Current Cardiovascular Risk Reports (2019) 13: 18
https://doi.org/10.1007/s12170-019-0616-y

LIPIDS (E MICHOS, SECTION EDITOR)

The Use of Risk-Enhancing Factors to Personalize ASCVD Risk Assessment: Evidence and Recommendations from the 2018 AHA/ACC Multi-Society Cholesterol Guidelines

Anandita Agarwala[1] · Jing Liu[2] · Christie M. Ballantyne[2,3] · Salim S. Virani[2,3,4]

Published online: 23 May 2019

Abstract

Purpose of Review In 2018, the AHA/ACC Multi-Society Cholesterol Guidelines introduced the novel concept of risk-enhancing factors to be used as a supplement to the pooled cohort risk equations to personalize atherosclerotic cardiovascular disease risk assessment in primary prevention. In this review, we discuss the rationale and evidence behind each of the risk-enhancing factors to help clinicians perform a more personalized cardiovascular risk assessment.

Recent Findings The risk-enhancing factors are high-risk features that may guide the use of lipid-lowering therapy particularly in intermediate and select borderline-risk patients. For the purpose of this review, these factors are divided into five categories: (i) race and genetics, (ii) conditions specific to women, (iii) lipid-related risk, (iv) concurrent high-risk medical conditions, and (v) biomarkers.

Summary The addition of the risk-enhancing factors to the pooled cohort equations provides a more individualized and comprehensive approach to cardiovascular disease risk assessment.

Keywords Risk-enhancing factors · Atherosclerotic cardiovascular disease · Risk assessment · Race and genetics · Biomarkers · Lipid

This article is part of the Topical Collection on *Lipids*

✉ Salim S. Virani
virani@bcm.edu

Anandita Agarwala
anandita@wustl.edu

Jing Liu
Jing.Liu@bcm.edu

Christie M. Ballantyne
cmb@bcm.edu

[1] Division of Cardiology, Washington University School of Medicine, 660 S. Euclid, Campus Box 8086, St. Louis, MO, USA

[2] Section of Cardiology, Department of Medicine, Baylor College of Medicine, Houston, TX, USA

[3] Section of Cardiovascular Research, Department of Medicine, Baylor College of Medicine, Houston, TX, USA

[4] Section of Cardiology, Health Services Research and Development, Michael E. DeBakey Veterans Affairs Medical Center, 2002 Holcombe Boulevard, Houston, TX 77030, USA

Introduction

The 2018 AHA/ACC/Multi-Society Cholesterol Guidelines introduced the novel concept of risk-enhancing factors as a supplement to the pooled cohort equations (PCE) to personalize risk assessment for the primary prevention of atherosclerotic cardiovascular disease (ASCVD) [1]. Since the publication of the 2013 ACC/AHA guidelines, the PCE has been the mainstay for assessing ASCVD risk over a 10-year time frame [2]. As per the 2018 Cholesterol Guidelines and the 2019 Primary Prevention Guidelines, patients are stratified into low (< 5%), borderline (5% to < 7.5%), intermediate (≥ 7.5% to 19.9%), and high (≥ 20%) risk groups based on 10-year ASCVD risk estimation and this stratification has been recommended to guide statin therapy use [1, 3]. However, the PCE has several notable limitations at the individual level. Although it is derived from epidemiologic data that is valid at a population level, it may underestimate or overestimate ASCVD risk in specific individuals [4–7]. Several baseline and acquired characteristics significantly affect an individual's

actual ASCVD risk beyond traditional risk factors, such as ethnicity, genetic makeup, and concurrent comorbid conditions. Although these factors may or may not be independently associated with ASCVD, their presence may denote higher risk and could inform a more personalized risk discussion. Additionally, although some risk-enhancing factors may not increase risk in the short or intermediate term, their presence may lead to an increased lifetime risk of ASCVD and thus merits consideration during risk discussion.

The 2018 AHA/ACC Cholesterol Guidelines recommend the application of risk-enhancing factors to patients in the borderline- and intermediate-risk groups to identify those who may be at greater risk for ASCVD than suggested by the PCE alone. Incorporation of these factors allows for an individualized risk assessment and a personalized discussion regarding the need to initiate or intensify statin therapy. In this review, we will discuss the rationale and evidence behind these factors. We have divided the risk-enhancing factors into five categories: (i) race and genetics, (ii) conditions specific to women, (iii) lipid-related risk, (iv) concurrent high-risk medical conditions, and (v) biomarkers. Additionally, we will highlight the importance of shared decision-making between clinicians and patients when applying these guidelines. The risk-enhancing factors are summarized in Table 1.

