness	3 mm	0.5–0.75 mm
ECG-gating	Yes	Yes
Tube potential	120 kVp	70–120 kVp
Radiation dose	~1 mSv	Variable
Availability	+++	++
Cost	Lower	Higher

stratification over a model with traditional risk factors and CAC. The C-index for prediction of cardiac events improved from 0.72 with risk factors and CAC score to 0.82 with risk factors, CAC score, and the number of vessels with obstructive CAD (Kang et al. 2016).

Another study followed 665 patients with mean age 56 years and at least one major risk factor for CAD who underwent CCTA and CAC scoring for a median of 3.0 years. Approximately 81% of patients had CAD on CCTA. The composite endpoint of myocardial infarction, unstable angina, or coronary revascularization occurred in 6.0% of individuals. The addition of CCTA to a model including risk factors and CAC scoring significantly improved prediction and reclassification, particularly among patients with a positive CAC score. The C-statistic increased from 0.81 to 0.84 (Dedic et al. 2016).

The use of CCTA to screen for CAD in asymptomatic patients was evaluated in the FACTOR-64 randomized trial, in which 900 asymptomatic participants with type 1 or type 2 diabetes for at least 3 years were randomized to standard diabetes care with or without CCTA for screening of CAD (Muhlestein et al. 2014). Patients randomized to CCTA were recommended specific interventions for risk factors modification according to the results of CCTA: (1) standard diabetes care if no CAD; (2) patients with CAD were instructed to initiate aggressive risk factor modification, including lower LDL-C (<70 mg/dL), A1C (<6.0%), and systolic blood pressure goals (<120 mmHg). Patients randomized to standard care alone were treated according to guideline recommendations for diabetes care.

The study enrolled 900 patients, with a mean age of 61 years, mean A1C 7.5%, and average diabetes duration of ~13 years. In the CCTA group, 46%, 12%, and 11% had mild, moderate, or severe coronary stenosis, respectively. Additional testing with protocol-driven functional imaging was indicated in 14% of patients in the CCTA group, whereas invasive coronary angiography and revascularization were performed in 8% and 6% of patients, respectively (Muhlestein et al. 2014). In the control group, 5% and 2% underwent invasive angiography and revascularization, respectively.

Over a mean follow-up time of 4 years, the incidence of the primary outcome of all-cause mortality, nonfatal myocardial infarction or unstable angina requiring hospitalization was not significantly different between groups (CCTA 6.2%, control 7.6%; HR 0.80; 95% CI 0.49–1.32; $p = 0.38$). Although the outcomes of FACTOR-64 dampened enthusiasm for CAD screening with CCTA in asymptomatic patients, the results of the study corroborated the notion that plaque visualization has the potential to improve risk factor management. When compared with subjects in the control group, individuals in the CCTA group had significant improvements in LDL-C, HDL-C, and blood pressure parameters (Muhlestein et al. 2014). Nevertheless, the overall event rates in this well-treated population were low which reduced the ability to identify a difference between the two groups.

The role of CCTA in primary prevention is being explored further in the Computed Tomography Coronary Angiography for the Prevention of Myocardial Infarction (SCOT-HEART 2) Trial (NCT03920176). The study is enrolling 6000 individuals 40–70 years of age, with at least one major risk factor. Patients will be

randomized to CCTA or a risk factor-based assessment and followed for the primary outcome of coronary death or nonfatal myocardial infarction.

CCTA vs. CAC Testing in Primary Prevention: Understanding the Trade-Offs

While current guidelines suggest that CCTA should be mostly reserved for symptomatic patients while CAC may be used when there is uncertainty regarding the role of preventive therapies for asymptomatic patients, it is reasonable to question whether CCTA should have a bigger role in assessing risk among selected asymptomatic individuals. Collectively, the studies discussed above suggest that the incremental prognostic value of CCTA beyond CAC is small. However, it is conceivable that the added value of CCTA may be greater in several sub-groups: (1) younger individuals – especially if they have significant risk factors (e.g., heterozygote familial hypercholesterolemia, systemic inflammatory diseases, strong family history of premature MI in several family members). Such individuals are less likely to have calcified plaque and the identification of plaque at an early age may prompt preventive therapies that may lower long-term risk. (2) Patients who have a larger burden of noncalcified plaque or who are more likely to have exclusively noncalcified plaque – this would include patients with systemic inflammatory conditions, HIV, and tobacco use. However, when considering the potential advantages of identifying noncalcified plaque burden via use of CCTA, it is important to recognize several limitations of CCTA, especially when applied to asymptomatic patients. When compared with CAC testing, CCTA is more likely to be associated with higher cost, higher rate of downstream testing, and higher radiation dose. Of particular concern, is the potential for asymptomatic patients to be referred for unnecessary noninvasive or invasive testing following CCTA. Thus, it is imperative that when CCTA is used for the purposes of plaque imaging and prevention among asymptomatic patients that medical therapy remains the focus of subsequent patient management.

There are a few other potential attributes and future developments in CCTA that may further strengthen the role of this test in preventive cardiology. As discussed above, automatic plaque quantification may enable a more reproducible assessment of plaque volume that can be performed on any CCTA, and which integrates information on the location, amount, and type of plaque (Williams et al. 2022). Another technique that may be particularly useful for prevention is the identification of coronary inflammation by analyzing the pericoronary fat attenuation index (FAI), which provided incremental risk assessment beyond CCTA (Fig. 23.5) (Oikonomou et al. 2018). In fact, abnormalities in this signal may precede the development of plaque, and may also signify a specific role for anti-inflammatory therapies (Klüner et al. 2021).

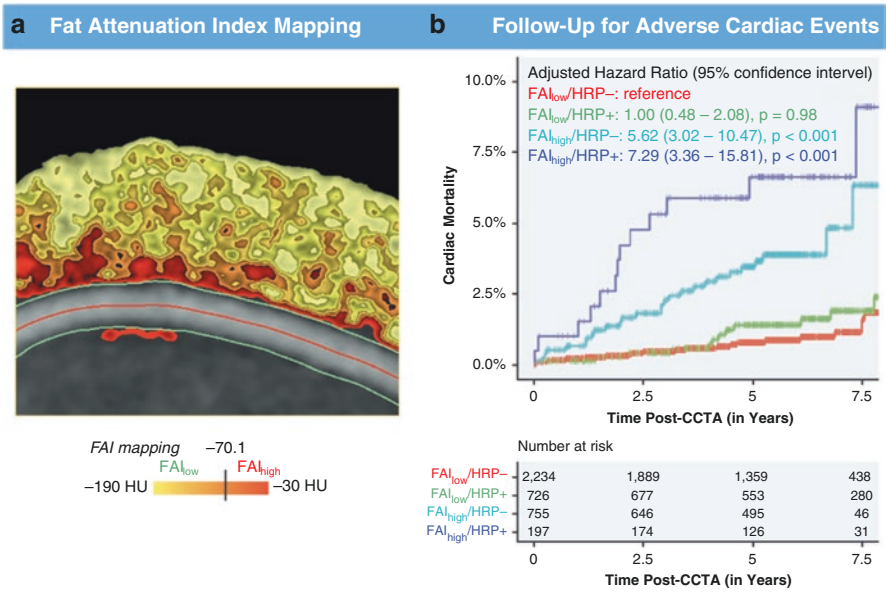

Fig. 23.5 Perivascular Fat Attenuation Index Stratifies the Risk Associated With High Risk Plaque Features. (**a**) A visual example of pericoronary fat attenuation index (FAI) mapping. (**b**) Unadjusted Kaplan–Meier curves with adjusted hazard ratios for patients stratified based on FAI around the right coronary artery (cutoff: −70.1 HU) and high-risk plaque (HRP) presence, illustrating how FAI mapping identifies distinct risk groups among HRP(+) and HRP(−) patients. CCTA coronary computed tomography angiography. (Source: Fig. 1 from JACC. 2020;76(6):755–756)

Summary and Recommendations

CCTA is an established noninvasive imaging modality to evaluate for nonobstructive and obstructive CAD in symptomatic patients. When used in this context, one of the greatest advantages of CCTA is the ability to identify the presence, amount, and type of plaque, and thus enhance risk assessment and guide the need for more aggressive preventive therapies (Table 23.2). Several decades of research in atherosclerosis imaging with either CAC (mostly in asymptomatic patients) or CCTA (mostly in symptomatic patients) has reinforced the concept that the total burden of atherosclerosis (or its absence) is strongly associated with future cardiovascular events. Randomized controlled trials have subsequently demonstrated that the use of CCTA among patients who have chest pain results in higher use of preventive therapies and may result in a lower rate of major adverse cardiovascular events. Prior trials have reinforced that in order to derive maximal risk reduction with the use of CCTA it is important that testing is done in patients who have sufficient risk (i.e., lower risk patients are less likely to benefit from such testing). Moreover, it is imperative that CCTA test results are used in defining the need and intensity of future preventive therapies. After all, the CCTA test results do not impact patient outcomes, but how clinicians and patients act on these results is what ultimately

Table 23.2 Recommendations for CCTA use to prevent major adverse cardiovascular events

1. CCTA may be considered as a first-line test in patients with symptoms suspicious for chronic coronary syndromes.
2. CCTA reports should include an assessment of the total burden of coronary atherosclerosis. A high burden of atherosclerosis, even if nonobstructive, implies a higher risk for atherosclerotic events.
3. The global burden of atherosclerosis on CCTA should be communicated clearly to referring physicians for an implementation of risk-based lifestyle and pharmacologic preventive therapies, guided by shared decision-making.
4. When CT-based risk stratification is indicated in asymptomatic patients, CAC is recommended over CCTA. However, in specific circumstances where patients may have a high burden of noncalcified plaque, CCTA may be considered.

