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AHA SCIENTIFIC STATEMENT

Novel Prediction Equations for Absolute Risk Assessment of Total Cardiovascular Disease Incorporating Cardiovascular-Kidney-Metabolic Health: A Scientific Statement From the American Heart Association

Sadiya S. Khan, MD, MSc, FAHA, Chair; Josef Coresh, MD, PhD, FAHA, Vice Chair; Michael J. Pencina, PhD; Chiadi E. Ndumele, MD, PhD, FAHA; Janani Rangaswami, MD, FAHA; Sheryl L. Chow, PharmD, FAHA; Latha P. Palaniappan, MD, MS, FAHA; Laurence S. Sperling, MD, FAHA; Salim S. Virani, MD, PhD, FAHA; Jennifer E. Ho, MD, FAHA; Ian J. Neeland, MD, FAHA; Katherine R. Tuttle, MD, FAHA; Radhika Rajgopal Singh, PhD, FAHA; Mitchell S.V. Elkind, MD, MS, FAHA; Donald M. Lloyd-Jones, MD, ScM, FAHA; on behalf of the American Heart Association

ABSTRACT: Cardiovascular-kidney-metabolic (CKM) syndrome is a novel construct recently defined by the American Heart Association in response to the high prevalence of metabolic and kidney disease. Epidemiological data demonstrate higher absolute risk of both atherosclerotic cardiovascular disease (CVD) and heart failure as an individual progresses from CKM stage 0 to stage 3, but optimal strategies for risk assessment need to be refined. Absolute risk assessment with the goal to match type and intensity of interventions with predicted risk and expected treatment benefit remains the cornerstone of primary prevention. Given the growing number of therapies in our armamentarium that simultaneously address all 3 CKM axes, novel risk prediction equations are needed that incorporate predictors and outcomes relevant to the CKM context. This should also include social determinants of health, which are key upstream drivers of CVD, to more equitably estimate and address risk. This scientific statement summarizes the background, rationale, and clinical implications for the newly developed sex-specific, race-free risk equations: PREVENT (AHA Predicting Risk of CVD Events). The PREVENT equations enable 10- and 30-year risk estimates for total CVD (composite of atherosclerotic CVD and heart failure), include estimated glomerular filtration rate as a predictor, and adjust for competing risk of non-CVD death among adults 30 to 79 years of age. Additional models accommodate enhanced predictive utility with the addition of CKM factors when clinically indicated for measurement (urine albumin-to-creatinine ratio and hemoglobin A1c) or social determinants of health (social deprivation index) when available. Approaches to implement risk-based prevention using PREVENT across various settings are discussed.

Key Words: AHA Scientific Statements ■ cardiovascular diseases ■ heart failure ■ kidney diseases ■ metabolic syndrome ■ models, cardiovascular ■ risk assessment ■ social determinants of health

Obesity, diabetes, and chronic kidney disease (CKD) are each associated with a high burden of cardiovascular disease (CVD) morbidity and mortality; they commonly co-occur and disproportionately affect disenfranchised populations (eg, underrepresented racial and ethnic groups).[1–4] Given the complex interplay of these chronic conditions, a comprehensive focus on CVD prevention that conceptually and therapeutically integrates prevention and management of obesity, diabetes, and CKD is needed.[5,6] This requires moving beyond individual risk factor management approaches and toward a more comprehensive framework.[7] As a result, the American Heart Association (AHA) recently developed a consensus definition for cardiovascular-kidney-metabolic (CKM) syndrome as a systemic disorder that includes those at risk for, and with existing CVD, as well.[8,9]

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In defining the CKM construct, the CKM Health Science Advisory Group (SAG) highlighted the need for preventive approaches that reflect the progressive pathophysiology along the spectrum of the CKM syndrome and associated stepwise increases in absolute CVD risk. The CKM syndrome is thus defined by a staging construct beginning with stage 0, which represents no CKM risk factors; stage 1, excess or dysfunctional adiposity; stage 2, metabolic risk factors or moderate to high-risk chronic kidney disease; stage 3, subclinical CVD in CKM, or risk equivalents of subclinical CVD (high-risk CKD or high predicted risk of CVD); and stage 4, clinical CVD with CKM risk factors.[8] It is important to note that the CKM staging path can be bidirectional and allows the opportunity for individuals to progress or regress along CKM stages. The latter is particularly important and highlights the potential for remission of CKM conditions (eg, restoration of insulin sensitivity to ideal glycemic status, normalization of blood pressure),[10] even back to stage 0 with targeted preventive interventions (eg, health behavior interventions to promote ideal cardiovascular health [CVH]).[11,12]

The CKM stages highlight the central role of excess and dysfunctional adiposity as a key inciting pathophysiological mechanism. This offers the opportunity to identify individuals earlier in their disease process to promote preventive efforts before the progression to overt clinical CVD (stage 4).[1] However, not everyone with stage 2 risk factors (eg, hypertension, diabetes, CKD) will have preceding excess or dysfunctional adiposity.[13–15] Given that the risk implications and therapeutic strategies are similar for hypertension, diabetes, and CKD, regardless of cause, stage 2 is defined by the presence of these conditions with or without excess or dysfunctional adiposity.

Central to the CKM framework is the emphasis on risk-based primary prevention of CVD among CKM stages 0 to 3 that integrates both qualitative (CKM stages) and quantitative (multivariable risk estimation) approaches. Although risk-based prevention has been the cornerstone of CVD prevention for >2 decades,[16] an opportunity to address unmet needs for CVD risk assessment and prevention relevant to the CKM population was identified. As detailed in the CKM Health Presidential Advisory, novel risk prediction algorithms to assess risk of CVD in this context are needed to equitably improve individual- and population-level CKM health with a life course perspective.[8,17]

The CKM Health SAG was appointed by the AHA and asked to develop or recommend a quantitative approach to absolute risk assessment for CVD that could be used to further inform care and complement the qualitative staging system that defines the CKM syndrome. A Prediction Work Group within the CKM Health SAG began by evaluating the scientific evidence on risk assessment for incident CVD (and CVD subtypes), identified gaps in existing multivariable risk prediction equations, and subsequently developed a novel suite of risk prediction equations.[17a]

The purpose of the present scientific statement is to critically review the body of available evidence to support the rationale and development of the PREVENT equations (AHA Predicting Risk of CVD Events). PREVENT is designed to use data readily available to clinicians to estimate absolute risk of CVD, so that it can be implemented easily in routine clinical practice. Herein, we highlight the conceptual and methodological advances of the newly developed sex-specific, race-free risk prediction equations that estimate short- and long-term risk, incorporate kidney function into routine CVD risk assessment, allow for additional consideration of CKM-focused clinical variables and social determinants of health (SDOH) metrics, include heart failure (HF) and atherosclerotic cardiovascular disease (ASCVD) in a total CVD outcome, and adjust for competing risk of non-CVD death. We offer considerations for the future dissemination and implementation of PREVENT in clinical and community-based settings with a focus on clinician-patient risk communication and shared decision-making.

For the purposes of these risk prediction equations, we began with the targeted focus on primary prevention (ie, prevention of first CVD events) in the general population with application intended for the typical adult without baseline CVD. An overarching framework is displayed in Figure 1 that outlines the key goals, which include the following: (1) screen for CKM risk, (2) assess CVD risk, (3) determine CKM stage, and (4) reduce CKM risk. Of note, this does not address or mitigate the importance of risk assessment and prevention in those with prevalent CVD (eg, secondary prevention,[18] stroke prevention in atrial fibrillation[19]), in those with symptoms suggestive of CVD (eg, chest pain[20]), or in selected patient subgroups enriched with inherited risk (eg, familial hyperlipidemia,[21] hypertrophic cardiomyopathy[22]), because these were considered outside the scope of this risk prediction initiative and require distinct clinical algorithms.

EXISTING CVD PREDICTION EQUATIONS

The concept of matching the intensity of preventive interventions that target traditional or causal risk factors for CVD with the absolute risk of the patient has been the paradigm in CVD prevention since the 27th Bethesda Conference held in 1996.[23] As a result, multivariable risk prediction equations have emerged and remain a cornerstone of clinical prevention strategies with evolution of methodological details of the population, predictors, and outcomes included, which was reviewed in detail in the 2013 Report on the Assessment of Cardiovascular Risk.[24] In brief, the Third Report of the National Cholesterol Education Program Expert Panel on Diagnosis, Evaluation, and Treatment of High Blood Cholesterol in Adults recommended the use of the Framingham 10-year risk score (Framingham Risk Score) for coronary heart disease (CHD) risk assessment.[25] However, this model was

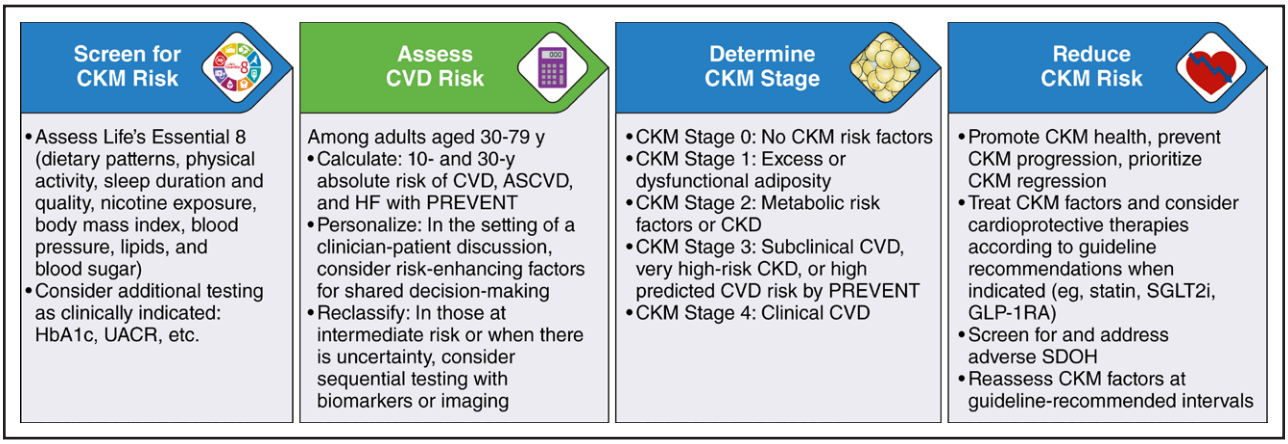

Figure 1. Conceptual framework for risk-based prevention of cardiovascular disease integrating risk assessment with PREVENT and cardiovascular-kidney-metabolic health staging.