Race and Genetics

A family history of premature ASCVD (first-degree male relative age < 55 years or first-degree female age < 65 years) has shown to be independently associated with ASCVD and is not included in PCE. In a study by Lloyd-Jones et al., individuals with a family history of premature CVD in at least one parent were at a twofold increased risk of incident CVD in men and a non-significantly increased risk in women [8]. There also appear to be differences by maternal versus paternal inheritance. A meta-analysis of 26 studies focusing on the impact of maternal versus paternal transmission of ASCVD risk demonstrated that the highest odds of developing ASCVD were in patients with a maternal family history of ASCVD < 50 years of age (odds ratio 3.15, 95% CI 2.18–4.55). A paternal family history < 55 years of age (odds ratio 2.82, 95% CI 2.25–3.54) also contributed to a significantly elevated risk [9]. The magnitude of the association between parental history of premature ASCVD and the risk of events in the offspring emphasizes the importance of obtaining a thorough family history for risk stratification.

South Asians are a high-risk ethnic group with an increased risk for premature ASCVD due to several reasons [10, 11]. There is a higher prevalence of elevated triglycerides and lower high-density lipoprotein cholesterol (HDL-C) levels among South Asians compared to whites. Additionally, despite a high prevalence of South Asian patients with low levels of low-density lipoprotein cholesterol (LDL-C), a substantial number still developed ASCVD with LDL-C levels below 100 mg/dL as shown in the INTERHEART study [12]. South Asians have disproportionately high apolipoprotein B (ApoB) levels relative to their LDL-C, suggesting a higher concentration of atherogenic lipoprotein particles at similar LDL-C levels and smaller LDL-C particle size. Metabolic syndrome is seen more frequently with lower waist circumference in South Asians than in whites and diabetes develops at a lower lean body mass and at earlier ages. Notably, South Asians tend to present with their first ASCVD event at a younger age than individuals from other countries. The INTERHEART study showed that the mean age at presentation for acute myocardial infarction (AMI) in South Asians was lower than that of individuals from other countries (53.0 ± 11.4 vs. 58.8 ±

Table 1 Major categories of risk-enhancing factors recommended to further personalize clinician-patient risk discussion

Race and genetics	Family history of premature ASCVD (male age < 55 years; female age < 65 years)
	South Asian ethnicity
Conditions specific to women	Pre-eclampsia, premature menopause (age < 40 years)
Lipid-related risk	Primary hypercholesterolemia (LDL-C 160–189 mg/dL, non-HDL-C 190–219 mg/dL)
	Persistently elevated triglycerides (≥ 175 mg/dL)
Concurrent high-risk conditions	Ankle-Brachial Index < 0.9 (if measured)
	Chronic inflammatory conditions (rheumatoid arthritis, systemic erythematous lupus, psoriasis, vasculitis, ankylosing spondylitis, hepatitis C infection, HIV/AIDS, or both HIV/HCV)
	Metabolic syndrome
	Chronic kidney disease (eGFR 15–59 mL/min/1.73m^2 with or without albuminuria; not treated with dialysis or kidney transplantation)
Biomarkers (if measured)	Elevated high-sensitivity C-reactive protein levels (≥ 2.0 mg/L)
	Elevated lipoprotein(a) levels (≥ 50 mg/dL or ≥ 125 nmol/L)
	Elevated apolipoprotein B levels (≥ 130 mg/dL)

12.2 years). While the prevalence of three metabolic risk factors (Apolipoprotein B100/Apolipoprotein A-I ratio, diabetes, and waist-to hip-ratio) was higher in South Asian cases and controls, the prevalence of lifestyle factors such as physical activity, fruit and vegetable consumption, and alcohol intake were lower in South Asians as compared to individuals from other areas. After adjusting for the aforementioned risk factors, the predicted probability of having an AMI at a younger age (< 40 years) was similar between South Asian natives and those from other regions. Thus, the earlier presentation of AMI in South Asians could be explained by a higher prevalence of modifiable ASCVD risk factors that are present earlier in life [13]. A recent study of the distribution of Lipoprotein(a) [Lp(a)] across various ethnic groups showed that the population attributable risk (PAR) of myocardial infarction in individuals with Lp(a) concentrations greater than 50 mg/dL was the highest among South Asians compared to other ethnic groups, even after adjustment for age, sex, ApoA1, and ApoB (PAR 0.095, 95% CI 0.051, 0.138) [14].

Taken together, patients with South Asian ancestry or a family history of premature ASCVD are at an increased risk for future ASCVD events and clinicians should take these factors into consideration during risk stratification.