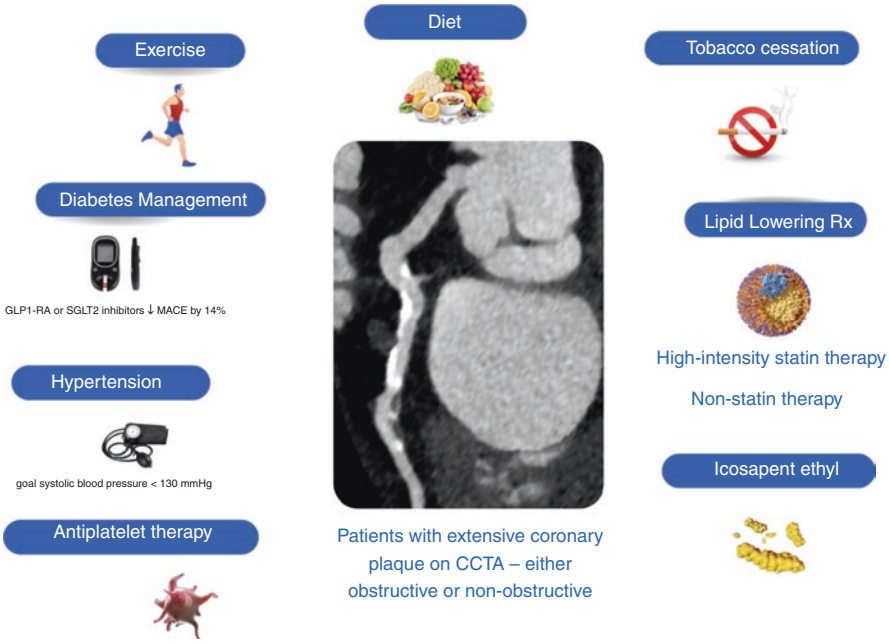

Fig. 23.6 Aggressive prevention therapies that should be considered for individuals who have extensive amount of plaque on coronary CTA**.** The presence of a large amount of plaque identifies individual who have a significantly higher risk of future cardiovascular events, often similar to the level of risk observed in secondary prevention trials. Accordingly, it is important to identify all sources of modifiable risk, and to implement both lifestyle and pharmacologic therapies. While not all therapies on this figure will be appropriate for all patients, all are reasonable to consider for lowering the risk of cardiovascular events. Illustration courtesy of Ana Vitória Cordeiro Rocha, Federal University of Goias, Brazil

matters most. Given the strong association between plaque burden and future cardiovascular risk, it is useful to consider preventive therapies for all patients who are found to have plaque on CCTA. However, patients who have large amount of plaque should be considered for a multipronged intervention incorporating lifestyle changes and aggressive secondary prevention pharmacotherapies (Fig. 23.6).

In asymptomatic patients, the wider availability and lower cost of CAC testing make it the preferred imaging test for risk stratification and guidance of primary prevention therapies (Cardoso et al. 2020). Although some studies have shown that CCTA in asymptomatic patients can improve risk prediction beyond CAC testing, its current role remains limited, but may evolve over time. A wider adoption of CCTA in this context will require more data on subgroups that are more likely to benefit from CCTA (vs. CAC testing), as well as future clinical trials demonstrating improved cardiovascular outcomes among individuals who are selected based on CCTA findings. Current studies are ongoing to define the role of CCTA among asymptomatic patients, as well as its impact on downstream patient management and outcomes.

References

Andreini D, Pontone G, Mushtaq S, Bartorelli AL, Bertella E, Antonioli L, et al. A long-term prognostic value of coronary CT angiography in suspected coronary artery disease. JACC Cardiovasc Imaging. 2012;5(7):690–701.

Bittencourt MS, Hulten E, Ghoshhajra B, O'Leary D, Christman MP, Montana P, et al. Prognostic value of nonobstructive and obstructive coronary artery disease detected by coronary computed tomography angiography to identify cardiovascular events. Circ Cardiovasc Imaging. 2014;7(2):282–91.

Blaha MJ, Cainzos-Achirica M, Greenland P, McEvoy JW, Blankstein R, Budoff MJ, et al. Role of coronary artery calcium score of zero and other negative risk markers for cardiovascular disease: the multi-ethnic study of atherosclerosis (MESA). Circulation. 2016;133(9):849–58.

Budoff MJ, Dowe D, Jollis JG, Gitter M, Sutherland J, Halamert E, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. J Am Coll Cardiol. 2008;52(21):1724–32.

Cardoso R, Dudum R, Ferraro RA, Bittencourt M, Blankstein R, Blaha MJ, et al. Cardiac computed tomography for personalized management of patients with type 2 diabetes mellitus. Circ Cardiovasc Imaging. 2020;13(9):e011365.

Cho I, Chang HJ, Sung JM, Pencina MJ, Lin FY, Dunning AM, et al. Coronary computed tomographic angiography and risk of all-cause mortality and nonfatal myocardial infarction in subjects without chest pain syndrome from the CONFIRM Registry (coronary CT angiography evaluation for clinical outcomes: an international multicenter registry). Circulation. 2012;126(3):304–13.

Cury RC, Abbara S, Achenbach S, Agatston A, Berman DS, Budoff MJ, et al. CAD-RADS(TM) Coronary Artery Disease - Reporting and Data System. An expert consensus document of the Society of Cardiovascular Computed Tomography (SCCT), the American College of Radiology (ACR) and the North American Society for Cardiovascular Imaging (NASCI). Endorsed by the American College of Cardiology. J Cardiovasc Comput Tomogr. 2016;10(4):269–81.

Davenport MS, Khalatbari S, Cohan RH, Dillman JR, Myles JD, Ellis JH. Contrast material-induced nephrotoxicity and intravenous low-osmolality iodinated contrast material: risk stratification by using estimated glomerular filtration rate. Radiology. 2013;268(3):719–28.

Dedic A, Ten Kate GJ, Roos CJ, Neefjes LA, de Graaf MA, Spronk A, et al. Prognostic value of coronary computed tomography imaging in patients at high risk without symptoms of coronary artery disease. Am J Cardiol. 2016;117(5):768–74.

Deseive S, Chen MY, Korosoglou G, Leipsic J, Martuscelli E, Carrascosa P, et al. Prospective randomized trial on radiation dose estimates of CT angiography applying iterative image reconstruction: the PROTECTION V study. JACC Cardiovasc Imaging. 2015;8(8):888–96.

Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B, et al. Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med. 2015;372(14):1291–300.

Ferencik M, Mayrhofer T, Bittner DO, Emami H, Puchner SB, Lu MT, et al. Use of high-risk coronary atherosclerotic plaque detection for risk stratification of patients with stable chest pain: a secondary analysis of the PROMISE randomized clinical trial. JAMA Cardiol. 2018;3(2):144–52.

Gulati M, Levy PD, Mukherjee D, Amsterdam E, Bhatt DL, Birtcher KK, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain. J Am Coll Cardiol. 2021;78(22):e187–285.

Gupta A, Lau E, Varshney R, Hulten EA, Cheezum M, Bittencourt MS, et al. The identification of calcified coronary plaque is associated with initiation and continuation of pharmacological and lifestyle preventive therapies: a systematic review and meta-analysis. JACC Cardiovasc Imaging. 2017;10(8):833–42.

Hausleiter J, Meyer TS, Martuscelli E, Spagnolo P, Yamamoto H, Carrascosa P, et al. Image quality and radiation exposure with prospectively ECG-triggered axial scanning for coronary CT angiography: the multicenter, multivendor, randomized PROTECTION-III study. JACC Cardiovasc Imaging. 2012;5(5):484–93.

Hulten EA, Carbonaro S, Petrillo SP, Mitchell JD, Villines TC. Prognostic value of cardiac computed tomography angiography: a systematic review and meta-analysis. J Am Coll Cardiol. 2011;57(10):1237–47.

Hulten E, Bittencourt MS, Singh A, O'Leary D, Christman MP, Osmani W, et al. Coronary artery disease detected by coronary computed tomographic angiography is associated with intensification of preventive medical therapy and lower low-density lipoprotein cholesterol. Circ Cardiovasc Imaging. 2014;7(4):629–38.

Investigators S-H. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. Lancet. 2015;385(9985):2383–91.

Investigators S-H, Newby DE, Adamson PD, Berry C, Boon NA, Dweck MR, et al. Coronary CT angiography and 5-year risk of myocardial infarction. N Engl J Med. 2018;379(10):924–33.

Kang SH, Park GM, Lee SW, Yun SC, Kim YH, Cho YR, et al. Long-term prognostic value of coronary CT angiography in asymptomatic type 2 diabetes mellitus. JACC Cardiovasc Imaging. 2016;9(11):1292–300.