ASCVD indicates atherosclerotic cardiovascular disease; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; HF, heart failure; PREVENT, AHA Predicting Risk of CVD Events; SDOH, social determinants of health; SGTL2i, sodium glucose co-transporter 2 inhibitor; and UACR, urine albumin-to-creatinine ratio.

derived in a population of exclusively White individuals from a geographically restricted sample, predicted CHD alone, and did not include diabetes as a predictor.

Therefore, in 2013 a revised approach to risk assessment with the American College of Cardiology (ACC)/AHA pooled cohort equations (PCEs) provided significant advances with (1) addition of stroke as part of the composite end point of ASCVD, (2) inclusion of Black adults, and (3) inclusion of diabetes as a risk factor rather than the assumption that it is a risk equivalent.[24] The PCEs are sex- and race-specific equations that were derived from 5 community-based cohorts (ARIC [Atherosclerosis Risk in Communities]; CHS [Cardiovascular Health Study]; CARDIA [Coronary Artery Risk Development in Young Adults]; FHS [Framingham Heart Study]; FOS [Framingham Offspring Study]) and included data from 11 240 White women, 9098 White men, 2641 Black women, and 1647 Black men 40 to 79 years of age who were free of CHD (defined as history of myocardial infarction [recognized or unrecognized], percutaneous coronary intervention, coronary bypass surgery), stroke, HF, or atrial fibrillation.

The 2013 risk assessment guideline was paired with recommendations for the management of blood cholesterol prioritizing absolute CVD risk assessment to guide clinician-patient discussions for consideration of treatment.[26] Updated or new guidelines for the management of cholesterol (2018),[21] blood pressure (2017),[27] and primary prevention of CVD (2019)[28] have all reiterated and refined recommendations for risk prediction, risk assessment with the PCEs, and risk-based prevention. In addition, the most recent guidelines for the management of HF (2022) suggested biomarkers (eg, natriuretic peptide such as B-type natriuretic peptide) or multivariable risk models be considered to estimate absolute risk (eg, PCP-HF [Pooled Cohort Equations to Prevent Heart Failure]), but a specific risk prediction model was not recommended.[29] A focused summary of contemporary AHA/ACC guideline-based recommendations for use of multivariable risk assessment is detailed in Table 1. In addition, the American Diabetes Association 2023 Standards of Care endorses the use of the PCEs for the assessment of ASCVD risk among individuals with diabetes.[30]

RATIONALE FOR THE DEVELOPMENT OF NOVEL RISK PREDICTION EQUATIONS

General Overview

The 2013 ACC/AHA PCEs have been widely referenced in guidelines as detailed in the previous section,[21,24,28] validated extensively in external datasets,[31–34] and implemented broadly in clinical care.[35–38] With changing prevalence of risk factors (eg, tobacco use), secular trends in risk factor levels (eg, declines in lipid levels in the past decade[39,40]), changes in care patterns (eg, more widespread use of various antihypertensive therapies), risk for incident ASCVD can be overestimated with the PCEs.[41] As a result, the CKM Health SAG agreed that it was now time to revise and update risk equations to address several key gaps in risk prediction with the PCEs and other existing models. Although machine learning approaches were considered and have been evaluated for CVD risk prediction, it was decided they would not add methodological value because the focus of the current model development was on established risk factors with well-understood risk gradients and age-specific interactions.[42] In this context, regression techniques do as well as machine learning approaches and have the benefit of directly providing the strength of association between each risk factor and subsequent risk.[43–45] This results in a parsimonious approach to model development and may also enhance implementation in clinical

Table 1. Summary of Current AHA/ACC Guideline Recommendations for Multivariable Risk Assessment and Risk-Based Prevention for CVD

COR	LOE	Recommendations
2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease[28]		
I	B-NR	For adults 40–75 years of age, clinicians should routinely assess traditional cardiovascular risk factors and calculate 10-year risk of ASCVD by using the PCE.
IIa	B-NR	In adults at borderline risk (5% to <7.5% 10-year ASCVD risk) or intermediate risk (≥7.5% to <20% 10-year ASCVD risk), it is reasonable to use additional risk-enhancing factors to guide decisions about preventive interventions (eg, statin therapy).
IIa	B-NR	For adults 20–39 years of age, it is reasonable to assess traditional ASCVD risk factors at least every 4–6 years.
IIb	B-NR	For adults 20–39 years of age and for those 40–59 years of age who have <7.5% 10-year ASCVD risk, estimating lifetime or 30-year ASCVD risk may be considered.
2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol[21]		
I	B-NR	For the primary prevention of clinical ASCVD in adults 40–75 years of age without diabetes with an LDL-C level of 70–189 mg/dL (1.7–4.8 mmol/L), the 10-year ASCVD risk of a first "hard" ASCVD event (fatal and nonfatal myocardial infarction or stroke) should be estimated by using the race- and sex-specific PCE, and adults should be categorized as being at low risk (<5%), borderline risk (5% to <7.5%), intermediate risk (≥7.5% to <20%), and high risk (≥20%).
I	A	In adults 40–75 years of age with diabetes regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated.
IIa	B-R	In adults 40–75 years of age with LDL-C 70–189 mg/dL (1.7–4.8 mmol/L) who are at 10-year ASCVD risk of ≥7.5%, CKD not treated with dialysis or kidney transplantation is a risk-enhancing factor and initiation of a moderate-intensity statin combined with ezetimibe can be useful.
IIa	B-NR	For clinical decision-making in adults of different race and ethnicities, it is reasonable for clinicians to review racial and ethnic features that can influence ASCVD risk so as to adjust choice of statin or intensity of treatment.
I	B-NR	Clinicians should consider conditions specific to women, such as premature menopause (age <40 years) and history of pregnancy-associated disorders (hypertension, preeclampsia, gestational diabetes, small-for-gestational-age infants, preterm deliveries), when discussing lifestyle intervention and potential for benefit of statin therapy.
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[27]		
I	SBP: A	Use of BP-lowering medications is recommended for secondary prevention of recurrent CVD events in patients with clinical CVD and an average SBP of ≥130 mm Hg or an average DBP of ≥80 mm Hg, and for primary prevention in adults with an estimated 10-year ASCVD risk of ≥10% and an average SBP ≥130 mm Hg or an average DBP ≥80 mm Hg.
I	C-LD	Use of BP-lowering medication is recommended for primary prevention of CVD in adults with no history of CVD and with an estimated 10-year ASCVD risk <10% and an SBP of ≥140 mm Hg or a DBP of ≥90 mm Hg.
2022 ACC/AHA/HFSA Guideline for the Management of Heart Failure[29]		
2a	B-NR	In the general population, validated multivariable risk scores can be useful to estimate subsequent risk of incident HF.
2a	B-R	For patients at risk of developing HF, natriuretic peptide biomarker–based screening followed by team-based care, including a cardiovascular specialist optimizing guideline-directed medical therapy, can be useful to prevent the development of left ventricular dysfunction (systolic or diastolic) or new-onset HF.

AACVPR indicates American Association of Cardiovascular and Pulmonary Rehabilitation; AAPA, American Academy of Physician Assistants; ABC, Association of Black Cardiologists; ACC, American College of Cardiology; ACPM, American College of Preventive Medicine; ADA, American Diabetes Association; AGS, American Geriatrics Society; AHA, American Heart Association; APhA, American Pharmacists Association; ASH, American Society of Hypertension; ASPC, American Society for Preventive Cardiology; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; COR, class of recommendation; CVD, cardiovascular disease; HF, heart failure; HFSA, Heart Failure Society of America; LDL-C, low-density lipoprotein cholesterol; LOE, level of evidence; NLA, National Lipids Association; NMA, National Medical Association; PCE, pooled cohort equation; PCNA, Preventive Cardiovascular Nurses Association; and SBP, systolic blood pressure.

practice.[42] In the future, machine learning approaches may be considered if numerous risk factors and unknown interactions in model development need to be included.

Availability of Electronic Medical Record Data Sources for Model Development

The use of electronic medical records (EMRs) has increased dramatically from only 12% of hospitals having an EMR system in 2009 to nearly 96% of all nonfederal acute care hospitals and nearly 80% of office-based physicians having a certified EMR system.[46] With the near-ubiquitous use of EMRs in clinical health systems, access to real-world clinical data to generate modern, generalizable cohorts of clinically relevant and diverse population-based samples is now possible. EMR data have been used extensively in scientific publications to examine epidemiology, implementation gaps in guideline recommendations, and risk prediction, with reliable and valid estimates.[47–50] Given the inherently larger size of these datasets, with millions of individuals from various racial and ethnic, socioeconomic, and geographic backgrounds available for model development, their use is expected to result in greater generalizability of CVD risk estimates. The use of diverse samples in the derivation and validation datasets will ensure that the study populations used to derive the models match the ones in which they are intended for application (eg, general population receiving clinical care).[51]

However, there are challenges and limitations with the use of electronic health records data. One recent systematic review outlined key issues with the use of EMR

data, including limited use of multicenter data, missingness and nonstandardized measurement of key variables, absence of validation across sites, and loss to follow-up.[52] Another systematic review compared types of datasets and demonstrated better predictive utility of EMR data compared with administrative data, but noted that most studies failed to include socioeconomic predictors or metrics of model calibration, and did not consider clinical implications.[53] With the growth of available data sources for research (eg, All of Us, UK Biobank),[54–56] EMR data for these applications will only continue to grow. The Work Group considered all available data sources and reviewed the advantages and challenges of each and judged that the inclusion of EMR data in the derivation and validation datasets would be highly innovative, and would, on balance, enhance the predictive utility and generalizability of newly developed risk prediction equations.