Conditions Specific to Women

Several conditions specific to women have been identified as risk-enhancing factors in the 2018 guidelines. These include premature menopause, premature ovarian failure, pre-eclampsia, gestational hypertension, gestational diabetes, pre-term delivery, and delivery of small-for-gestational-age infants. Premature ovarian failure and early onset of menopause have been shown to be associated with an increased risk of incident CVD events [15–17]. Two meta-analyses suggested that a shorter duration of the reproductive lifespan, mainly driven by early onset of menopause, has been associated with a higher risk of incident CVD [15, 17]. One study showed that women who experience menopause at an age younger than 45 years, compared to those 45 years or older, experienced an increased relative risk of coronary heart disease (CHD) (1.50, 95% CI 1.28, 1.76) [16]. The hypothesized mechanism for this increased risk involves early loss of ovarian function through menopause with associated changes in sex hormones that may contribute to long-term activation of the renin-angiotensin-aldosterone system. These effects are thought to lead to endothelial dysfunction and inflammation that result in vascular damage. Additionally, alterations in the levels of endogenous estrogens during menopause could potentially affect lipid and lipoprotein levels and composition and contribute to the increased risk of ASCVD.

Gestational conditions or complications such as pre-eclampsia and gestational hypertension are also associated with an increased risk for incident ASCVD [18–20]. The CHAMPS study included 1.03 million women without a pre-existing diagnosis of ASCVD before their first pregnancy. Women who experienced a placentally mediated condition during pregnancy such as gestational hypertension, pre-eclampsia, placental abruption, or placental infarction were twice as likely to develop ASCVD (hazards ratio 2.0, 95% CI 1.7, 2.2) after a median follow-up of 8.7 years [21]. There are several proposed mechanisms explaining the association between gestational complications and incident ASCVD: (1) increased arterial stiffness, (2) endothelial dysfunction in the spiral arteries of the uterus, and (3) a chronically abnormal metabolic milieu that exists even prior to pregnancy and continues after delivery affecting both the mother and fetus [15]. In a study of 8127 women, those with a history of gestational diabetes mellitus (GDM) had 63% higher odds (95% CI 1.02, 2.62, $p = 0.04$) of developing incident ASCVD. The absolute risk increase was 2.83% and the average time between a pregnancy complicated by GDM and the diagnosis of CVD was 22.9 years [22]. A large proportion of the increased ASCVD risk seen in women with GDM has been attributed to subsequent development of type II diabetes. A study by Retnakaran and Shah included 13,888 women with GDM, 71,831 women with an abnormal 50-g glucose response but no GDM, and 349,977 women with a normal glucose response over a median follow-up of 12.3 years. The investigators found that the hazards ratio of developing ASCVD was 1.66 (95% CI 1.30, 2.13, $p < 0.01$) for women with GDM and 1.19 (95% CI 1.02, 1.39, $p = 0.03$) for women with an abnormal glucose test result compared to women with normal glucose response. Adjusting for subsequent development of type 2 diabetes led to an attenuation in the hazard ratios for ASCVD to 1.25 (95% CI 0.96, 1.62, $p = 0.1$) for the GDM group and 1.16 (95% CI 0.99, 1.36, $p = 0.06$) for the group with abnormal glucose response [23]. Alternatively, other studies have shown that GDM itself is independently associated with increased future ASCVD risk, irrespective of subsequent development of type 2 diabetes mellitus, though the exact mechanism remains unclear [24].

Women who had pre-term deliveries or delivered small-for-gestational-age infants were also found to be at a substantially increased risk for incident ASCVD [25]. Although the exact mechanism responsible for this observed association is uncertain, inflammatory processes, genetic polymorphisms, and familial predisposition to prematurity are thought to play a role [26, 27].

Overall, a wide body of evidence suggests that the presence of gestational complications, premature menopause, and ovarian failure is associated with a higher lifetime risk of ASCVD. These findings highlight the importance of taking a thorough obstetrical history and obtaining information regarding age of menopause to identify those women who may need early and aggressive lipid-lowering therapy in addition to lifestyle modification.