Klüner LV, Oikonomou EK, Antoniades C. Assessing cardiovascular risk by using the fat attenuation index in coronary CT angiography. Radiol Cardiothorac Imaging. 2021;3(1):e200563.

Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020;41(3):407–77.

Kosmala A, Petritsch B, Weng AM, Bley TA, Gassenmaier T. Radiation dose of coronary CT angiography with a third-generation dual-source CT in a "real-world" patient population. Eur Radiol. 2019;29(8):4341–8.

Lipton MJ, Higgins CB, Farmer D, Boyd DP. Cardiac imaging with a high-speed Cine-CT Scanner: preliminary results. Radiology. 1984;152(3):579–82.

Marwick TH, Cho I, Hartaigh BÓ, Min JK. Finding the gatekeeper to the cardiac catheterization laboratory: coronary CT angiography or stress testing? J Am Coll Cardiol. 2015;65(25):2747–56.

McDonald JS, McDonald RJ, Comin J, Williamson EE, Katzberg RW, Murad MH, et al. Frequency of acute kidney injury following intravenous contrast medium administration: a systematic review and meta-analysis. Radiology. 2013;267(1):119–28.

McDonald RJ, McDonald JS, Carter RE, Hartman RP, Katzberg RW, Kallmes DF, et al. Intravenous contrast material exposure is not an independent risk factor for dialysis or mortality. Radiology. 2014;273(3):714–25.

Min JK, Labounty TM, Gomez MJ, Achenbach S, Al-Mallah M, Budoff MJ, et al. Incremental prognostic value of coronary computed tomographic angiography over coronary artery calcium score for risk prediction of major adverse cardiac events in asymptomatic diabetic individuals. Atherosclerosis. 2014;232(2):298–304.

Mitchell Joshua D, Fergestrom N, Gage Brian F, Paisley R, Moon P, Novak E, et al. Impact of statins on cardiovascular outcomes following coronary artery calcium scoring. J Am Coll Cardiol. 2018;72(25):3233–42.

Mortele KJ, Oliva MR, Ondategui S, Ros PR, Silverman SG. Universal use of nonionic iodinated contrast medium for CT: evaluation of safety in a large urban teaching hospital. AJR Am J Roentgenol. 2005;184(1):31–4.

Mortensen MB, Dzaye O, Steffensen FH, Botker HE, Jensen JM, Ronnow Sand NP, et al. Impact of plaque burden versus stenosis on ischemic events in patients with coronary atherosclerosis. J Am Coll Cardiol. 2020;76(24):2803–13.

Moss AJ, Williams MC, Newby DE, Nicol ED. The updated NICE guidelines: cardiac CT as the first-line test for coronary artery disease. Curr Cardiovasc Imaging Rep. 2017;10(5):15.

Muhlestein JB, Lappe DL, Lima JA, Rosen BD, May HT, Knight S, et al. Effect of screening for coronary artery disease using CT angiography on mortality and cardiac events in high-risk patients with diabetes: the FACTOR-64 randomized clinical trial. JAMA. 2014;312(21):2234–43.

Oikonomou EK, Marwan M, Desai MY, Mancio J, Alashi A, Hutt Centeno E, et al. Non-invasive detection of coronary inflammation using computed tomography and prediction of residual cardiovascular risk (the CRISP CT study): a post-hoc analysis of prospective outcome data. Lancet. 2018;392(10151):929–39.

Patel J, Al Rifai M, Blaha MJ, Budoff MJ, Post WS, Polak JF, et al. Coronary artery calcium improves risk assessment in adults with a family history of premature coronary heart disease: results from multiethnic study of atherosclerosis. Circ Cardiovasc Imaging. 2015;8(6):e003186.

Peng AW, Mirbolouk M, Orimoloye OA, Osei AD, Dardari Z, Dzaye O, et al. Long-term all-cause and cause-specific mortality in asymptomatic patients with CAC >/=1,000: results from the CAC consortium. JACC Cardiovasc Imaging. 2020;13(1 Pt 1):83–93.

Pereira B, Mazzitelli M, Milinkovic A, Moyle G, Ranasinghe S, Mandalia S, et al. Use of coronary artery calcium scoring to improve cardiovascular risk stratification and guide decisions to start statin therapy in people living with HIV. J Acquir Immune Defic Syndr. 2020;85(1):98–105.

Sharma A, Coles A, Sekaran NK, Pagidipati NJ, Lu MT, Mark DB, et al. Stress testing versus CT angiography in patients with diabetes and suspected coronary artery disease. J Am Coll Cardiol. 2019;73(8):893–902.

Shaw LJ, Blankstein R, Bax JJ, Ferencik M, Bittencourt MS, Min JK, et al. Society of Cardiovascular Computed Tomography/North American Society of Cardiovascular Imaging - expert consensus document on coronary CT imaging of atherosclerotic plaque. J Cardiovasc Comput Tomogr. 2021;15(2):93–109.

Stein PD, Yaekoub AY, Matta F, Sostman HD. 64-slice CT for diagnosis of coronary artery disease: a systematic review. Am J Med. 2008;121(8):715–25.

Tao SM, Wichmann JL, Schoepf UJ, Fuller SR, Lu GM, Zhang LJ. Contrast-induced nephropathy in CT: incidence, risk factors and strategies for prevention. Eur Radiol. 2016;26(9):3310–8.

Williams MC, Moss AJ, Dweck M, Adamson PD, Alam S, Hunter A, et al. Coronary artery plaque characteristics associated with adverse outcomes in the SCOT-HEART study. J Am Coll Cardiol. 2019;73(3):291–301.

Williams MC, Earls JP, Hecht H. Quantitative assessment of atherosclerotic plaque, recent progress and current limitations. J Cardiovasc Comput Tomogr. 2022;16(2):124–37.

Chapter 24
Carotid Intima-Media Thickness and Plaque Assessment

Matthew C. Tattersall and James H. Stein

Carotid Intima-Media Thickness

Definitions

Carotid IMT is a noninvasive ultrasound measure, which can quantify the presence of subclinical arterial injury (Stein et al. 2008). It measures the sum of the thicknesses of the arterial intima and media, which are delineated by two echogenic lines on a B-mode ultrasound image (Stein et al. 2008; Pignoli et al. 1986; Wikstrand 2007) (Fig. 24.1). Carotid IMT increases with age, representing both adaptive and pathologic processes (Stein et al. 2008). Increased IMT in the absence of plaque is not atherosclerosis; however, it shares underlying pathophysiologic processes that lead to atherosclerosis, so increased carotid IMT represents "arterial injury." (Stein et al. 2008; Finn et al. 2010; Raggi and Stein 2020) Adaptive changes to the carotid artery occur as part of the aging process in response to oxidative stress, inflammation, cellular senescence, and epigenetic modifications which result in functional and structural changes to the artery that cause carotid wall thickening with aging, regardless of presence of carotid plaque (Ungvari et al. 2018). Pathologic thickening represents accelerated thickening in the context of ASCVD risk factors, which leads to maladaptive arterial aging or pathologic arterial remodeling (Nagai et al. 1998). The degree of pathologic arterial remodeling is an independent risk factor for future ASCVD events (Prati et al. 2008; Johnsen et al. 2007; Chambless et al. 1997, 2000; Lorenz et al. 2006; Folsom et al. 2008; O'Leary et al. 1999; Kitamura et al. 2004; Rosvall et al. 2005a; van der Meer et al. 2004) and has been used to refine

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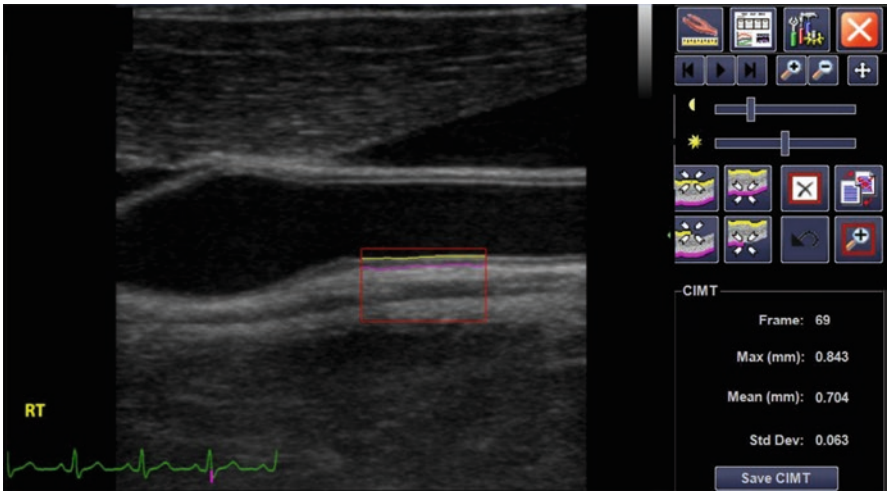

Fig. 24.1 Measurement of right common carotid artery intima-media thickness. *Legend*: Screenshot of ultrasound image of the right carotid artery processed for IMT measurement at the time of the ECG R-wave. The right common carotid artery is on the right of the image with bifurcation into internal carotid artery on the left. The red box outlines the distal 1 cm of the far wall of the right common carotid arterial segment. The blood-intima (yellow line) and media-adventitia (purple line) interfaces of the far wall were traced using a semi-automatic border detection program. CIMT carotid IMT measurement

ASCVD risk (Stein et al. 2008; Greenland et al. 2010), identify ASCVD risk factors, measure the impact of pharmacologic or lifestyle modifications of ASCVD risk (Willeit et al. 2020).