Established Risk Factors for CVD

It is well-established that the majority of risk for CVD is attributable to traditional risk factors, even at subclinical elevations in levels (eg, elevated blood pressure without meeting criteria for hypertension).[57–60] In an analysis of 3 large prospective studies, nearly all individuals (92% of men and 87% of women) who experienced a nonfatal CHD event had at least 1 clinically elevated major risk factor (which was defined as elevated total cholesterol [≥6.22 mmol/L or ≥240 mg/dL], systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, current cigarette smoking, or diabetes) before the event. Similar estimates were observed for fatal CHD events.[61] Among individuals in the VIRGO study (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients), a prospective observational cohort of individuals 18 to 55 years of age who presented with premature-onset myocardial infarction, the population-attributable fraction for traditional risk factors was 85%. These studies, and others (eg, INTERHEART[62]), highlight the major contribution of traditional risk factors to CVD risk assessment,[57] necessitating their inclusion in updated risk equations. When possible, modeling risk factor levels as continuous predictors can also help to identify individuals with subclinical elevations in multiple risk factors (eg, blood pressure in the prehypertension range, blood sugar in the prediabetes range) who are at higher risk even in the absence of a threshold-based risk factor (eg, hypertension, diabetes). In addition, traditional risk factors are also routinely measured in clinical practice and are the targets of preventive therapies, creating consonance between risk assessment and therapeutic intervention. Although age and sex are not modifiable, they are both key components of CVD risk and are important predictors in CVD risk equations.

Health behaviors, including physical activity and dietary quality, are important targets for CVD risk reduction.[11] These factors have not previously been included in risk prediction because the risks conferred by these factors are mediated, in large part, by the CVD risk factors included in model development (eg, hypertension, diabetes).[63,64] Low or unhealthy cardiorespiratory fitness (CRF), an integrative measure of cardiometabolic health, is associated with higher risk of CVD and all-cause mortality in adults.[65] Raising awareness about the importance of assessment of CRF, modifiability of CRF, and associations of CRF with CVD, and cognitive and mental health, as well, was the focus of a previous AHA scientific statement.[66] However, CRF assessment has not been widely implemented in clinical settings because of cost and scalability and, therefore, has not been integrated into risk prediction algorithms.[67]

Novel Risk Markers for CVD and CKM Health Metrics

There is, however, an ongoing desire to improve on risk assessment on the basis of only the traditional risk factors for CVD, resulting in an ongoing search for new risk markers of CVD that might further enhance risk assessment. Epidemiological data support the robust associations of CKM risk markers (eg, kidney function, metabolic health) with total CVD and individual CVD subtypes, ASCVD, and HF.[68–72] Longer-term studies are emerging to provide direct evidence for links between these factors and lifetime risk of total CVD, ASCVD, and HF.[73–77] In addition to greater burden of CVD, data demonstrate earlier onset of CVD among those with poor CKM health.[78–80] Herein, we review the evidence for risk markers of CKM health and their utility to improve precision and accuracy of risk assessment.

The higher risk of CVD among people with CKD is well-established and was the focus of a previous AHA scientific statement.[68] In fact, individuals with CKD are more likely to die of a CVD event than to progress to kidney failure.[81,82] In an analysis from the CKD Prognosis Consortium that included >9 million individuals, risk of ASCVD (adjusted hazard ratio, 1.30 [95% CI, 1.26–1.35]) and fatal CHD (1.72 [1.46–2.04]) was higher for every 15 mL·min^{-1}·1.73 m^{-2} lower estimated glomerular filtration rate (eGFR), independent of other risk factors, among those with CKD (eGFR <60 mL·min^{-1}·1.73 m^{-2}).[83] Factors that support the addition of eGFR to CVD risk prediction include its routine measurement and accessibility with automated calculation provided in almost all clinical laboratory systems, and the availability of novel therapies that simultaneously target CKD and CVD risk (eg, sodium glucose cotransporter-2 inhibitors, finerenone).[84,85] Although the inclusion of measures of kidney function was evaluated in the PCEs, few individuals having low eGFR (eg, stage 4 CKD with eGFR <30 mL·min^{-1}·1.73 m^{-2}) were present in the samples used for the derivation, leading to limited predictive utility of

eGFR in that sample.[24] In contrast, model development for PREVENT included a much larger population of individuals with impaired kidney function by including data from the EMR samples and broader research cohorts.

At present, annual albuminuria screening, or more often based on CKD risk status, with urine albumin-to-creatinine ratio is recommended in patients with diabetes or CKD (at any time of day).[86–88] The test is simple to perform, inexpensive, and should be repeated at regular intervals for ongoing monitoring and therapeutic decision-making.[89] In addition, robust evidence demonstrates a graded, dose-dependent association between higher levels and incident CVD in people living with and without hypertension, diabetes, and CKD.[85–87] In data from the Heart Outcomes Prevention Evaluation trial, even low levels of albuminuria (previously termed "microalbuminuria") in those with or without diabetes were associated with higher risk of myocardial infarction, stroke, or cardiovascular death.[90] Among CVD subtypes, higher burden of the urine albumin-to-creatinine ratio was also associated with preclinical HF (eg, abnormalities in cardiac structure and function) and HF.[91] Therefore, annual urine albumin-to-creatinine ratio is advised among individuals with CKM stage 2 and higher.[8,9]

In terms of predictors that represent metabolic health, body mass index (BMI) is readily available as part of a routine primary care clinic visit. BMI is a well-established risk factor for CVD and has been the focus of a separate AHA scientific statement.[1] Although BMI is an independent risk factor specifically for HF,[79] the short-term association of BMI with ASCVD is largely mediated by more proximal major CVD risk factors in the causal pathway (eg, diabetes, hypertension) and, thus, inclusion of BMI in risk prediction equations has minimal added utility for discrimination.[34,92,93] However, when BMI is not included in a model, this may lead to less optimal calibration among individuals with a higher BMI. A recent study pooled 8 longitudinal cohorts (n=37 311) and demonstrated that the PCEs had good discrimination (C-statistic 0.760) but overestimated ASCVD risk with the poorest calibration among individuals with moderate or severe obesity (estimated to observed risk ratio 1.36).[34]

Available evidence supports the robust association between dysglycemia and CVD risk among individuals with and without diabetes.[94–96] Screening for dysglycemia can be performed with hemoglobin A1c (or a fasting glucose), which is recommended every 2 to 3 years for CKM stage 1 and every 3 to 5 years for CKM stage 0. Risk prediction equations that are optimized for patients with diabetes have the potential for better calibration with the inclusion of a continuous measure of glycemic status in model development.[97] In the PREVENT model, hemoglobin A1c is included in an additional model (and not the base model) because it is not routinely recommended to be assessed in the general US adult population.

Although the prevalence of abnormal levels of a biomarker may influence its predictive utility in risk prediction on a population level, that does not preclude its potential utility on an individual level. For example, ApoB (apolipoprotein B) levels offer better predictive utility in cases where there is discordance with low-density lipoprotein cholesterol or non–HDL-C (non–high-density lipoprotein cholesterol) levels.[98] Thus, elevated ApoB has been termed a risk-enhancing factor for ASCVD that can be considered in sequential testing, in particular, among those with poor CKM health (eg, insulin resistance).[98] High Lp(a) [lipoprotein (a)] has also been identified as a risk-enhancing factor for ASCVD.[99] Advantages of Lp(a) measurement include that it is largely genetically determined and stable over the life course, so one lifetime measurement is sufficient. Although explicit guideline recommendations are needed in the United States on when and in whom to measure Lp(a), a scientific statement from the AHA suggested the consideration of a multiplication factor to adjust predicted ASCVD risk (to multiply 10-year predicted risk calculated by the PCEs by 1.11-fold for each 50 nmol/L higher Lp(a) >50 nmol/L) when measured and available that was based on a recent analysis from the UK Biobank.[100] If novel therapies that directly target Lp(a) lowering demonstrate clinical efficacy and safety for ASCVD prevention, higher rates of Lp(a) screening and monitoring may be warranted in the future.[100,101]

The CKM Health SAG also reviewed several other risk markers (laboratory and imaging-based biomarkers) and determined that none (individually or combined into a multimarker approach) had a sufficient evidence base (eg, measures of incremental improvement in model discrimination, calibration, or reclassification) to support inclusion into current quantitative risk assessment according to previously outlined expert criteria.[102–105] Specifically, biomarkers of cardiac injury (high-sensitivity troponin, natriuretic peptides [eg, B-type natriuretic peptide]) and diagnostic imaging (CT, echocardiography) were discussed by the group in detail given their importance and clinical relevance for ASCVD and HF prediction and inclusion in the definition of CKM stage 3.[106] Although available data support the robust association between these biomarkers and CVD (because they represent subclinical disease or injury rather than merely risk factors), the absence of recommendations for widespread testing in the general population, issues of cost, and downstream implications of testing resulted in a decision not to include these in PREVENT model development.