Lipid-Related Risk

A recent study from the Cooper Center included 36,375 participants who were deemed to be at low risk for atherosclerotic ASCVD (10-year ASCVD risk < 7.5% using PCE). Patients with LDL-C ≥ 100 mg/dL were further categorized into LDL-C groups of (i) 100 to 129 mg/dL, (ii) 130 to 159 mg/dL, (iii) 160 to 189.9 mg/dL, and (iv) ≥ 190 mg/dL. Compared to individuals with LDL-C < 100 mg/dL, "low-risk" individuals with higher LDL-C had a higher risk of ASCVD mortality with hazard ratios of 1.4 (95% CI, 1.1–1.7), 1.3 (95% CI, 1.1–1.6), 1.9 (95% CI, 1.5–2.4), and 1.7 (95% CI, 1.3–2.3), respectively, after a median follow-up of 26.8 years. Even after adjustment for traditional risk factors for ASCVD, individuals with LDL-C levels in the 160–189.9- and ≥ 190-mg/dL categories remained at an increased risk for ASCVD mortality with hazards ratios of 1.7 (95% CI, 1.4–2.2) and 1.5 (95% CI, 1.2–2.1), respectively [28]. Patients in this study were also stratified into categories by non-HDL-C levels: (i) < 130 mg/dL (reference), (ii) 160 to 189 mg/dL, (iii) 190 to 219 mg/dL, and (iv) ≥ 220 mg/dL. Higher levels of non-HDL-C were also independently associated with increased risk of cardiovascular mortality with hazards ratios of 1.3 (95% CI, 1.1–1.6), 1.8 (95% CI, 1.4–2.2), and 1.5 (95% CI, 1.2–2.0), respectively. These findings suggest that a modest elevation in LDL-C (between 160 and 189 mg/dl) or non-HDL-C (≥ 160 mg/dL) even in low-risk patients poses a substantial increase in lifetime risk of cardiovascular mortality that is not readily identified using the PCE [29]. These results indicate that even among those at low-risk in the short to intermediate term, elevated levels of LDL-C and non-HDL-C confer a higher lifetime risk of ASCVD.

Persistently elevated triglyceride levels have proatherogenic properties that have been attributed to an increased risk of ASCVD [30–33]. A study from the Copenhagen City Heart Study stratified 13,981 men and women by non-fasting triglyceride levels: (i) < 88.5 mg/dL (reference), (ii) 88.5–176.1 mg/dL, (iii) 177.0–264.6 mg/dL, (iv) 265.5–353.0 mg/dL, (v) 354.0–441.6 mg/dL, and (vi) ≥ 442.5 mg/dL. A progressive increase in the adjusted hazards ratios for myocardial infarction, ischemic heart disease, and total mortality was noted in both men and women as triglyceride levels increased. Even the modestly elevated triglyceride level group of 88.5–176.1 mg/dL demonstrated an increase in the adjusted hazards ratios for myocardial infarction, ischemic heart disease, and total mortality compared to the reference range. These findings are attributed to persistently elevated levels of atherogenic remnant lipoproteins [32]. Genome-wide association studies (GWAS) have identified at least 28 loci associated with plasma triglyceride levels that are independently associated with the risk for CAD, further strengthening a causal relationship between elevated triglyceride levels and incident ASCVD [34, 35]. A Mendelian randomization study from the Copenhagen City Heart Study showed that genetic variants in 10,208 individuals that resulted in reduced levels of non-fasting plasma triglyceride levels were associated with a reduction in all-cause mortality [36].

Lipid-related risk factors (total cholesterol, high-density lipoprotein cholesterol) are included in traditional risk models. However, the evidence suggests that ASCVD events occur at LDL-C, non-HDL-C, and triglyceride levels that are even modestly elevated, further substantiating the importance of identifying and treating these patients early, who may be at a higher risk of ASCVD events than previously acknowledged.

Concurrent High-Risk Medical Conditions

High-risk medical conditions such as chronic inflammatory diseases (rheumatoid arthritis [RA], psoriasis, ankylosing spondylitis, vasculitis, and systemic erythematous lupus [SLE]), human immunodeficiency virus (HIV), hepatitis C (HCV), metabolic syndrome, and chronic kidney disease (CKD) have all been associated with an increased risk for ASCVD. Non-invasive imaging modalities such as the use of ankle-brachial index (ABI) for the diagnosis of PAD have been shown to be marker for the presence of subclinical atherosclerosis and have been shown to be independently associated with incident CVD. An ABI < 0.9 in patients in the borderline- or intermediate-risk category may suggest an even higher risk category than what is calculated by the PCE [6, 37]. A study in the Multiethnic Study of Atherosclerosis (MESA) cohort showed that the addition of ABI to the Framingham Risk Score (FRS) improved the net reclassification index for ASCVD risk prediction compared to using the FRS alone [38].

Chronic inflammatory conditions including RA [39], SLE [40], and psoriasis [41] have been associated with higher incident ASCVD risk secondary to an increase in underlying inflammatory processes. A meta-analysis of observational studies on patients with RA found a 50% increased risk in cardiovascular mortality in patients with RA compared to the general population (meta-standardized mortality ratio 1.50, 95% CI 1.39–1.61) [39]. Among the chronic inflammatory conditions, SLE showed the strongest association with cardiometabolic diseases (risk ratio (RR) 6.36, 95% CI 4/37–9.25), followed by ulcerative colitis (RR 1.69, 95% CI 1.51–1.89), ankylosing spondylitis (RR 1.28, 95% CI 1.09–1.52), vasculitis (RR 1.64, 95% CI: 1.42–1.90), and psoriasis (RR 1.25) [42]. Patients with HIV, HCV, and HIV/HCV co-infection are also at an increased risk for incident ASCVD that is not adequately accounted for by the PCE [42–44]. Of note, HIV/HCV co-infected individuals have a higher incidence of CVD events and/or death than either HIV mono-infected or HCV mono-infected individuals [43]. Underlying mechanisms related to HIV such as HIV viral load, CD4 count,

and T cell count have been shown to be associated with ASCVD [44].