Ultrasound Imaging Technique

To ensure accuracy and reproducibility, carotid ultrasound scanning to measure IMT should follow strict scanning protocols and guidelines (Stein et al. 2008). The patient should be positioned supine with the use of internal and external landmarks to standardize transducer angle (Stein et al. 2008). Images should be obtained using a state-of-the-art ultrasound system and a linear array ultrasound transducer with a fundamental frequency ≥ 7 MHz; semi-annual routine preventive maintenance and phantom scanning are necessary to maintain calibration and to assure image quality (Stein et al. 2008). A registered diagnostic cardiac sonographer, medical sonographer, or vascular technician should perform the scanning which should include a transverse sweep from the base of the common carotid artery (CCA) to the most superior visualized segment of the internal carotid artery to identify plaques, vessel orientation, and imaging landmarks. Then, dedicated longitudinal views of the distal 1 cm of the CCA and proximal bulb should be obtained from three complementary imaging planes for CIMT measurements. The "optimal angle of interrogation"

or "tuning fork" view of the carotid bifurcation, preferably stacking the jugular vein over the CCA, is obtained first, providing an ideal interface to improve image resolution of the near and far walls. This is followed by obtaining two additional imaging planes (typically 20–30 degrees anterior and posterior from the optimal angle of interrogation).

Measurement of Carotid IMT

On B-mode ultrasound images of the carotid artery, the IMT appears as two echogenic parallel lines that are measured from leading edge to leading edge (Fig. 24.1) (Stein et al. 2008; Wikstrand 2007). The sum of the intimal and medial layers is used to measure IMT because ultrasound resolution cannot reliably differentiate the interface of the intima from the media (Johnson and Stein 2011). Carotid IMT should be measured using a semi-automated border detection program with validated accuracy at end-diastole (Stein et al. 2008). Far wall measurements are more accurate and precise than near wall measurements, which are confounded by the inability to consistently demarcate the media-adventitia interface due to the echogenic adventitia layer, which varies between individuals and due to ultrasound gain settings (Stein et al. 2008; Pignoli et al. 1986; Wikstrand 2007; Johnson et al. 1989). The superficial nature and relatively straight course of the common carotid artery offers a reliable portion to measure prior to the transition into the carotid bifurcation (bulb) of the internal and external carotid arteries (Stein et al. 2008; Wikstrand 2007). Arterial injury occurs more rapidly in the carotid bulb and internal carotid artery than in the common carotid artery due to the anatomy of the bifurcation and effects of fluid dynamics resulting in regions of low and oscillatory shear stress, while the common carotid artery is exposed to a relatively similar shear stress circumferentially (Johnson and Stein 2011; Ku et al. 1985).

Predictive Value of Carotid IMT for Future ASCVD Events

A single measurement of carotid IMT is associated with prevalent ASCVD and predicts incident ASCVD events, based on extensive analyses from several population-based cohort studies (Prati et al. 2008; Johnsen et al. 2007; Chambless et al. 1997, 2000; Lorenz et al. 2006; Folsom et al. 2008; O'Leary et al. 1999; Kitamura et al. 2004; Salonen and Salonen 1991; Rosvall et al. 2005b; van der Meer et al. 2003). Previously, clinical practice guidelines recommended using carotid IMT as a tool to refine ASCVD risk in individuals at "intermediate risk" of an ASCVD event over the subsequent 10 years (Greenland et al. 2010). The USE-IMT meta-analysis of 14 population-based studies with 45,828 individuals found that CCA IMT measurement predicted future risks (hazard ratio [HR], 95% confidence intervals [CI] per 0.1 mm difference) for myocardial infarction of 1.08 (95% CI

1.05–1.11) and stroke of 1.12 (95% CI 1.10–1.15) (Den Ruijter et al. 2012). Adding carotid IMT to the 10-year predicted ASCVD risk modestly improved model calibration and discrimination but had only a small effect on reclassification (Den Ruijter et al. 2012). The Harrell C-index increased from 0.757 (95% CI 0.749–0.764) to 0.759 (95% 0.752–0.766) ($p < 0.001$) and the net reclassification index increased by 3.6% (95% CI 2.7–4.6%) for those at intermediate risk (Den Ruijter et al. 2012). The USE-IMT data solely focused on the CCA IMT and did not consider the presence or number of carotid plaques that commonly affect the carotid bulb and internal carotid artery prior to the CCA (Ku et al. 1985; Den Ruijter et al. 2012).

Because the presence of carotid plaque is a stronger predictor for future ASCVD events than carotid IMT (as discussed below), ASCVD risk prediction is improved when CCA IMT measurements are supplemented by assessment for the presence or absence of carotid artery plaques. (Stein et al. 2008; Inaba et al. 2012; Stein and Tattersall 2014; Gepner et al. 2015; Nambi et al. 2010) Consensus recommendations for clinical use of carotid IMT measurements are to perform them only in conjunction with carotid plaque imaging and in patients at intermediate ASCVD risk in whom this information may alter treatment recomendations (Stein et al. 2008; Johri et al. 2020). The American Society of Echocardiography specifically recommends comparing individual CCA IMT values to representative nomograms and considering IMT as "high" – indicating increased ASCVD risk – if either the right or left CCA far wall mean IMT is ≥75th percentile for the patient's age, sex, and race. Patients also are at increased ASCVD risk if carotid plaque is detected (Fig. 24.2) (Stein et al. 2008; Johri et al. 2020; Gepner et al. 2007). Serial measurement of IMT in individual patients is not recommended because of technical challenges with matching of segments over time, detecting very small changes in IMT, and limited predictive value (Stein et al. 2008; Johri et al. 2020). Currently, the only imaging modality the American Heart Association/American College of Cardiology lipid guidelines recommend for ASCVD risk refinement is CAC measurement for

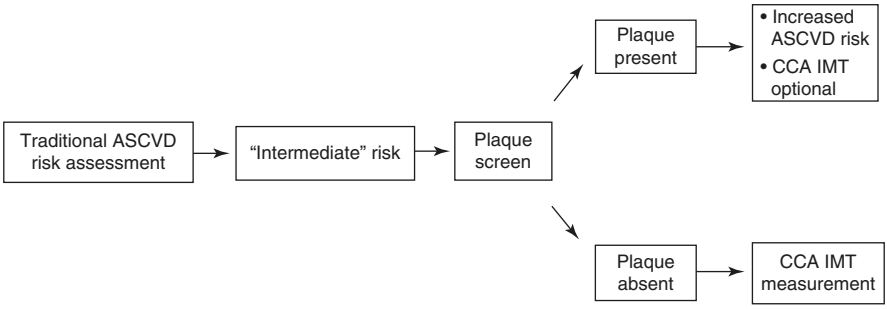

Fig. 24.2 Potential clinical utilization of carotid ultrasound in ASCVD risk refinement. *Legend*: If a patient is at intermediate risk for ASCVD using traditional risk factors, a carotid ultrasound can be performed to screen for plaque in as many carotid artery segments that can be visualized (i.e., entire CCA, bifurcation, and extra-cranial internal carotid artery segments, bilaterally). If present, the patient is at increased ASCVD and measuring common carotid artery IMT is optional. If no plaque is detected, measuring common carotid artery IMT can be performed to further refine risk

patients at borderline/intermediate risks (Arnett et al. 2019). Carotid ultrasound for plaque detection and IMT measurement might be more useful in patients who wish to avoid any radiation exposure or who might have increased ASCVD risk without CAC, such as younger female and African-Americans patients, though the effectiveness of an imaging-guided ASCVD prevention strategy using any modality has not been proven.

Limitations of Carotid IMT

Ultrasound measurement of carotid IMT is technically challenging and time-consuming. Scans can take 20–30 minutes to perform, depending on the scanning protocol, and another 10–20 minutes to measure and report. Furthermore, measurements depend on several patient factors, sonographer factors, and instrumentation settings (Stein et al. 2008). Rigorous standardized scanning and quality assurance protocols are required, since differences in protocols have major effects on carotid IMT measurements (Stein et al. 2008; Bots et al. 2012). Patients must be positioned properly to achieve high-quality images, as patient body habitus can affect image acquisition (Stein et al. 2008; Mitchell et al. 2004). Sonographers should complete training and perform at least 25 annual studies to maintain their skills. Interpretation of the studies should be performed in the context of normative population-based data with results reported in percentiles (Stein et al. 2008). A major limitation is that carotid IMT values need to be compared to population nomograms to determine if a patient's measurements are normal or elevated; however, population characteristics shift over time and absolute measures and percentiles vary from study to study. Of special importance to carotid IMT measurements is that technological advances in ultrasound have markedly changed how ultrasound images are generated. Because modern systems produce higher quality images with better resolution than historical systems, carotid IMT measurements made from modern ultrasound systems are not compatible with the historical population nomograms used to determine wall thickness thresholds for ASCVD risk assessment (Mitchell et al. 2020). Previous settings cannot be replicated easily, so carotid IMT measures have little role in clinical assessment of ASCVD risk, though they remain a powerful research tool, especially when studying children and young adults who may not have atherosclerotic plaque and in whom radiation exposure must be avoided (Mitchell et al. 2020).