Specifically, B-type natriuretic peptide levels have been demonstrated to have independent associations with incident HF across population-based samples, may potentially improve predictive utility when added to traditional risk factors, and are recommended by the 2022 AHA/ACC/Heart Failure Society of America HF guideline for asymptomatic individuals at risk for developing HF.[107–109] This is also consistent with a 2022 consensus

report by the American Diabetes Association that recommended measurement of natriuretic peptide (or high-sensitivity cardiac troponin) on an annual basis among people with diabetes who represent an at-risk group of individuals.[110] However, challenges remain in the implementation of widespread biomarker screening due to cost and clinical actionability when elevated levels are identified. In the current paradigm, they may be more appropriately considered for use as sequential diagnostic tests to evaluate for subclinical CVD and reclassify risk in selected patients. This would be analogous to diagnostic testing with CT for coronary artery calcium (CAC) measurement as recommended by the 2019 ACC/AHA primary prevention guideline for patients with borderline or intermediate 10-year risk for ASCVD when there is clinical uncertainty or patient indecision regarding drug therapy.[28]

Other biomarkers, such as high-sensitivity C-reactive protein, carotid intima media thickness, and ankle brachial index were also reviewed; given the lack of routine clinical measurement in asymptomatic individuals, they were not included in the current models. Family history of premature CVD was discussed given the strong heritable component of CVD[111] but was deemed to be inconsistently ascertained in most clinical settings, and data from previous cohort studies also demonstrated that it did not significantly improve model performance. Last, emergence of data on the association of "OMIC" markers (eg, proteomics, metabolomics, genomics) with risk for incident CVD has yielded great enthusiasm for the potential of precision medicine approaches in risk prediction.[103,104] Although substantive advances in the mechanistic pathways of disease have been borne out by these cutting-edge investigations, the available data do not support the utility of large-scale genomic and proteomic scores for risk prediction in the general population at this time.[112,113] For example, polygenic risk scores for CHD do not clinically meaningfully improve risk discrimination when added to traditional risk factors in middle-aged to older adults.[114–116] Furthermore, when CAC and polygenic risk scores were compared directly, only CAC improved risk discrimination in 2 population-based cohorts of middle-aged to older adults.[117] Future studies that focus on which subsets of the population may benefit from additional sequential testing with novel biomarkers are needed.[103]

Broadening CVD Outcomes

The burden of CVD is increasing in the United States with national prevalence estimated at 128 million affected adults ≥20 years of age with CHD, stroke, HF, and hypertension. Significant disparities exist whereby a disproportionate burden is experienced by individuals who identify as non-Hispanic Black, American Indian and Alaskan Native, or South Asian American individuals.[118–120] In addition, age-adjusted mortality rates due to CVD have increased since the onset of the COVID-19 pandemic.[121] Increases in mortality rates among CVD subtypes have been relatively greater for HF compared with ASCVD.[122–124] HF is also the leading cause of hospitalization in people >65 years of age and is increasing in all age groups.[125] Approximately 6.7 million US adults have prevalent HF with estimates suggesting that prevalence may increase to 8.5 million by 2030.[118] Lifetime risk for developing HF at 45 years of age is estimated to range approximately between 20% and 45%.[126] In aggregate, these observations regarding adverse trends and burden of mortality, hospitalizations, prevalence, and incidence of HF, all indicate the importance of prioritizing primary prevention of HF. Therefore, incident or first event of HF is a clinically relevant end point in risk-based prevention, particularly in the CKM context. In particular, HF is the leading cardiovascular manifestation among individuals with CKD.[127] Among individuals with diabetes, residual or excess risk for HF persists even when key risk factors are controlled (glycemia, blood pressure, cholesterol, albuminuria, and tobacco avoidance).[2]

For the first time, the "2022 ACC/AHA/Heart Failure Society of America Guideline for the Management of Heart Failure" provided recommendations for multivariable risk prediction of absolute risk for incident HF to guide its primary prevention.[29] Although they discussed several potential tools that could be applied (eg, PCP-HF,[128] which were derived from the same cohorts as the PCEs for ASCVD risk; Framingham Heart Failure Risk Score[129]; ARIC Risk Score[130]; Health ABC [Health Aging and Body Composition] Heart Failure Score[131]), the guidelines did not endorse the use of a specific risk score. At this time, the available data do not support the need to differentiate prediction of HF with reduced ejection fraction and HF with preserved ejection fraction, given shared risk factors and similar primary preventive strategies among asymptomatic individuals without left ventricular systolic dysfunction. Hypertension is the leading modifiable factor for both HF with reduced ejection fraction and HF with preserved ejection fraction.[72,132] Future studies should evaluate the need to predict risk for each of these HF subtypes, particularly if therapeutic options for prevention may differ and could be tailored for prevention of HF with reduced ejection fraction and HF with preserved ejection fraction.

Understanding the absolute risk estimate of a person's likelihood of developing total CVD by including relevant CVD subtypes in a composite is important to understand total risk burden and can inform the type and intensity of preventive strategies. The PREVENT model offers risk estimates for total CVD, and for each CVD subtype (ASCVD and HF), as well, included in the composite. PREVENT thus provides a single multivariable risk equation for a simplified framework that can be implemented readily by clinicians. PREVENT also conceptually builds

on the previously published Global CVD FHS model.[133] The high concordance in risk estimates identified for ASCVD and HF (correlation ≥0.9) in the PREVENT equations supports the approach of estimating total CVD as a composite. Prediction of total CVD also addresses the possibility of underaddressing absolute risk by only focusing on ASCVD, specifically in populations with poor CKM health (severe obesity, diabetes, and CKD) where risk for HF is relatively greater than risk for ASCVD.[71,79]

The Work Group also considered other CKM-related outcomes, including other subtypes of CVD (eg, clinical peripheral arterial disease events, atrial fibrillation), subclinical CVD (eg, CAC), and CVD risk factors (eg, hypertension, diabetes). However, there were concerns that both peripheral artery disease and atrial fibrillation lack uniform ascertainment in EMR datasets or research-based cohorts. Although prediction of nonzero CAC or other subclinical disease markers may have utility in younger adults where CVD events are rare, there is potential for misclassification when relying on a surrogate outcome. However, the presence of subclinical disease is important in the classification of CKM stages (eg, stage 3), and the role of integrated risk prediction models (eg, Multi-Ethnic Study of Atherosclerosis [MESA],[134] Astro-CHARM [Astronaut Cardiovascular Health and Risk Modification][135]) should be further studied. Last, a focus on prediction of risk factors themselves (eg, hypertension, diabetes, hyperlipidemia) was considered and thought to have greater relevance in youth and young adulthood when the focus is primordial prevention.

The Work Group also considered other CKM-related outcomes, such as adverse kidney outcomes, cognitive impairment, and dementia, which were deemed outside the scope of the current efforts given differences in pathophysiology and risk factors. Future efforts are encouraged that focus on expanding risk prediction efforts for all CKM-related conditions given the significant associated morbidity, mortality, and health care expenditures.[118]

Long-Term Risk Assessment

The PREVENT equations enable estimates of short-term, and long-term risk, as well, for CVD with accuracy and precision among adults 30 to 79 years of age. These new models apply a life course perspective, using age as the time scale. This will allow prevention efforts across a wider range of ages and provides the opportunity for earlier intervention in younger adults, where the presence of CKM risk factors is associated with an earlier presentation of CVD.[136,137] Although the lower absolute risk of CVD in young adults over a short-term time horizon has led to questions about the merits of risk assessment in this age range, data from nationally representative samples have demonstrated that more than half of adults who have a low estimated 10-year risk of either ASCVD or HF have a high long-term risk.[138,139] Absolute 10-year or short-term risk, in general, is low in young adults even in the presence of moderate elevations in risk factor levels or the presence of CVD risk factors (eg, hypertension, diabetes) known to be associated with high lifetime risk of CVD.[140–143] There is the possibility that when short-term risk is used alone, individuals with low short-term risk who are actually at high lifetime risk may be falsely reassured. Therefore, lifetime risk can inform more intensive risk factor modification earlier in life when these strategies may have greater benefit, as outlined in several recent expert consensus reports focused on prevention and treatment of CVD risk in young adults.[144,145]

REMOVAL OF RACE FROM CVD RISK PREDICTION EQUATIONS

The Work Group discussed the role of race in CVD risk prediction. Because race is a social construct and an historically fraught proxy representing various lived experiences, there is the potential for the harmful interpretation that it represents a biological risk factor when included in risk prediction, which may result in race-specific treatment decisions. Therefore, it was decided a priori not to include race as a predictor in the development of PREVENT and to use the recently developed race-free equations for eGFR on the basis of serum creatinine (CKD-EPI 2021 [Chronic Kidney Disease Epidemiology Collaboration]).[146,147] This is consistent with the growing consensus to remove the use of race from clinical algorithms broadly in medicine.[148] Racism, and not race, structures our social and individual lived experiences, is associated with adverse SDOH, and represents a key driver of adverse CVD outcomes. Therefore, many have advocated for the measurement and inclusion of measures of structural racism or other SDOH (eg, education, income, social deprivation index) that may be able to be intervened on.[149–151] For example, QRISK, a UK-based prediction model for CVD, incorporates a postcode–level deprivation index (Townsend deprivation score).[152]

Furthermore, the inclusion of race in risk prediction may imply that differences by race are not modifiable and may reify race as a biological construct, which may worsen health disparities. In this regard, it is important to note that there continue to be disparities in CVD risk factors and CVD incidence, with Black individuals having higher levels and rates, respectively. Thus, it is of crucial importance to assess and address the SDOH that underlie racial differences. However, most contemporary datasets do not routinely include comprehensive measures of SDOH, limiting the ability to integrate these factors in risk prediction. Furthermore, it should be highlighted that tools and measures to assess the direct effect of racism are currently limited. Therefore, perhaps most critically, concerted research efforts are needed to determine the nonbiological

factors that underlie racial differences in CVD risk and continue to update and revise risk prediction models to enhance assessment with these measures.