Metabolic syndrome is comprised of a number of medical conditions including central obesity, hypertension, elevated blood glucose, elevated serum triglycerides, and low serum HDL-C levels, all of which increase the propensity for incident ASCVD [45, 46].

Lower eGFRs in CKD and the presence of albuminuria have been associated with an increased risk of all-cause and cardiovascular mortality. Although the reduction in LDL-C and major vascular events tends to be attenuated at lower eGFRs, the evidence remains strong that patients with CKD (but without end-stage renal disease requiring dialysis) treated with statin and ezetimibe therapy have reduced ASCVD events [47, 48]. Therefore, clinicians should treat patients with CKD with aggressive lipid-lowering therapy to maximize the absolute reduction in ASCVD events.

As a number of comorbid medical conditions discussed above are associated with an increased risk of incident ASCVD, particular care should be given with eliciting a medical history to identify these conditions and to appropriately calibrate the assessment of future ASCVD risk.

Biomarkers

Several biomarkers have been shown to be associated with an increased risk of incident ASCVD and, if measured, could be used to further individualize risk stratification. These include high-sensitivity C-reactive protein (hs-CRP), Lp(a), and ApoB.

In the Framingham Heart Study, Wilson et al. studied the relationship between hs-CRP and CVD risk. In multivariable analyses that included factors such as age, sex, and systolic blood pressure, the log hs-CRP was found to be independently associated with the development of CHD and total CVD. Additionally, the net reclassification improved by 5.6% for total CVD ($P = 0.04$) and 11.8% for CHD ($P = 0.009$) when hs-CRP was added to traditional risk factors [49]. In a meta-analysis of 160,309 individuals from 54 long-term prospective studies, $\log_e$CRP concentration was found to be log-linearly related to the risk of ischemic vascular disease. RRs for CHD per 1-SD higher $\log_e$CRP concentration were 1.63 (95% CI 1.51–1.76) when adjusted for age and sex. After further adjustment for traditional risk factors, the relative risk was 1.37 (95% CI 1.27–1.48) [50]. Thus, both population studies and meta-analyses have demonstrated that CRP has independent association with ASCVD. The JUPITER trial took this association a step further by studying the effects of statin therapy in healthy individuals with elevated hs-CRP levels. The trial randomized 17,802 healthy men and women with elevated levels of hs-CRP at 2.0 mg/L or higher but relatively normal LDL-C levels to rosuvastatin versus placebo. After a median follow-up of 1.9 years, rosuvastatin reduced hs-CRP levels by 37%. Additionally, the rate of the combined primary endpoint of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, and cardiovascular mortality was 0.77 per 100 person-years in the rosuvastatin arm, in contrast to 1.36 per 100 person-years in the placebo arm [51]. Further analyses from the JUPITER trial showed that increasing levels of hs-CRP were associated with an absolute increased risk in ASCVD; every unit increase in log hs-CRP was associated with a 1.3-fold increase in vascular risk (95% CI 1.1–1.5, $p = 0.002$), and the greatest absolute risk reduction derived from rosuvastatin was in patients with the highest baseline levels of hs-CRP [52].

Several studies have demonstrated an independent association between elevated Lp(a) levels and CHD [53–56]. A meta-analysis of 126,634 participants from 36 prospective studies showed that the relative risk of CHD per 3.5-fold higher Lp(a) level adjusted for age and sex was 1.16 (95% CI 1.11–1.22). This risk remained significant after adjustment for risk factors including systolic blood pressure, smoking, history of diabetes, and total cholesterol. Mendelian randomization analyses have also demonstrated a linear association between the risk of CHD and absolute changes in Lp(a) levels. A 10-mg/dL lower genetically predicted Lp(a) concentration was associated with 5.8% lower risk of CHD, an association that was independent of changes in LDL-C level, suggesting a causal relationship between Lp(a) level and CHD risk [57].

ApoB levels also provide important information regarding atherogenic particle numbers that are independently associated with incident ASCVD [58–60]. A meta-analysis of 233,455 individuals from 12 studies demonstrated that apoB is strongly associated with ASCVD (relative risk ratio 1.43, 95% CI 1.35–1.51) risk, suggesting its clinical importance in risk stratification [59].