Finally, several pathophysiologic mechanisms can lead to carotid wall thickening, which limits the specificity of carotid IMT for assessing the influence of an individual ASCVD risk factor (Finn et al. 2010; Baroncini et al. 2015). Carotid wall thickening can be due to intimal thickening, as commonly seen in the early stages of atherosclerosis, medial hypertrophy due to hemodynamic stressors or inflammation, or interactive combinations of risk factors (Baroncini et al. 2015; Roman et al. 1992). In contrast, carotid plaque is a manifestation of atherosclerosis which includes intimal thickening, foam, and inflammatory cell infiltration with formation of a fibrous cap (Naqvi and Lee 2014). Although carotid IMT and carotid plaque

measures are related, they represent different pathophysiologic responses to different risk factors; for example, hypertension appears to be a larger driving risk factor for carotid IMT whereas dyslipidemia may drive carotid plaque formation (Baroncini et al. 2015).

Carotid Plaque

Definitions

Carotid plaque is defined as the presence of focal wall thickening of >1.5 mm or that is at least >50% thicker than that of the surrounding arterial wall that protrudes into the lumen and is distinct from the adjacent boundary (Stein et al. 2008; Johri et al. 2020; Roman et al. 2006; Touboul et al. 2004, 2007). Carotid plaque is a more specific manifestation of the atherosclerotic process than IMT and has stronger associations with incident ASCVD events. (Stein et al. 2008; Inaba et al. 2012; Gepner et al. 2015; Nambi et al. 2010) Carotid plaque is identified on ultrasound sweeps of the internal, bifurcation, and common carotid artery segments (Stein et al. 2008). It typically is characterized as present or absent, by number of plaques in the 12 scanned carotid artery segments (CCA, bifurcation, internal carotid artery, near wall/far wall, right/left sides), total plaque area, and total plaque volume (Naqvi and Lee 2014; Spence 2015a, 2020).

Predictive Value of Ultrasound Measured Carotid Plaque

The presence of carotid plaque is a powerful predictor of incident ASCVD events regardless of how the plaque is defined (Inaba et al. 2012; Wyman et al. 2006). Several longitudinal cohort studies have identified strong associations of carotid plaque presence, plaque number, plaque area/volume, and plaque characteristics with incident myocardial infarction, stroke, ASCVD death, and all-cause mortality (Table 24.1) (Johnsen et al. 2007; van der Meer et al. 2004; Salonen and Salonen 1991; Rosvall et al. 2005b; Nambi et al. 2010; Mathiesen et al. 2011; Cao et al. 2007). In addition to predicting incident ASCVD events, a single measure of carotid plaque may refine ASCVD risk assessment (Nambi et al. 2010). In the Atherosclerosis Risk in Communities Study (ARIC), addition of carotid plaque presence to the traditional risk factors improved coronary heart disease risk prediction with an area under the curve (AUC) of 0.751 compared with the risk factor only model (AUC 0.742; 95% CI for difference in adjusted AUC 0.006–0.013) (Nambi et al. 2010). Adding both carotid IMT and plaque led to a 23% overall reclassification of risk with a net reclassification improvement of 9.9% (Nambi et al. 2010). In the Tromsø study, carotid plaque was scored as total plaque area calculated by tracing individual

Table 24.1 Definitions and ASCVD event associations of carotid plaque in selected longitudinal cohorts

Study	Participants	Plaque definition	Endpoint	Results
ARIC (Nambi et al. 2010; Hunt et al. 2001)	12,375	2 of the 3 criteria (Nambi et al. 2010): CIMT >1.5 mm Protrusion into the lumen Abnormal wall texture Scored as present/absent (Nambi et al. 2010) Acoustic shadowing presence (Hunt et al. 2001)	Incident CHD and heart disease death	Adjusted RR (95% CI) 2.96 (1.54–3.30) C statistic improvement from 0.742 (TRF only) to 0.755 with CIMT + plaque
MDCS[16]	5163	CIMT > 1.2 mm, in focal area Scored as present/absent and semi-quantitative score	MI, CVD death	Adjusted RR (95% CI) 1.81 (1.14–2.87) plaque presence
Northern Manhattan (Prabhakaran et al. 2006)	1939	Focal CIMT protrusion >50% Scored as present/absent, number of plaques, surface characteristics and plaque stenosis	Stroke, MI, death	Adjusted HR (95% CI), irregular plaque 3.1, (1.1–8.5)
Rotterdam (van der Meer et al. 2004)	6389	Focal widening relative to adjacent segments, and protrusion into the lumen Scored as weighted plaque score ranging from 0 to 6	MI	Adjusted HR (95% CI) 1.83 (1.27–2.62)
Yao City (Kitamura et al. 2004)	1289	CIMT of the ICA ≥1.5 mm Scored present/absent and surface characteristics	Stroke	Adjusted RR (95% CI) 3.2 (1.4–7.1)
Tromso (Johnsen et al. 2007)	6226	Localized protrusion of the vessel wall into the lumen Scored as total plaque area	MI	Adjusted RR (95% CI) Men: 1.56 (1.04–2.36) Women: 3.95 (2.16–7.19)
Tromso (Mathiesen et al. 2011)	6584	Localized protrusion into the vessel lumen with thickening of the vessel wall of >50% compared to the adjacent IMT Scored as total plaque area	Stroke	Adjusted HR (95% CI) Men: HR 1.73, (1.19–2.52) Women: HR 1.62 (1.04–2.53)
MESA (Gepner et al. 2015)	6779	Focal abnormal wall thickness (IMT >1.5 mm) or a focal thickening of >50% of the surrounding IMT Scored as present/absent and total plaque score (range 0–12)	Incident CVD	Adjusted HR (95% CI) Present/Absent: 1.61 (1.17-2.21) Plaque Score: 1.27, (1.16–1.40)

(continued)

Table 24.1 (continued)

Study	Participants	Plaque definition	Endpoint	Results
CHS[47]	5020	Appearance of the largest focal lesion, classified by surface characteristics, echogenicity, and texture. Scored as no plaque, intermediate-risk plaque, and high-risk plaque.	MI, Stroke CVD death and all-cause mortality	Adjusted HR (95% CI) Total CVD: HR 1.38 (1.14–1.67)
BioImage	5808	CIMT>1.5 mm, a focal thickening of >50% of the surrounding IMT. Plaque measured in two imaging planes Scored as Total plaque area	CVD death, MI, ischemic stroke	Adjusted HR (95% CI) 2.38 (1.13–4.92)

Abbreviations: *CIMT* carotid intima-media thickness, *CHD* coronary heart disease, *RR* relative risk, *TRF* traditional risk factors, *CI* confidence intervals, *HR* hazard ratio, *MI* myocardial infarction, *CVD* cardiovascular disease

plaques and the summation of plaques throughout the carotid vasculature (Johnsen et al. 2007). There was a gradient in myocardial infarction risk with larger carotid plaque areas in women (relative risk [RR] 3.95 [95% CI 2.16–7.19]) and in men (RR 1.56 [95% CI 1.04–2.36]) for highest plaque tertile versus no plaque (Johnsen et al. 2007). Total plaque area also predicted incident stroke in both women and men (Mathiesen et al. 2011). These findings indicate the importance of quantifying carotid plaque burden for ASCVD risk assessment (Spence 2020).

Limitations of Ultrasound Measurement of Carotid Plaque

Carotid plaque identified by ultrasound is a strong predictor of incident ASCVD events; however, the magnitude of these associations have varied greatly, in part, due to the lack of standardization between studies in carotid plaque scanning approaches, definitions, and methods used for measuring and scoring plaque burden. Early studies described carotid plaque as present or absent, but that binary classification does not account for the significant heterogeneity in total carotid plaque burden and its impact on incident ASCVD events. Plaque scores (number of plaques in predefined segments) appear to predict incident ASCVD events better than binary presence or absence (Plichart et al. 2011; Gepner et al. 2017). Measuring total plaque area theoretically would improve predictive power compared to counting plaques, but it is more time-consuming to measure and it is not clear if there is an incremental benefit to this approach (Mitchell et al. 2018).

Because plaque propagates in three-dimensions along the arterial wall, two-dimensional imaging techniques may under- or over-estimate plaque burden (Finn et al. 2010; Touboul et al. 2004, 2007; Spence 2015a; Barnett et al. 1997). Newer

methods measuring plaque volumes are discussed below and hold promise; however, other imaging modalities like coronary artery computed tomography angiography and CAC measurement are easier to perform and better predict ASCVD risk; they more precisely quantitate plaque burden and correlate better with plaque burdens in different vascular territories (Johri et al. 2013; Spence 2015b). Carotid magnetic resonance imaging (MRI) is another technology that can be used to assess and quantify carotid artery plaque burden (Zavodni et al. 2014). Another limitation of ultrasound-defined carotid plaque is its modest ability to identify plaque characteristics that indicate a vulnerability to rupture, especially compared to MRI. Over 75% of thrombi in the carotid arteries are caused by plaque rupture (Finn et al. 2010) and MRI characteristics of intraplaque hemorrhage, lipid-rich necrotic core, and thinning/rupture of the fibrous cap are strongly associated with incident stroke/TIA (Gupta et al. 2013). Although these and other plaque features can be identified using carotid ultrasound, plaques are characterized less accurately with ultrasound due to operator dependence and intraplaque calcification with shadowing (Mitchell et al. 2017).