In the current model development of PREVENT, the social deprivation index at the zip code level was included in derivation among the subsets where available. However, despite interest in inclusion of measures that more directly reflect risk related to racism (eg, residential segregation, perceived racial discrimination) and additional individual- and place-based measures of social drivers (eg, income, education, residential green space), the lack of standardized assessment and capture in data sources was a key limitation. Therefore, although the PREVENT equations represent a critical step forward, integration of the social deprivation index is only a first step; the inclusion of relevant measures that represent individual experiences of discrimination, structural and systemic racism, and individual- and place-based SDOH should be a priority in risk prediction moving forward.[150,151,153]

As we move forward and strive to transform care delivery to equitably improve CKM health, we must acknowledge the contributions of structural and systemic racism in CVD risk. We should monitor for the potential of unintended consequences that may lead to systematically underestimating risk in disenfranchised groups who may already be less likely to be appropriately prescribed evidence-based medications (eg, statins, novel glucose-lowering drugs) to reduce CVD risk.[154–156] Therefore, calibration of PREVENT across key sociodemographic subgroups (eg, race and ethnicity, strata of social deprivation index) was carefully assessed and demonstrated good calibration among Black individuals (base PREVENT equations calibration slope 1.11 [0.79–1.24]).

It is also important to note that all risk estimates are based on population averages and may under- or overestimate risk in any given individual. Risk estimates are intended to be guides and a starting point for a clinician-patient discussion. However, recommendations should be personalized and contextualized for each patient's lived experiences and comprehensive assessment of social determinants of health. In patients where uncertainty remains, sequential diagnostic testing may be considered, and, if used equitably, can reliably reclassify risk in all individuals and groups.

DEVELOPMENT AND CLINICAL IMPLICATIONS OF THE PREVENT RISK EQUATIONS

As detailed in Khan et al,[17a] the PREVENT models were derived and validated in a total of 46 observational cohort studies and EMR datasets, which included 6 612 004 US adults 30 to 79 years of age. As a result, the newly developed sex-specific, race-free models are broadly generalizable to the target population of interest. The PREVENT equations predict risk of total CVD (a composite of ASCVD and HF) among the general population of primary prevention adults (ie, individuals free of CVD at baseline). The calculated risk estimates newly incorporate HF as an end point, incorporate age as the time scale, and adjust for the competing risk of non-CVD death.

The base PREVENT model includes traditional CVD risk factors and kidney function (eGFR) as predictors with additional models tailored (1) for high-risk subsets of the population with impaired CKM health with urine albumin-to-creatinine ratio or hemoglobin A1c when clinically indicated or available (ie, individuals free of CVD but with CKD or diabetes at baseline) and (2) to incorporate SDOH with social deprivation index when available. The model options reflect an add-on approach for selected individuals when these data are available with modeling of a missing indicator to allow use even if these variables are not available. This is summarized in an infographic in Figure 2. The PREVENT (base and add-on) model performance demonstrates excellent accuracy and precision in the external validation samples for the composite of CVD (median C-statistics ranging from 0.757 to 0.813 and median calibration slopes ranging from 0.94 to 1.05). Similar results were obtained for each CVD subtype individually (median C-statistics ranging from 0.736 to 0.799 for ASCVD and 0.809 to 0.841 for HF; median calibration slopes ranging from 1.00 to 1.11 for ASCVD and 0.81 to 1.00 for HF).

With the use of age as a time scale, estimates for any age and time horizon can be constructed. We chose to present 10- and 30-year risk as the primary model outputs given clinician familiarity with these 2 time points for prediction. As an example, cumulative predicted incidence across the life course of total CVD, ASCVD, and HF, for an individual at index age 30 years is demonstrated in Figure 3. In addition to lower risk of CVD, there is substantially later onset of CVD or compression of morbidity among individuals with all optimal risk factors compared with the presence of 5 suboptimal factors.

The PREVENT models apply age as a time scale, which means follow-up is measured in years of age rather than calendar time. This approach is more consistent with the process of development of CVD outcomes, which is related to a person's age rather than calendar time.[157–160] It also offers the added flexibility of obtaining risk estimates for any duration of follow-up by aggregating estimates from the age at entry and the desired age at end of follow-up. Our age-scale approach mirrors that used by the newer European risk prediction algorithms (SCORE [Systematic Coronary Risk Evaluation]) for CVD.[161] This improves on the time-to-event approach in previous US-based risk prediction models (eg, FHS). Previously published longitudinal or lifetime risk models required use of empiric observation of event incidence in the same individuals over the long term, resulting in baseline data collection

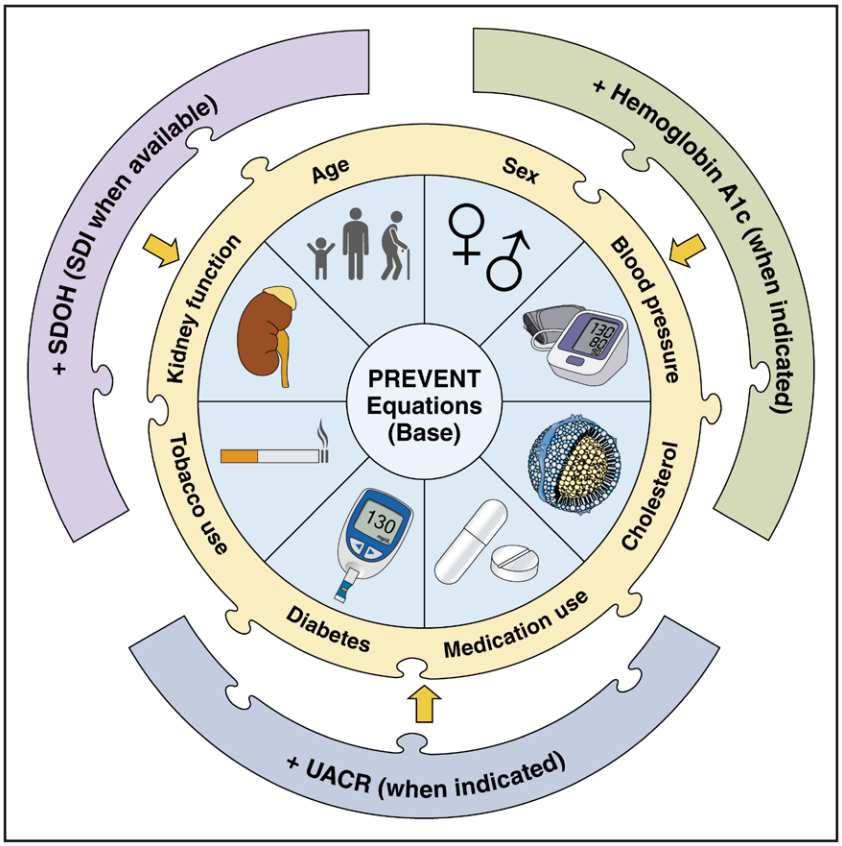

Figure 2. PREVENT base and additional equations.
CVD indicates cardiovascular disease; PREVENT, AHA Predicting Risk of CVD Events; SDI, social deprivation index; SDOH, social determinants of health; and UACR urine albumin-to-creatinine ratio.

from older, noncontemporary cohorts to have sufficient follow-up.[162]

A comparison of the demographic and clinical predictor variables and relevant outcomes in the PREVENT and PCEs are displayed in Supplemental Table 1. Of note, neither PREVENT nor PCEs include individual-level SDOH as predictors.

Clinical Implications

Supplemental Figures 1 and 2 illustrate the range of estimated 10-year predicted risk for incident total CVD, ASCVD, and HF, across a broad range of risk factor levels and selected combinations. The risk factor values were selected in an effort to translate clinically meaningful ranges into absolute risk estimates. The columns are first stratified by diabetes status followed by smoking status and systolic blood pressure levels (with or without antihypertensive treatment). The rows are grouped by age strata and specific total and HDL-C levels. The estimated risk probabilities shown are specific to a hypothetical set of risk factor levels to demonstrate how risk may vary across a broad spectrum of potential clinical profiles. For risk factor levels that are higher than those included, the estimated risk of CVD will be higher. Recommendations for choice of therapy on the basis of differing scenarios of risk should continue to follow available guideline recommendations according to specific comorbidities (eg, diabetes). Risk estimates calculated by PREVENT should be considered in future iterations of guidelines to incorporate absolute risk estimation into risk-based prevention approaches to guide therapeutic choices.

Predicted estimates of ASCVD from PREVENT were lower than previous estimates of ASCVD from the PCEs, as a result of lower ASCVD risk in the contemporary derivation samples for PREVENT compared with older cohorts from which PCEs were developed. The new risk estimates for PREVENT assess total CVD, which is a composite of ASCVD and HF, account for competing risk of noncardiovascular death, are based on more contemporary data with reflection of secular trends and include statin treatment as a predictor, each of which has a meaningful effect on risk estimates.

Among individuals with diabetes, it is important to highlight the distribution of total CVD risk, which reinforces the concept that diabetes is not automatically associated with high risk for CVD and there is significant variability in predicted risk among individuals with diabetes that can inform and tailor novel therapeutic options for mitigation of CVD risk.[163,164] In the future, this may be considered when discussing combinations of cardioprotective antihyperglycemic therapies among those at highest risk with diabetes. Regardless of predicted risk, current guidelines recommend lipid-lowering therapy with statins in all individuals with diabetes who are 40 to 75 years of age on the basis of available clinical trial data of benefit.