The guidelines recommend that biomarkers, if measured, provide additive information and could further inform the decision regarding early initiation of statin therapy in borderline- and intermediate-risk patients.

Shared Decision-Making

The 2018 AHA/ACC Multi-Society Guideline on the management of blood cholesterol and the 2019 AHA/ACC Primary Prevention Guidelines reinforce the importance of shared decision to tailor care to the needs and preferences of individual patients [1, 3]. Clinicians should first perform the 10-year ASCVD risk assessment using the PCE. Risk-enhancing factors should then be integrated with the information obtained from the PCE to inform clinical decision-making. Patients should be informed of their personal ASCVD risk and risk-enhancing factors before discussing potential therapeutic options. As it is

difficult to precisely quantify how much an individual's ASCVD risk increases by the presence of one or more risk-enhancing factors, clinical and open communication are crucial. Clinicians should consider the number of risk-enhancing factors, duration of their presence, severity, and patient preference to inform decision-making regarding use of statin therapy along with lifestyle modification. In some cases, the presence of risk-enhancing factors could also inform decision to use a higher intensity of statin therapy. In intermediate-risk or select borderline-risk adults, if the decision about statin therapy remains uncertain after assessment of 10-year risk and after accounting for the risk-enhancers discussed above, it is reasonable to then measure a coronary artery calcium score to decide whether to withhold, postpone, or initiate statin therapy. In summary, risk assessment includes three major steps (a) risk assessment with the PCE, (b) personalization of risk using risk-enhancers, and (c) reclassification of risk using coronary calcium scoring in select individuals. Discussion related to the coronary calcium score in ASCVD risk reclassification is beyond the scope of this review and therefore not discussed in detail here.

Conclusion

In conclusion, the concept of risk-enhancing factors is an important addition to the 2018 AHA/ACC Cholesterol Guidelines. In this review, we summarized the evidence and rationale behind each of the risk-enhancing factors and its association with ASCVD. While the PCE remains an important tool for estimation of ASCVD risk, it is important to understand its limitations at the individual patient level. Incorporating risk-enhancing factors along with global ASCVD risk assessment allows for a more individualized and comprehensive approach to cardiovascular risk assessment.

Funding This study was supported by Abbott Diagnostic, Akcea, Amgen, Esperion, Novartis, Regeneron, Roche Diagnostic, Sanofi-Synthelabo, NIH, AHA, and ADA. All were paid to institution, not individual.

The following acted as consultants: Abbott Diagnostics, Akcea, Amarin, Amgen, Astra Zeneca*, Boehringer Ingelheim, Denka Seiken, Esperion, Intercept, Janssen, Matinas BioPharma Inc., Merck*, Novartis, Novo Nordisk, Regeneron, Roche Diagnostic, and Sanofi-Synthelabo* (*significant where noted (> $10,000); remainder modest (< $10,000)).

Compliance with Ethical Standards

Conflict of Interest Anandita Agarwala MD, Jing Liu MD, and Salim S. Virani MD declare that they have no conflict of interest. Dr. Virani was supported by research funding from the Department of Veterans Affairs Health Services Research & Development Service Investigator Initiated Grant, World Heart Federation, and the Jooma and Tahir Family. Dr. Ballantyne was supported by R01-HL134320.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of blood cholesterol. Circulation. 2018;2018:CIR0000000000000625.
2. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 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.
3. 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: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019.
4. Kavousi M, Leening MJ, Nanchen D, Greenland P, Graham IM, Steyerberg EW, et al. 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(14):1416–23.
5. Wolfson J, Vock DM, Bandyopadhyay S, Kottke T, Vazquez-Benitez G, Johnson P, et al. Use and customization of risk scores for predicting cardiovascular events using electronic health record data. J Am Heart Assoc. 2017;6(4).
6. 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. Circulation. 2014;129(25 Suppl 2):S49–73.
7. Muntner P, Colantonio LD, Cushman M, Goff DC, Howard G, Howard VJ, et al. Validation of the atherosclerotic cardiovascular disease Pooled Cohort risk equations. JAMA. 2014;311(14):1406–15.
8. 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. JAMA. 2004;291(18):2204–11.
9. Weijmans M, van der Graaf Y, Reitsma JB, Visseren FL. 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;179:409–16.
10. •• Volgman AS, Palaniappan LS, Aggarwal NT, Gupta M, Khandelwal A, Krishnan AV, 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(1):e1–e34. **This paper summarizes the evidence and risk factors behind the increased risk of ASCVD in South Asians.**
11. Jose PO, Frank AT, Kapphahn KI, Goldstein BA, Eggleston K, Hastings KG, et al. Cardiovascular disease mortality in Asian Americans. J Am Coll Cardiol. 2014;64(23):2486–94.