Comparison of Carotid IMT, Plaque Detection, and Coronary Calcium Measurement

CAC and carotid ultrasound measures are modestly correlated, which suggests that these imaging modalities represent different, albeit related, pathophysiological processes. Noncalcified plaque is a manifestation of early atherosclerosis, whereas calcification tends to occur later, though with age-dependent and significant interindividual variability. Also, CAC is measured in the coronary arteries and ultrasound assesses plaque in the carotid arteries, so differential total and event-specific ASCVD risk would be expected.

A few longitudinal cohort studies have compared the predictive abilities of these imaging modalities. In the Cardiovascular Health Study of adults >70 years old, the highest quartiles compared to the lowest quartiles of both CAC and carotid IMT similarly predicted overall ASCVD events; however, CCA IMT had a stronger association with incident stroke than CAC (Newman et al. 2008). An early report from the Multi-Ethnic Study of Atherosclerosis (MESA) with a median 3.9 years of follow-up found that CAC and carotid IMT were independent predictors of ASCVD events; however, CAC was a stronger predictor of incident total ASCVD and coronary heart disease events, whereas CIMT was a stronger predictor of incident stroke (Folsom et al. 2008). A subsequent report from the MESA with a mean of 9.5 years follow-up showed that CAC was a better predictor of incident total ASCVD (HR 3.12, 95% CI 2.44–3.99) and coronary heart disease events (HR 4.48, 95% CI 3.24–6.17) versus carotid plaque presence, high carotid IMT (≥75th percentile) or both carotid artery measures for predicting ASCVD events (HR 2.06 [95% CI 1.46–2.91]) (Gepner et al. 2015). Addition of

carotid plaque to traditional risk factors marginally improved prediction of incident stroke events, but addition of CAC did not (Gepner et al. 2015). After 11.3 years of follow-up in MESA, both CAC and carotid plaque score predicted incident ASCVD events (CAC HR 1.78, 95% CI 1.16–1.98; carotid plaque score HR 1.27, 95% CI, 1.16–1.40) (Gepner et al. 2017). Similar to the other studies, CAC (HR 2.09, 95% CI 1.84–2.38) was a more robust predictor of incident coronary heart disease events compared with carotid plaque score (HR 1.35, 95% CI 1.21–1.51) (Gepner et al. 2017). CAC and carotid plaque scores were weak predictors of stroke/TIA (Gepner et al. 2017). The CAC score had better reclassification statistics than carotid plaque score, except for stroke/TIA, which had similar predictive values (Gepner et al. 2017). In the BioImage study, carotid plaque area and CAC independently predicted ASCVD events, though model fit, discrimination, and net reclassification were somewhat better for CAC (Baber et al. 2015). The BioImage study measured carotid plaque burden by using both longitudinal and cross-sectional images to improve precision (Baber et al. 2015). These data support that both carotid ultrasound measures and CAC independently predict ASCVD events, with carotid plaque being a stronger predictor of incident ASCVD events than carotid IMT, but that CAC is a more robust predictor than any of the carotid ultrasound measures (Gepner et al. 2015; Gepner et al. 2017; Baber et al. 2015).

Effects of Carotid Ultrasound Screening on Patient and Physician Behaviors

Limited data suggest that knowing a patient's carotid IMT or plaque burden can affect patient and physician behaviors. In one study of 50 primary prevention patients with two or more traditional ASCVD risk factors, over half (58%) had at least one plaque and identification of carotid plaque led to changes in physician recommended pharmacotherapy with more prescription of aspirin and lipid-lowering therapies (Wyman et al. 2007). Patients with carotid plaques perceived themselves to be at higher ASCVD risk; however, this did not translate into increased motivations for lifestyle changes (Wyman et al. 2007). In a multicenter study of 355 patients from five nonacademic community practices, an abnormal carotid ultrasound screening examination resulted in significant physician altering of low-density lipoprotein-cholesterol and systolic blood pressure goals while increasing the number of prescriptions of aspirin and lipid-lowering therapies (Johnson et al. 2011). Interestingly, patients indicated an increased perceived ability to make healthy lifestyle changes regardless of the carotid ultrasound study results, suggesting that screening alone increased the perceived ability to make lifestyle changes (Johnson et al. 2011). Other studies also show that abnormal carotid ultrasound results alter physician prescription of antiplatelet and lipid-lowering medications and led to more aggressive modifiable risk factor targets, and that carotid ultrasound

screening, regardless of the results, improved patient's behaviors and perceptions toward lifestyle modifications (Hong et al. 2014; Jeong et al. 2016).

The Visualization of Asymptomatic Atherosclerotic Disease for Optimum Cardiovascular Prevention (VIPVIZA) trial was a pragmatic, open-label trial with patients randomized to receive a pictorial display of carotid IMT and carotid plaque versus standard clinical care (Näslund et al. 2019). Overall, participants who received pictorial displays of their carotid ultrasound images had lower 10-year ASCVD risk scores and lower total cholesterol and calculated low-density lipoprotein levels after 1 year (Näslund et al. 2019).

Collectively, these studies show consistent improvements in physician-directed ASCVD risk factor management through more prescriptions and more aggressive cholesterol and blood pressure goals; however, the impact of carotid screening on patient behavior has been more variable (Wyman et al. 2007; Johnson et al. 2011; Jeong et al. 2016; Rodondi et al. 2012). In an observational study of patients with type II diabetes, patients informed and educated on their carotid ultrasound results had improved rates of smoking cessation and dietary changes at 6 months (Jeong et al. 2016). The same results were not demonstrated in a randomized controlled trial of over 500 smokers randomized to carotid ultrasound screening with smoking cessation counseling versus standard smoking cessation counseling (Rodondi et al. 2012). In this trial, there was no difference in smoking cessation rates between the two groups; however, smoking cessation rates were > 20% at 1 year in both groups, which highlights the study's recruitment of smokers who were motivated to quit smoking (Rodondi et al. 2012). In this trial, similar to prior studies, antihypertensive medication prescriptions were higher in the carotid ultrasound screening group (2.1% versus 0%, $p = 0.03$); however, there was no difference in systolic blood pressure or other ASCVD risk factors between the groups (Rodondi et al. 2012). Taken together, these studies suggest carotid ultrasound screening improves physician-guided management of ASCVD risk factors but has limited impact on sustained behavior changes in patients.

Future Directions – Tissue Characterization and Quantification of Plaque Volume

Although advances in ultrasound instrumentation limit comparability of carotid IMT measurements from modern ultrasound images to historical nomograms, they permit acquisition of higher quality images that can be used for tissue characterization and volumetric assessment of the carotid artery wall and plaques. Low levels of carotid wall echogenicity, gray level contrast, and grayscale entropy are associated with higher ASCVD risk after controlling for ASCVD risk factors (Fig. 24.3) (Wohlin et al. 2009; Andersson et al. 2009; Mitchell et al. 2019). Software packages that permit offline assessment of detailed grayscale analysis are available for commercial use, but have not been validated outside of research studies.

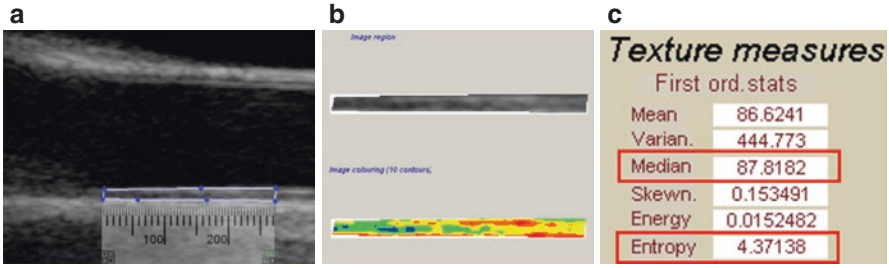

Fig. 24.3 Far wall common carotid artery intima-media echogenicity and texture. *Legend*: (**a**) Left panel. Screenshot of ultrasound image of the right carotid artery processed for grayscale texture feature extraction with a ruler overlay. White box is area of interest for extraction. (**b**) Center panel. Extracted grayscale segment on top; colorized areas segmentation based on pixel brightness. (**c**) Right panel. Derived first-order grayscale texture measures such as median pixel brightness and entropy

Recognition that carotid plaque propagates along the vessel wall and advances in three-dimensions has improved the ability to track changes in carotid plaque volume over time (Wannarong et al. 2013). Methods to quantify carotid plaque burden seem to provide additional benefit beyond methods using plaque presence/absence (Johnsen et al. 2007; Baber et al. 2015; Wannarong et al. 2013). Advances in ultrasound technology with the introduction of three-dimensional matrix array ultrasound probes and analysis software allow for measurement of carotid plaque in all planes and may permit more precise quantification and characterization of carotid plaques (Johri et al. 2020). Semi-automatic three-dimensional plaque quantification methods may enhance speed and reproducibility for measuring carotid plaque volume (Johri et al. 2020). (Zhou et al. 2019) These new techniques for assessing plaque volume and plaque characteristics over time are promising. However, they are limited by numerous barriers including the inability to adequately define and measure heavily calcified plaques, the additional time and software required for analysis, costs, lack of protocol validation outside a research setting and limited data demonstrating whether these three-dimensional plaque quantification methods add significant data to refine ASCVD risk beyond the current two-dimensional plaque characterization methods (Johri et al. 2020).