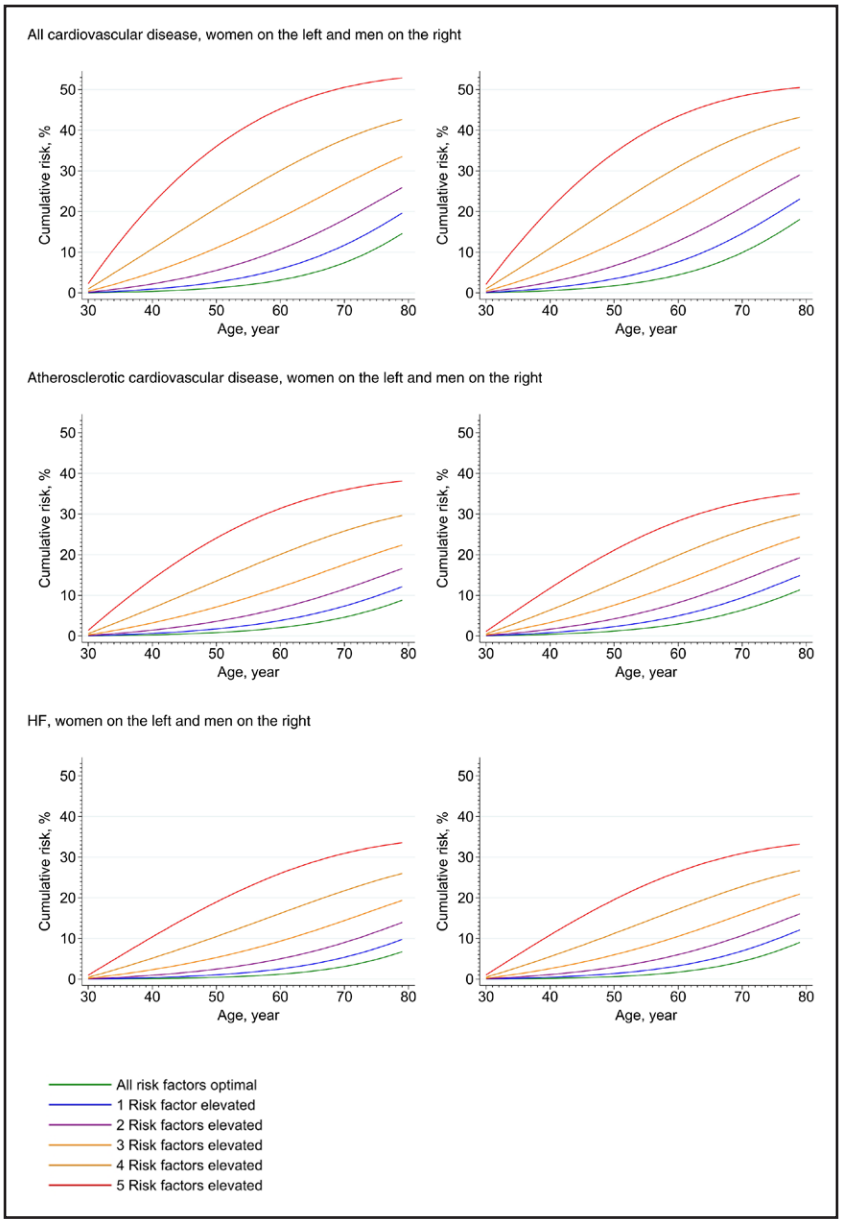

Figure 3. Sex-specific predicted cumulative risk of cardiovascular disease (and subtypes) at index age of 30 years.
Optimal risk factor levels defined as non–high-density lipoprotein cholesterol 3.5 mmol/L or 135 mg/dL; systolic blood pressure 120 mm Hg; no diabetes, nonsmoking, no use of antihypertensives or statins, and estimated glomerular filtration rate 90 mL·min^{-1}·1.73 m^{-2}. Elevated risk factor levels were defined as non–high-density lipoprotein cholesterol 5.5 mmol/L or 213 mg/dL; systolic blood pressure 150 mm Hg, diabetes, current smoking, and estimated glomerular filtration rate 45 mL·min^{-1}·1.73 m^{-2} with average risk of all combinations displayed when >1 risk factor was elevated. Models were adjusted for competing risk of noncardiovascular death. HF indicates heart failure.

IMPLEMENTATION OF RISK ESTIMATION AND RISK COMMUNICATION

In defining CKM, the AHA acknowledged 2 key concepts: (1) health in the early CKM stages should be prioritized as a positive construct beyond just the absence of risk factors, which builds on the existing framework provided by the AHA's construct of CVH first defined in 2010 and revised in 2022 as the Life's Essential 8; and (2) risk for CVD expands beyond ASCVD and should include the presence or absence of relevant chronic conditions that co-occur, are associated with CVD, and have shared therapeutic implications (eg, CKD). The CKM staging framework is meant to be integrated with absolute risk assessment with PREVENT to provide complementary information on CVD risk as depicted in Figure 4.

Risk estimates calculated from PREVENT may be used in the future by clinicians and patients to engage in patient-centered risk discussions to lead to shared decision-making for therapeutic strategies once acceptable risk thresholds are established by guidelines. Thus, the risk assessed by PREVENT may be implemented in the existing ACC/AHA prevention guideline framework and allow clinicians and patients to incorporate further tailoring of recommendations, in particular, in the borderline- to intermediate-risk group, which included a broad range of absolute predicted risk from 5% to <20%. Considerations could include qualitative factors discussed as risk-enhancing factors for (1) CKM progression as detailed in the AHA presidential advisory[8] (eg, chronic inflammatory disease, gestational diabetes, family history of diabetes) and (2) CVD (eg, family history of premature ASCVD) as detailed in the 2019 ACC/AHA primary prevention

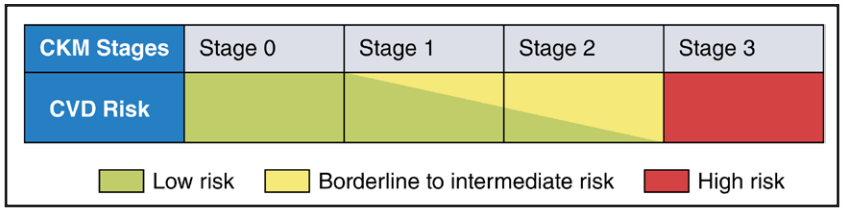

Figure 4. Spectrum of absolute CVD risk across the CKM stages.
Depiction of the gradient of absolute risk for CVD distribution within each CKM stage with green representing low predicted risk, yellow representing borderline to intermediate predicted risk, and red representing high predicted risk. The CKM stages depicted include stage 0 (no CKM risk factors), stage 1 (excess or dysfunctional adiposity), stage 2 (metabolic risk factors or CKD), stage 3 (subclinical CVD in CKM or risk equivalents of subclinical CVD [high-risk CKD or high predicted risk]). CKM indicates cardiovascular-kidney-metabolic; and CVD, cardiovascular disease.

guideline.[28] This framework will support a more personalized prevention approach for CVD as was outlined by the 2019 ACC/AHA primary prevention guideline.

All patients should be counseled on health and behavior modifications to promote ideal CVH metrics aligned with the Life's Essential 8 framework (diet, physical activity, sleep, tobacco avoidance) and receive guideline-directed medical therapy for prevalent risk factors (eg, glucagon-like peptide-1 receptor agonists for individuals with obesity or statins for individuals with diabetes).[165,166] In a risk-based framework, those with higher predicted 10-year risk should have patient-centered discussions for intensification of risk factor modification and consideration of combination therapies to maximally reduce CVD risk (eg, angiotensin-converting enzyme inhibitor plus sodium glucose cotransporter-2 inhibitors plus finerenone; or glucagon-like peptide-1 receptor agonist plus sodium glucose cotransporter-2 inhibitors).[167,168] However, future research should prioritize the generation of evidence needed for guideline revisions to determine the integration of absolute risk assessment from the PREVENT equations with risk-based prevention approaches to inform specific therapeutic choices.

Emerging research evaluating novel biomarkers and broad-based genetic testing merits further investigation, but it is important to keep in mind that nonspecific biomarkers that do not identify a targeted therapeutic pathway or actionable response (beyond those currently available) would have limited utility in clinical management. Targeted or sequential diagnostic testing might be best reserved for those strategies that are deemed to have additive predictive utility (eg, CAC) and may preferentially be applied in those with other risk-enhancing factors where the aggregate burden of these qualitative markers may have relevance.[169,170] Shared decision-making around these issues with appropriate framing of risks and potential benefits will lead to greater patient satisfaction and adherence. Development of online risk estimators, EMR plug-ins, and web-based applications on the basis of these equations will be critical for widespread dissemination and implementation to optimize CVD prevention. In particular, the multiple PREVENT model options can flexibly allow for inclusion of the extended CKM/SDOH variables when available or clinically indicated, and help catalyze clinician consideration for CKM/SDOH variables, as well, to inform use and discussions and communication. The greater precision provided by PREVENT, in addition to their greater relevance to contemporary populations, should enhance clinician and patient confidence in their use. Thus, such an approach integrating quantitative and qualitative risk assessment and shared decision-making to guide risk factor treatment algorithms could also be considered by individual practice guidelines (eg, management of cholesterol, blood pressure) to modify causal risk factors across the life course.

To be successful, formulation of preventive strategies should also consider critically important individual-level contextual factors (eg, ability to access and prepare healthy foods or participate in physical activity, access and affordability of prescribed medications, and health literacy), and societal-level factors (such as cost-effectiveness), as well.[171,172] Likewise, successful CVD prevention also depends on appropriate follow-up and monitoring of intermediate and physiological markers of adherence and response (eg, controlled blood pressure, stable or declining weight, and increased proportion of lean body mass) that requires ongoing access to health care.