12. Karthikeyan G, Teo KK, Islam S, McQueen MJ, Pais P, Wang X, et al. Lipid profile, plasma apolipoproteins, and risk of a first myocardial infarction among Asians: an analysis from the INTERHEART Study. J Am Coll Cardiol. 2009;53(3):244–53.
13. Joshi P, Islam S, Pais P, Reddy S, Dorairaj P, Kazmi K, et al. Risk factors for early myocardial infarction in South Asians compared with individuals in other countries. JAMA. 2007;297(3):286–94.
14.•• 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. **This study highlights ethnic differences in Lp(a) isoform size distribution and concentrations among multiple ethnic groups.**
15. Muka T, Oliver-Williams C, Kunutsor S, Laven JS, Fauser BC, Chowdhury R, 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(7):767–76.
16. Ley SH, Li Y, Tobias DK, Manson JE, Rosner B, Hu FB, et al. Duration of reproductive life span, age at menarche, and age at menopause are associated with risk of cardiovascular disease in women. J Am Heart Assoc. 2017;6(11).
17. Roeters van Lennep JE, Heida KY, Bots ML, Hoek A, Disorders cotDMGDGoCRMaR. Cardiovascular disease risk in women with premature ovarian insufficiency: a systematic review and meta-analysis. Eur J Prev Cardiol. 2016;23(2):178–86.
18. Ahmed R, Dunford J, Mehran R, Robson S, Kunadian V. Pre-eclampsia and future cardiovascular risk among women: a review. J Am Coll Cardiol. 2014;63(18):1815–22.
19. Brown MC, Best KE, Pearce MS, Waugh J, Robson SC, Bell R. Cardiovascular disease risk in women with pre-eclampsia: systematic review and meta-analysis. Eur J Epidemiol. 2013;28(1):1–19.
20. Grandi SM, Vallée-Pouliot K, Reynier P, Eberg M, Platt RW, Arel R, et al. Hypertensive disorders in pregnancy and the risk of subsequent cardiovascular disease. Paediatr Perinat Epidemiol. 2017;31(5):412–21.
21. Ray JG, Vermeulen MJ, Schull MJ, Redelmeier DA. Cardiovascular health after maternal placental syndromes (CHAMPS): population-based retrospective cohort study. Lancet. 2005;366(9499):1797–803.
22. Shostrom DCV, Sun Y, Oleson JJ, Snetselaar LG, Bao W. History of gestational diabetes mellitus in relation to cardiovascular disease and cardiovascular risk factors in US women. Front Endocrinol (Lausanne). 2017;8:144.
23. Retnakaran R, Shah BR. Mild glucose intolerance in pregnancy and risk of cardiovascular disease: a population-based cohort study. CMAJ. 2009;181(6–7):371–6.
24. Carr DB, Utzschneider KM, Hull RL, Tong J, Wallace TM, Kodama K, et al. Gestational diabetes mellitus increases the risk of cardiovascular disease in women with a family history of type 2 diabetes. Diabetes Care. 2006;29(9):2078–83.
25. Catov JM, Newman AB, Roberts JM, Kelsey SF, Sutton-Tyrrell K, Harris TB, et al. Preterm delivery and later maternal cardiovascular disease risk. Epidemiology. 2007;18(6):733–9.
26. Sattar N. Do pregnancy complications and CVD share common antecedents? Atheroscler Suppl. 2004;5(2):3–7.
27. DeFranco E, Teramo K, Muglia L. Genetic influences on preterm birth. Semin Reprod Med. 2007;25(1):40–51.
28.•• Abdullah SM, Defina LF, Leonard D, Barlow CE, Radford NB, Willis BL, et al. Long-term association of low-density lipoprotein cholesterol with cardiovascular mortality in individuals at low 10-year risk of atherosclerotic cardiovascular disease. Circulation. 2018;138(21):2315–25. **This study shows that even in a low risk cohort, LDL-C and non-HDL-C ≥ 160 mg/dL are independently associated with a 50% to 80% increased relative risk of CVD mortality.**
29. Virani SS, Ballantyne CM. Low-density lipoprotein cholesterol: is 160 the new 190? Circulation. 2018;138(21):2326–9.
30. Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, et al. Major lipids, apolipoproteins, and risk of vascular disease. JAMA. 2009;302(18):1993–2000.
31. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. J Cardiovasc Risk. 1996;3(2):213–9.
32. Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. JAMA. 2007;298(3):299–308.
33. Karlson BW, Palmer MK, Nicholls SJ, Lundman P, Barter PJ. A VOYAGER meta-analysis of the impact of statin therapy on low-density lipoprotein cholesterol and triglyceride levels in patients with hypertriglyceridemia. Am J Cardiol. 2016;117(9):1444–8.
34. 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 Diabetes Endocrinol. 2016;4(10):829–39.
35. Bauer RC, Khetarpal SA, Hand NJ, Rader DJ. Therapeutic targets of triglyceride metabolism as informed by human genetics. Trends Mol Med. 2016;22(4):328–40.
36. Thomsen M, Varbo A, Tybjærg-Hansen A, Nordestgaard BG. Low nonfasting triglycerides and reduced all-cause mortality: a Mendelian randomization study. Clin Chem. 2014;60(5):737–46.
37. Lee AJ, Price JF, Russell MJ, Smith FB, van Wijk MC, Fowkes FG. Improved prediction of fatal myocardial infarction using the ankle brachial index in addition to conventional risk factors: the Edinburgh Artery Study. Circulation. 2004;110(19):3075–80.
38. 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(8):788–95.
39. Aviña-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.
40. Westerweel PE, Luyten RK, Koomans HA, Derksen RH, Verhaar MC. Premature atherosclerotic cardiovascular disease in systemic lupus erythematosus. Arthritis Rheum. 2007;56(5):1384–96.
41. Mehta NN, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM. Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database. Eur Heart J. 2010;31(8):1000–6.
42. Dregan A, Chowienczyk P, Molokhia M. Cardiovascular and type 2 diabetes morbidity and all-cause mortality among diverse chronic inflammatory disorders. Heart. 2017;103(23):1867–73.
43. Fernández-Montero JV, Barreiro P, de Mendoza C, Labarga P, Soriano V. Hepatitis C virus coinfection independently increases the risk of cardiovascular disease in HIV-positive patients. J Viral Hepat. 2016;23(1):47–52.
44. Feinstein MJ, Nance RM, Drozd DR, Ning H, Delaney JA, Heckbert SR, et al. Assessing and refining myocardial infarction risk estimation among patients with human immunodeficiency virus: a study by the centers for AIDS Research Network of Integrated Clinical Systems. JAMA Cardiol. 2017;2(2):155–62.
45. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, et al. The metabolic syndrome and cardiovascular risk: a systematic review and meta-analysis. J Am Coll Cardiol. 2010;56(14):1113–32.
46. Gami AS, Witt BJ, Howard DE, Erwin PJ, Gami LA, Somers VK, 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(4):403–14.