References

Andersson J, Sundstrom J, Gustavsson T, et al. Echogenecity of the carotid intima-media complex is related to cardiovascular risk factors, dyslipidemia, oxidative stress and inflammation: the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. Atherosclerosis. 2009;204(2):612–8. https://doi.org/10.1016/j.atherosclerosis.2008.10.038.

Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart

Association Task Force on Clinical Practice Guidelines. Circulation. 2019;140(11):e596–646. https://doi.org/10.1161/cir.0000000000000678.

Baber U, Mehran R, Sartori S, et al. Prevalence, impact, and predictive value of detecting subclinical coronary and carotid atherosclerosis in asymptomatic adults: the BioImage study. J Am Coll Cardiol. 2015;65(11):1065–74. https://doi.org/10.1016/j.jacc.2015.01.017.

Barnett PA, Spence JD, Manuck SB, Jennings JR. Psychological stress and the progression of carotid artery disease. J Hypertens. 1997;15(1):49–55. https://doi.org/10.1097/00004872-199715010-00004.

Baroncini LAV, de Castro SL, Filho RP. Carotid intima-media thickness and carotid plaque represent different adaptive responses to traditional cardiovascular risk factors. Int J Cardiol Heart Vasc. 2015;9:48–51. https://doi.org/10.1016/j.ijcha.2015.08.003.

Bots ML, Taylor AJ, Kastelein JJ, et al. Rate of change in carotid intima-media thickness and vascular events: meta-analyses can not solve all the issues. A point of view. J Hypertens. 2012;30(9):1690–6. https://doi.org/10.1097/HJH.0b013e32835644dc.

Cao JJ, Arnold AM, Manolio TA, et al. Association of carotid artery intima-media thickness, plaques, and C-reactive protein with future cardiovascular disease and all-cause mortality: the cardiovascular health study. Circulation. 2007;116(1):32–8. https://doi.org/10.1161/CIRCULATIONAHA.106.645606.

Chambless LE, Heiss G, Folsom AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987–1993. Am J Epidemiol. 1997;146(6):483–94. https://doi.org/10.1093/oxfordjournals.aje.a009302.

Chambless LE, Folsom AR, Clegg LX, et al. Carotid wall thickness is predictive of incident clinical stroke: the Atherosclerosis Risk in Communities (ARIC) study. Am J Epidemiol. 2000;151(5):478–87. https://doi.org/10.1093/oxfordjournals.aje.a010233.

Den Ruijter HM, Peters SA, Anderson TJ, et al. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. JAMA. 2012;308(8):796–803. https://doi.org/10.1001/jama.2012.9630.

Finn AV, Kolodgie FD, Virmani R. Correlation between carotid intimal/medial thickness and atherosclerosis: a point of view from pathology. Arterioscler Thromb Vasc Biol. 2010;30(2):177–81. https://doi.org/10.1161/atvbaha.108.173609.

Folsom AR, Kronmal RA, Detrano RC, et al. Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the Multi-Ethnic Study of Atherosclerosis (MESA). Arch Intern Med. 2008;168(12):1333–9. https://doi.org/10.1001/archinte.168.12.1333.

Gepner AD, Young R, Delaney Joseph A, et al. Comparison of carotid plaque score and coronary artery calcium score for predicting cardiovascular disease events: the multi-ethnic study of atherosclerosis. J Am Heart Assoc. 2017;6(2):e005179. https://doi.org/10.1161/JAHA.116.005179.

Gepner AD, Wyman RA, Korcarz CE, Aeschlimann SE, Stein JH. An abbreviated carotid intima-media thickness scanning protocol to facilitate clinical screening for subclinical atherosclerosis. J Am Soc Echocardiogr. 2007;20(11):1269–75. https://doi.org/10.1016/j.echo.2007.03.009.

Gepner AD, Young R, Delaney JA, et al. Comparison of coronary artery calcium presence, carotid plaque presence, and carotid intima-media thickness for cardiovascular disease prediction in the Multi-Ethnic Study of Atherosclerosis. Circ Cardiovasc Imaging. 2015;8(1) https://doi.org/10.1161/circimaging.114.002262.

Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2010;122(25):2748–64. https://doi.org/10.1161/CIR.0b013e3182051bab.

Gupta A, Baradaran H, Schweitzer AD, et al. Carotid plaque MRI and stroke risk: a systematic review and meta-analysis. Stroke. 2013;44(11):3071–7. https://doi.org/10.1161/STROKEAHA.113.002551.

Hong SJ, Chang HJ, Song K, et al. Impact of atherosclerosis detection by carotid ultrasound on physician behavior and risk-factor management in asymptomatic hypertensive subjects. Clin Cardiol. 2014;37(2):91–6. https://doi.org/10.1002/clc.22220.

Hunt KJ, Sharrett AR, Chambless LE, Folsom AR, Evans GW, Heiss G. Acoustic shadowing on B-mode ultrasound of the carotid artery predicts CHD. Ultrasound Med Biol. 2001;27(3):357–65.

Inaba Y, Chen JA, Bergmann SR. Carotid plaque, compared with carotid intima-media thickness, more accurately predicts coronary artery disease events: a meta-analysis. Atherosclerosis. 2012;220(1):128–33. https://doi.org/10.1016/j.atherosclerosis.2011.06.044.

Jeong IK, Kim SG, Cho DH, et al. Impact of carotid atherosclerosis detection on physician and patient behavior in the management of type 2 diabetes mellitus: a prospective, observational, multicenter study. BMC Cardiovasc Disord. 2016;16(1):220. https://doi.org/10.1186/s12872-016-0401-5.

Johnsen SH, Mathiesen EB, Joakimsen O, et al. Carotid atherosclerosis is a stronger predictor of myocardial infarction in women than in men: a 6-year follow-up study of 6226 persons: the Tromsø study. Stroke. 2007;38(11):2873–80. https://doi.org/10.1161/STROKEAHA.107.487264.

Johnson HM, Stein JH. Measurement of carotid intima-media thickness and carotid plaque detection for cardiovascular risk assessment. J Nucl Cardiol. 2011;18(1):153–62. https://doi.org/10.1007/s12350-010-9319-y.

Johnson LW, Lozner EC, Johnson S, et al. Coronary arteriography 1984-1987: a report of the registry of the Society for Cardiac Angiography and Interventions. I. Results and complications. Catheter Cardiovasc Diagn. 1989;17(1):5–10.

Johnson HM, Turke TL, Grossklaus M, et al. Effects of an office-based carotid ultrasound screening intervention. J Am Soc Echocardiogr. 2011;24(7):738–47. https://doi.org/10.1016/j.echo.2011.02.013.

Johri AM, Chitty DW, Matangi M, et al. Can carotid bulb plaque assessment rule out significant coronary artery disease? A comparison of plaque quantification by two- and three-dimensional ultrasound. J Am Soc Echocardiogr. 2013;26(1):86–95. https://doi.org/10.1016/j.echo.2012.09.005.

Johri AM, Nambi V, Naqvi TZ, et al. Recommendations for the assessment of carotid arterial plaque by ultrasound for the characterization of atherosclerosis and evaluation of cardiovascular risk: from the American Society of Echocardiography. J Am Soc Echocardiogr. 2020;33(8):917–33. https://doi.org/10.1016/j.echo.2020.04.021.

Kitamura A, Iso H, Imano H, et al. Carotid intima-media thickness and plaque characteristics as a risk factor for stroke in Japanese elderly men. Stroke. 2004;35(12):2788–94. https://doi.org/10.1161/01.STR.0000147723.52033.9e.

Ku DN, Giddens DP, Zarins CK, Glagov S. Pulsatile flow and atherosclerosis in the human carotid bifurcation. Positive correlation between plaque location and low oscillating shear stress. Arteriosclerosis. 1985;5(3):293–302.

Lorenz MW, von Kegler S, Steinmetz H, Markus HS, Sitzer M. Carotid intima-media thickening indicates a higher vascular risk across a wide age range: prospective data from the Carotid Atherosclerosis Progression Study (CAPS). Stroke. 2006;37(1):87–92. https://doi.org/10.1161/01.STR.0000196964.24024.ea.

Mathiesen EB, Johnsen SH, Wilsgaard T, Bønaa KH, Løchen ML, Njølstad I. Carotid plaque area and intima-media thickness in prediction of first-ever ischemic stroke: a 10-year follow-up of 6584 men and women: the Tromsø study. Stroke. 2011;42(4):972–8. https://doi.org/10.1161/STROKEAHA.110.589754.

Mitchell CK, Aeschlimann SE, Korcarz CE. Carotid intima-media thickness testing: technical considerations. J Am Soc Echocardiogr. 2004;17(6):690–2. https://doi.org/10.1016/j.echo.2004.03.019.

Mitchell CC, Stein JH, Cook TD, et al. Histopathologic validation of grayscale carotid plaque characteristics related to plaque vulnerability. Ultrasound Med Biol. 2017;43(1):129–37. https://doi.org/10.1016/j.ultrasmedbio.2016.08.011.