DIRECTIONS AND UNANSWERED QUESTIONS

A growing body of evidence supports the importance of risk assessment and risk-based prevention.[28,173] However, important knowledge gaps remain, which are outlined in Table 2.

Incorporating Expected Treatment Benefit Into CVD Prevention

To be actionable, risk estimates need to be translated into meaningful clinical decisions. One approach is to classify individuals as low, intermediate, or high risk on the basis of output from the risk prediction algorithm. A more clinically actionable approach is to combine

Table 2. Key Gaps and Future Directions in CVD Risk Prediction and Risk-Based Prevention

Areas of research	Key gaps and unanswered question
SDOH	What are the individual- and place-based SDOH factors with predictive utility in models for CVD risk prediction?
	What are the best approaches to analyze and integrate multilevel SDOH factors for CVD risk prediction?
	How should we address SDOH to reduce risk of CVD associated with CKM risk?
	Identify approaches to measurement of key SDOH factors in the clinical setting?
Novel predictors and outcomes	Incorporate prediction of CKD progression as a risk factor and modifiable target for CVD risk-based prevention
	Evaluate the clinical utility of prediction of CVD risk factors (eg, hypertension, diabetes) or subclinical CVD (eg, coronary artery calcium)
	Investigate the predictive utility of broad-based omic predictors or aggregate scores for CVD
	Determine cost-effectiveness of diagnostic imaging in risk-enriched populations to identify subclinical CVD (eg, echocardiography among those with atrial fibrillation) to improve accuracy of CKM staging
Interventional and implementation research	Determine the risk threshold at which net benefit is favorable for each cardioprotective therapy that treats CVD risk factors, address underlying risk, and prevent progression of CKD
	Define strategies to implement the Life's Essential 8 as a framework to measure, modify, and monitor CKM health
	Conduct randomized clinical trials in young adults to inform interventions at earlier ages and prevent onset of CVD risk factors or subclinical disease
Dissemination and implementation research	Integration of PREVENT into electronic medical records to support widespread use of risk assessment
	What are the optimal strategies to optimize CVD risk factor control among those at increased predicted risk of CVD
	Can pharmacist-delivered health-system intervention or a community-based intervention improve risk factor control among those at increased predicted risk of CVD

CKM indicates cardiovascular-kidney-metabolic; CVD, cardiovascular disease; PREVENT, AHA Predicting Risk of CVD Events; and SDOH, social determinants of health.

these absolute risks with relative risk reductions expected from the treatment strategies being considered to quantify the anticipated "treatment benefit." Treatment recommendations are then made on the basis of this expected benefit. This benefit model for prevention has been shown to be optimal among strategies that recommend the same numbers of people for a given treatment.[174,175] It can be illustrated by considering a simple example: a person with a high level of non–HDL-C and intermediate predicted CVD risk would be expected to derive a higher benefit (higher reduction in absolute risk) from a lipid-lowering treatment than a person with higher risk but optimal levels of non–HDL-C.[175,176] This is displayed conceptually in Figure 5 and this approach will be particularly important to inform the use of cardioprotective antihyperglycemic therapies for individuals with poor CKM health.

Refining Assessment and Inclusion of SDOH in CVD Risk Prediction

Some limitations that are present in the PREVENT equations should be considered as focus for future iterations. The number of Hispanic and Asian individuals included in the sample is relatively lower than national estimates in the population.[48] The absence of disaggregated racial and ethnic subgroup identification in most datasets limits the assessment of calibration in these subgroups. This is particularly relevant among South Asian individuals who are at a disproportionately higher risk of metabolic disease and ASCVD compared with White adults.[177–179] One analysis demonstrated equivalent risk for diabetes in South Asian adults at a BMI of 18.5 kg/m^2 compared with White adults at a BMI of 24.9 kg/m^2. South Asian ethnicity, which is a social construct, is specifically highlighted in the CKM presidential advisory[8] and scientific statement[9] as a risk-enhancing factor and has been identified to be associated with higher risk of CKM conditions and CVD risk.[180] Therefore, application of PREVENT in this subgroup may lead to underestimation of CVD risk and reinforces the need for diverse samples that represent the diversity of the intended target population when developing risk prediction equations. Future research should assess calibration of PREVENT among disaggregated racial and ethnic groups.

It is well-documented that significantly higher incidence of CVD is present among certain racial and ethnic groups.[118] Emerging data identify that social factors are the upstream drivers of this disproportionate CVD risk.[181] In one analysis from the CARDIA study, excess risk for diabetes among Black individuals compared with White individuals was nearly completely attributed to differences in neighborhood, socioeconomic, psychosocial, and behavioral factors.[182] In another analysis from the CARDIA study, similar findings were observed to explain the difference in racial disparities in premature CVD.[137] SDOH as determinants of CVH is highlighted in the contextualization of the Life's Essential 8 framework, which identifies important individual-, clinical-, and policy-level approaches needed to equitably promote health and reduce CVD risk.[11] The Centers for Medicare & Medicaid Services recently issued guidance to integrate the assessment of SDOH within the health care system. However, significant gaps exist, and future research should prioritize assessment and interventional tools before their implementation is feasible but begins with the imperative to rigorously expand the collection, reporting, and standardization of SDOH data.

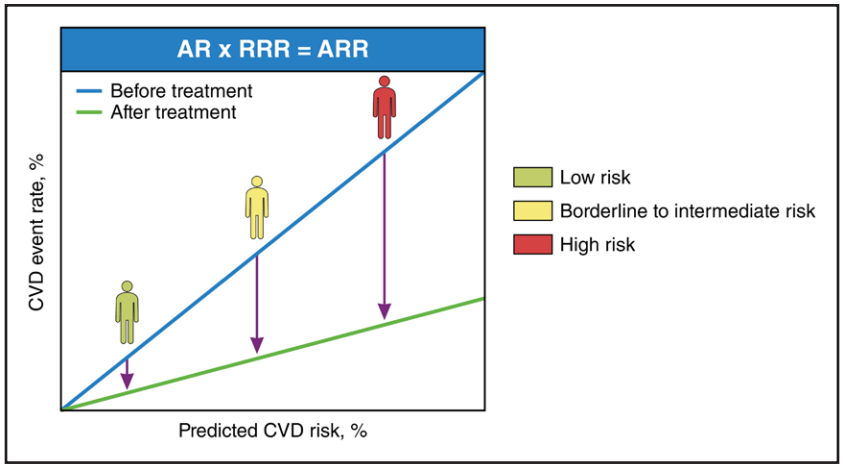

Figure 5. Estimating the expected treatment benefit (absolute risk reduction) on the basis of absolute risk and relative risk reduction of treatment.
Depiction of the conceptual framework to calculate net benefit or expected benefit (defined as absolute risk reduction [ARR]) from a preventive therapy, which assumes that the relative risk reduction (RRR) across the spectrum of predicted absolute risk (AR) is similar. The green individual represents low predicted risk, the yellow individual represents borderline to intermediate predicted risk, and the red individual represents high predicted risk. Therefore, the ARR for an individual with higher predicted risk before treatment is greater than an individual with lower predicted risk before treatment (ie, $ARR_{red} > ARR_{yellow} > ARR_{green}$). CVD indicates cardiovascular disease.

This is consistent with the recommendations put forth in the CKM health care model and will also serve to inform future iterations of CVD risk prediction models.[8,9]

Moving CVD Risk Assessment and Prevention Earlier in the Life Course

A growing body of evidence supports the importance of risk prediction beginning earlier in the life course, even in childhood or, perhaps, in utero. A complete life course approach to CVH promotion, CKM staging, and CVD risk assessment is depicted in a conceptual diagram in Figure 6. The yield of effective strategies may be greatest if the strategies can be implemented when CKM health is declining, and risk is becoming manifest. From the perspective of prevention, risk estimation beginning earlier in the life course has substantial merit to begin patient-clinician discussions on measurement, monitoring, and

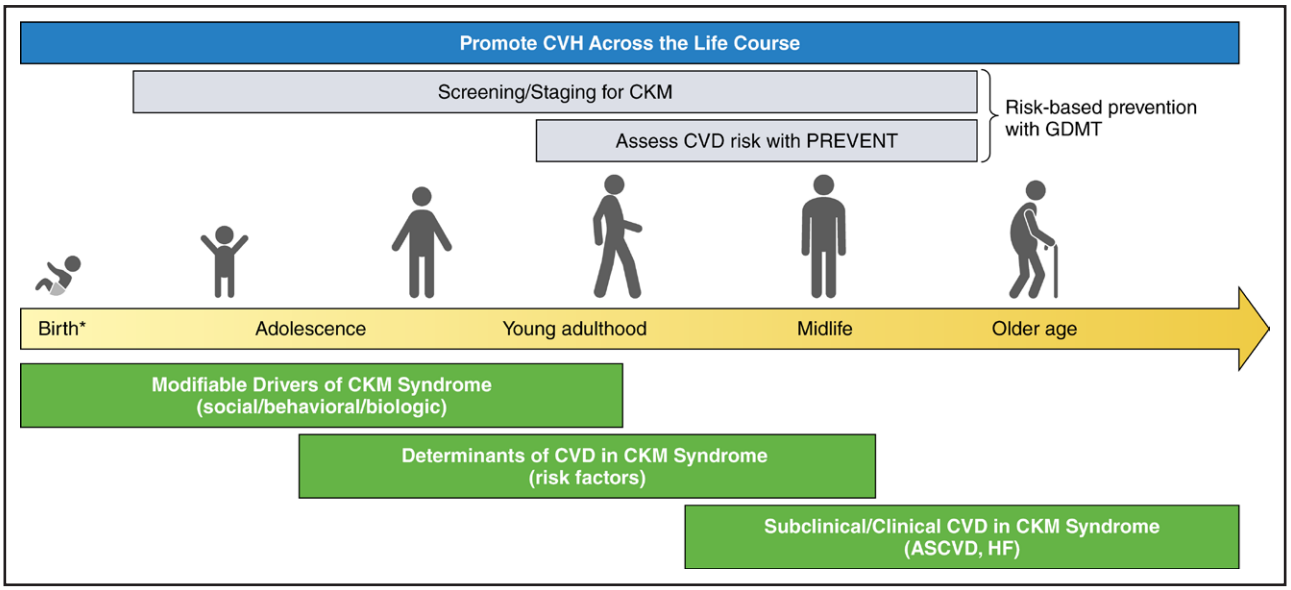

Figure 6. A life course approach to the promotion of CVH, staging of CKM health, and risk assessment: drivers, determinants, and disease.
*Risk for poor CKM may begin before birth with adverse exposures in utero (eg, gestational diabetes). ASCVD indicates atherosclerotic cardiovascular disease; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; CVH, cardiovascular health; GDMT, guideline-directed management and therapy; HF, heart failure; and PREVENT, AHA Predicting Risk of CVD Events.