47. 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. 2010;375(9731):2073–81.
48. 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.
49. Wilson PW, Pencina M, Jacques P, Selhub J, D'Agostino R, O'Donnell CJ. C-reactive protein and reclassification of cardiovascular risk in the Framingham Heart Study. Circ Cardiovasc Qual Outcomes. 2008;1(2):92–7.
50. Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, Collins R, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet. 2010;375(9709):132–40.
51. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM, Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359(21):2195–207.
52. 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.
53. Erqou S, Kaptoge S, Perry PL, Di Angelantonio E, Thompson A, White IR, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. JAMA. 2009;302(4):412–23.
54.• Verbeek R, Hoogeveen RM, Langsted A, Stiekema LCA, Verweij SL, Hovingh GK, et al. Cardiovascular disease risk associated with elevated lipoprotein(a) attenuates at low low-density lipoprotein cholesterol levels in a primary prevention setting. Eur Heart J. 2018;39(27):2589–96. **This study demonstrates that both Lp(a) and LDL-C levels are independent risk factors for CVD. However, at LDL-C levels below < 2.5 mmol/L, the risk associated with elevated Lp(a) is attenuated in a primary prevention setting.**
55. Virani SS, Brautbar A, Davis BC, Nambi V, Hoogeveen RC, Sharrett AR, 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(2):241–9.
56. Cook NR, Mora S, Ridker PM. Lipoprotein(a) and cardiovascular risk prediction among women. J Am Coll Cardiol. 2018;72(3):287–96.
57.• Burgess S, Ference BA, Staley JR, Freitag DF, Mason AM, Nielsen SF, et al. Association of LPA variants with risk of coronary disease and the implications for lipoprotein(a)-lowering therapies: a Mendelian randomization analysis. JAMA Cardiol. 2018;3(7):619–27. **This study shows that lowering Lp(a) is likely to be proportional to the absolute reduction in Lp(a) concentration. Large absolute reductions in Lp(a) of approximately 100 mg/dL may be required to produce a clinically meaningful reduction in the risk of CHD.**
58. Di Angelantonio E, Gao P, Pennells L, Kaptoge S, Caslake M, Thompson A, et al. Lipid-related markers and cardiovascular disease prediction. JAMA. 2012;307(23):2499–506.
59. 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.
60. 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.