Mitchell C, Korcarz CE, Gepner AD, et al. Ultrasound carotid plaque features, cardiovascular disease risk factors and events: the multi-ethnic study of atherosclerosis. Atherosclerosis. 2018;09(276):195–202. https://doi.org/10.1016/j.atherosclerosis.2018.06.005.

Mitchell CC, Korcarz CE, Gepner AD, et al. Carotid artery echolucency, texture features, and incident cardiovascular disease events: The MESA Study. J Am Heart Assoc. 2019;8(3):e010875. https://doi.org/10.1161/JAHA.118.010875.

Mitchell CKC, Zagzebski J, Stein JH. Effects of ultrasound technology advances on measurement of carotid intima-media thickness: a review. Vasc Med. 2020;26:81.

Nagai Y, Metter EJ, Earley CJ, et al. Increased carotid artery intimal-medial thickness in asymptomatic older subjects with exercise-induced myocardial ischemia. Circulation. 1998;98(15):1504–9. https://doi.org/10.1161/01.cir.98.15.1504.

Nambi V, Chambless L, Folsom AR, et al. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study. J Am Coll Cardiol. 2010;55(15):1600–7. https://doi.org/10.1016/j.jacc.2009.11.075.

Naqvi TZ, Lee MS. Carotid intima-media thickness and plaque in cardiovascular risk assessment. JACC Cardiovasc Imaging. 2014;7(10):1025–38. https://doi.org/10.1016/j.jcmg.2013.11.014.

Näslund U, Ng N, Lundgren A, et al. Visualization of asymptomatic atherosclerotic disease for optimum cardiovascular prevention (VIPVIZA): a pragmatic, open-label, randomised controlled trial. Lancet. 2019;393(10167):133–42. https://doi.org/10.1016/S0140-6736(18)32818-6.

Newman AB, Naydeck BL, Ives DG, et al. Coronary artery calcium, carotid artery wall thickness, and cardiovascular disease outcomes in adults 70 to 99 years old. Am J Cardiol. 2008;101(2):186–92. https://doi.org/10.1016/j.amjcard.2007.07.075.

O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med. 1999;340(1):14–22. https://doi.org/10.1056/NEJM199901073400103.

Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R. Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. Circulation. 1986;74(6):1399–406. https://doi.org/10.1161/01.cir.74.6.1399.

Plichart M, Celermajer DS, Zureik M, et al. Carotid intima-media thickness in plaque-free site, carotid plaques and coronary heart disease risk prediction in older adults. The Three-City Study. Atherosclerosis. 2011;219(2):917–24. https://doi.org/10.1016/j.atherosclerosis.2011.09.024.

Prabhakaran S, Rundek T, Ramas R, et al. Carotid plaque surface irregularity predicts ischemic stroke: the northern Manhattan study. Stroke. 2006;37(11):2696–701. https://doi.org/10.1161/01.STR.0000244780.82190.a4.

Prati P, Tosetto A, Vanuzzo D, et al. Carotid intima media thickness and plaques can predict the occurrence of ischemic cerebrovascular events. Stroke. 2008;39(9):2470–6. https://doi.org/10.1161/STROKEAHA.107.511584.

Raggi P, Stein JH. Carotid intima-media thickness should not be referred to as subclinical atherosclerosis: a recommended update to the editorial policy at atherosclerosis. Atherosclerosis. 2020; https://doi.org/10.1016/j.atherosclerosis.2020.09.015.

Rodondi N, Collet TH, Nanchen D, et al. Impact of carotid plaque screening on smoking cessation and other cardiovascular risk factors: a randomized controlled trial. Arch Intern Med. 2012;172(4):344–52. https://doi.org/10.1001/archinternmed.2011.1326.

Roman MJ, Saba PS, Pini R, et al. Parallel cardiac and vascular adaptation in hypertension. Circulation. 1992;86(6):1909–18. https://doi.org/10.1161/01.cir.86.6.1909.

Roman MJ, Naqvi TZ, Gardin JM, et al. American society of echocardiography report. Clinical application of noninvasive vascular ultrasound in cardiovascular risk stratification: a report from the American Society of Echocardiography and the Society for Vascular Medicine and Biology. Vasc Med. 2006;11(3):201–11. https://doi.org/10.1177/1358863x06070511.

Rosvall M, Janzon L, Berglund G, Engstrom G, Hedblad B. Incident coronary events and case fatality in relation to common carotid intima-media thickness. J Intern Med. 2005a;257(5):430–7. https://doi.org/10.1111/j.1365-2796.2005.01485.x.

Rosvall M, Janzon L, Berglund G, Engström G, Hedblad B. Incident coronary events and case fatality in relation to common carotid intima-media thickness. J Intern Med. 2005b;257(5):430–7. https://doi.org/10.1111/j.1365-2796.2005.01485.x.

Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. Arterioscler Thromb. 1991;11(5):1245–9.

Spence JD. Measurement of carotid plaque burden. JAMA Neurol. 2015a;72(4):383–4. https://doi.org/10.1001/jamaneurol.2014.3002.

Spence JD. Carotid ultrasound phenotypes are biologically distinct. Arterioscler Thromb Vasc Biol. 2015b;35(9):1910–3. https://doi.org/10.1161/ATVBAHA.115.306209.

Spence JD. Measurement of carotid plaque burden. Curr Opin Lipidol. 2020;31(5):291–8. https://doi.org/10.1097/MOL.0000000000000706.

Stein JH, Tattersall MC. Carotid intima-media thickness and cardiovascular disease risk prediction. J Am Coll Cardiol. 2014;63(21):2301–2. https://doi.org/10.1016/j.jacc.2014.02.528.

Stein JH, Korcarz CE, Hurst RT, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr. 2008;21(2):93–111.; ; quiz 189–90. https://doi.org/10.1016/j.echo.2007.11.011.

Touboul PJ, Hennerici MG, Meairs S, et al. Mannheim intima-media thickness consensus. Cerebrovasc Dis. 2004;18(4):346–9. https://doi.org/10.1159/000081812.

Touboul PJ, Hennerici MG, Meairs S, et al. Mannheim carotid intima-media thickness consensus (2004-2006). An update on behalf of the Advisory Board of the 3rd and 4th Watching the Risk Symposium, 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. Cerebrovasc Dis. 2007;23(1):75–80. https://doi.org/10.1159/000097034.

Ungvari Z, Tarantini S, Donato AJ, Galvan V, Csiszar A. Mechanisms of vascular aging. Circ Res. 2018;123(7):849–67. https://doi.org/10.1161/circresaha.118.311378.

van der Meer IM, Iglesias del Sol A, Hak AE, Bots ML, Hofman A, Witteman JC. Risk factors for progression of atherosclerosis measured at multiple sites in the arterial tree: the Rotterdam study. Stroke. 2003;34(10):2374–9. https://doi.org/10.1161/01.str.0000088643.07108.19.

van der Meer IM, Bots ML, Hofman A, del Sol AI, van der Kuip DA, Witteman JC. Predictive value of noninvasive measures of atherosclerosis for incident myocardial infarction: the Rotterdam study. Circulation. 2004;109(9):1089–94. https://doi.org/10.1161/01.cir.0000120708.59903.1b.

Wannarong T, Parraga G, Buchanan D, et al. Progression of carotid plaque volume predicts cardiovascular events. Stroke. 2013;44(7):1859–65. https://doi.org/10.1161/STROKEAHA.113.001461.

Wikstrand J. Methodological considerations of ultrasound measurement of carotid artery intima-media thickness and lumen diameter. Clin Physiol Funct Imaging. 2007;27(6):341–5. https://doi.org/10.1111/j.1475-097X.2007.00757.x.

Willeit P, Tschiderer L, Allara E, et al. Carotid intima-media thickness progression as surrogate marker for cardiovascular risk: meta-analysis of 119 clinical trials involving 100 667 patients. Circulation. 2020;142(7):621–42. https://doi.org/10.1161/circulationaha.120.046361.

Wohlin M, Sundstrom J, Andren B, Larsson A, Lind L. An echolucent carotid artery intima-media complex is a new and independent predictor of mortality in an elderly male cohort. Atherosclerosis. 2009;205(2):486–91. https://doi.org/10.1016/j.atherosclerosis.2009.01.032.

Wyman RA, Mays ME, McBride PE, Stein JH. Ultrasound-detected carotid plaque as a predictor of cardiovascular events. Vasc Med. 2006;11(2):123–30. https://doi.org/10.1191/1358863x06vm666ra.

Wyman RA, Gimelli G, McBride PE, Korcarz CE, Stein JH. Does detection of carotid plaque affect physician behavior or motivate patients? Am Heart J. 2007;154(6):1072–7. https://doi.org/10.1016/j.ahj.2007.06.046.

Zavodni AE, Wasserman BA, McClelland RL, et al. Carotid artery plaque morphology and composition in relation to incident cardiovascular events: the Multi-Ethnic Study of Atherosclerosis (MESA). Radiology. 2014;271(2):381–9. https://doi.org/10.1148/radiol.14131020.

Zhou R, Fenster A, Xia Y, Spence JD, Ding M. Deep learning-based carotid media-adventitia and lumen-intima boundary segmentation from three-dimensional ultrasound images. Med Phys. 2019;46(7):3180–93. https://doi.org/10.1002/mp.13581.

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