modification of CVD risk factors, which emerge in the adolescent to adult transition.[183] This topic was the focus of a 2023 science advisory from the AHA: "Toward a Roadmap for Best Practices in Pediatric Preventive Cardiology."[184]

Another key life period in young adulthood that may benefit from additional research for CVD risk prediction and prevention is the peripartum (prepregnancy, pregnancy, and postpartum) period. This is especially important because prepregnancy CVH and adverse pregnancy outcomes have been associated with risk for CVD in birthing adults.[185] Furthermore, prenatal exposure to maternal CVH has been associated with offspring CVH, suggesting the potential for interventions in pregnancy to improve intergenerational transmission of CVD risk.[186] The incorporation of adverse pregnancy outcomes (eg, gestational diabetes, hypertensive disorders of pregnancy) as novel predictors or relevant outcomes in risk prediction should thus be considered in future research. In addition, with the expansion of the age range included in the PREVENT model beginning at 30 years of age when individuals may be pregnant, how well the models perform when risk factors are assessed in pregnancy should be evaluated. Because there can be physiological changes in metabolic factors (eg, glucose, lipids) during the second and third trimester of pregnancy, the implementation of PREVENT may need to be limited to the first trimester before physiological changes of pregnancy have manifested. Pregnancy represents an ideal "window" of opportunity when there is greater access to health care and increased contact with clinicians that can be leveraged to allow for the earlier initiation of discussions about lifetime prevention of CVD if PREVENT is validated in pregnant samples.

Predicting Adverse Kidney Outcomes to Optimize Prevention of CVD

It is well-established that cumulative exposures to known modifiable or traditional CVD risk factors are largely responsible for CVD risk. Changes in risk factor levels and resultant modification of CVD risk as a result of treatment have been modeled for traditional risk factors in the Million Hearts Model.[187] However, changes in kidney function over time were not included. It has become increasingly recognized that decline in kidney health is associated with worse CVD outcomes, and conversely kidney protective therapies improve CVD outcomes.[188] Several models have been developed that predict key kidney outcomes (eg, acute kidney injury, decline in kidney function, and kidney failure) among people with and without diabetes.[189–191] The CKD Prognosis Consortium derived and validated novel risk equations specifically to predict kidney function decline ≥40% or kidney failure from 43 datasets, including ≥1 million individuals with excellent discrimination and calibration.[189]

Risk prediction models for kidney disease progression have also been applied recently to stratify and identify those who may have greater absolute benefit from therapies that target kidney health (ie, risk-based prevention). In an analysis from 4 TIMI (Thrombolysis in Myocardial Infarction) clinical trials, those with higher baseline risk of adverse kidney outcomes had greater absolute benefit with sodium glucose cotransporter-2 inhibitors.[192] Future research should investigate whether risk-based prevention of kidney function decline translates into risk reduction of CVD. In addition, novel risk factors for decline in kidney function over time should be explored. For example, a recent study from the CHS demonstrated that subclinical myocardial dysfunction on echocardiography was associated with a decline in kidney function, suggesting bidirectional pathways between pre-HF and risk for worsening CKD.[193] In addition, models should consider inclusion of eGFR calculation with use of cystatin C as this becomes more widely available and used in clinical practice.

CONCLUSIONS

Absolute risk assessment for CVD remains the cornerstone of clinical primary prevention efforts. The PREVENT models reflect the interrelatedness and upstream effect of CKM conditions on CVD risk. These sex-specific risk equations newly include eGFR as a predictor, HF as an outcome, and critically remove race from risk prediction estimates. In optional models, incorporation of additional markers of kidney, metabolic, and social risk highlight the opportunities to further personalize risk assessment and tailor risk-based recommendations. PREVENT can be applied in a broad range of clinical and community settings given the use of readily available clinical factors. PREVENT can be implemented by all clinicians who care for adult patients, including primary care, obstetrics and gynecology, cardiology, nephrology, and endocrinology settings. Although quantitative risk assessment for CVD will continue to be an evolving process that reflects the secular trends in risk factor prevalence and treatment patterns, refinement of social and biological predictors, and emergence of novel therapies, the development of PREVENT provides a critical next step forward to prioritize primary prevention across the spectrum of CKM and equitably improve health in the population.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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Disclosures

Writing Group Disclosures

Writing group member	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/advisory board	Other
Sadiya S. Khan	Northwestern University Feinberg School of Medicine	None	None	None	None	None	None	None
Josef Coresh	Johns Hopkins University	None	None	None	None	None	Healthy.io†; Soma Logic†	None
Sheryl L. Chow	Western University of Health Sciences	Beth Israel Deaconness Medical Center	None	None	None	None	None	None
Mitchell S.V. Elkind	Columbia University	None	None	None	None	None	None	American Heart Association†
Jennifer E. Ho	Beth Israel Deaconness Medical Center	NIH†	None	None	None	Pfizer, Inc†	None	None
Donald M. Lloyd-Jones	Northwestern University Feinberg School of Medicine	None	None	None	None	None	None	None
Chiadi E. Ndumele	Johns Hopkins University	None	None	None	None	None	None	None
Ian J. Neeland	UH Cleveland Medical Center - Case Western Reserve University	None	None	None	None	None	Boehringer Ingelheim†; Eli Lilly and Co†; Nestle Health Science†; Bayer Pharmaceuticals*	None
Latha P. Palaniappan	Stanford University	None	None	None	None	None	None	None
Michael J. Pencina	Duke University	McGill University Health Centre†	None	Janssen	None	Azra Care*	Cleerly†; Polish Medical Research Agency†; JAMA†	None
Radhika Rajgopal Singh	American Heart Association	None	None	None	None	None	None	None
Janani Rangaswami	Washington DC VA Medical Center	None	None	Boehringer Ingelheim*	None	None	Boehringer Ingelheim†; Procyrion*; Edwards LifeSciences*	None
Laurence S. Sperling	Emory University School of Medicinewright	None	None	None	None	None	None	None
Katherine R. Tuttle	Providence Health Care/ University of Washington	NIH†; CDC†; Travere†; JDRF†	None	None	None	None	None	Providence Inland Northwest Health†
Salim S. Virani	Michael E. DeBakey VA Medical Center Health Services Research and Development Center for Innovation; Baylor College of Medicine; Michael E. DeBakey VAMC; Methodist DeBakey Heart and Vascular Center	NIH† Department of Veterans Affairs†; Tahir and Jooma Family Endowment Fund†	None	None	None	None	None	None

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*Modest.

†Significant.

Reviewer Disclosures

Reviewer	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/advisory board	Other
Roger S. Blumenthal	Johns Hopkins University	None	None	None	None	None	None	None
Roxana Mehran	Icahn School of Medicine at Mount Sinai	Abbott*; Abiomed*; Affluent Medical*; Alleviant Medical*; Amgen*; AM-Pharma*; Arena*; AstraZeneca*; AtriCure Inc*; Biosensors*; Biotronik*; Bristol-Myers Squibb*; CardiaWave*; CeloNova*; Chiesi*; Concept Medical*; Cytosorbents*; Daiichi Sankyo*; Duke*; Element Science*; Faraday*; Idorsia*; Janssen*; MedAlliance*; Medscape*; Mediasphere*; Medtelligence*; Medtronic*; Novartis†; OrbusNeich*; Penumbra*; PhaseBio*; Philips*; Pi-Cardia*; PLx Pharma*; Protembis*; RenalPro*; RM Global*; Shockwave*; Vivasure*	Affluent Medical*; Cardiovascular Research Foundation (CRF)*; Esperion Science/ Innovative Biopharma*; Ionis Pharmaceuticals*; IQVIA*; J-CalC*; Novartis*; NovoNordisk*; Vectura*; VoxMedia*; IQVIA*; SL Solutions*; WebMD†	*JAMA Cardiology* (Associate Editor)*; ACC (BOT Member, SC Member CTR Program)*	None	Applied Therapeutics†; Elixir Medical†; Stel†; ControlRad (spouse)*	None	None
Susan E. Quaggin	Northwestern University	None	None	None	None	None	Astra Zeneca*; Novartis*; Boehringer-Ingelheim*; Pfizer*	None
Ravi V. Shah	Vanderbilt University Medical Center	None	None	None	None	None	None	None
Karol E. Watson	David Geffen School of Medicine at UCLA	None	None	None	None	None	None	None

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†Significant.

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