

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

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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 fibrillation¹⁹), in those with symptoms suggestive of CVD (eg, chest pain²⁰), or in selected patient subgroups enriched with inherited risk (eg, familial hyperlipidemia,²¹ hypertrophic cardiomyopathy²²), 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

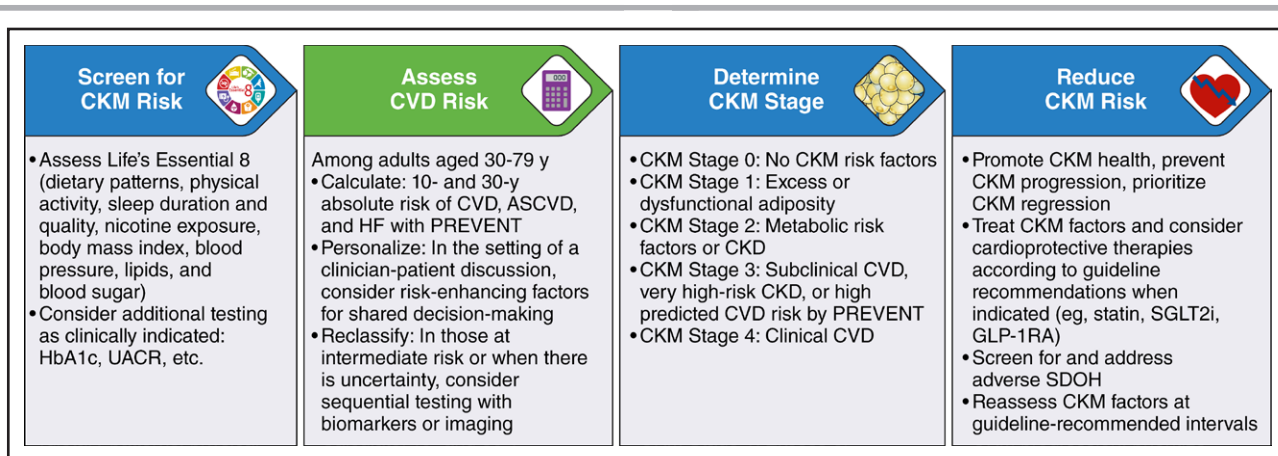


Figure 1. Conceptual framework for risk-based prevention of cardiovascular disease integrating risk assessment with PREVENT and cardiovascular-kidney-metabolic health staging.

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; SGLT2i, 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 recom-

mended.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 Disease²⁸		
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 Cholesterol²¹		
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 Adults²⁷		
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 mmHg or an average DBP of ≥80 mmHg, and for primary prevention in adults with an estimated 10-year ASCVD risk of ≥10% and an average SBP ≥130 mmHg or an average DBP ≥80 mmHg.
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 mmHg or a DBP of ≥90 mmHg.

(Continued)

Table 1. Continued

COR	LOE	Recommendations
2022 ACC/AHA/HFSA Guideline for the Management of Heart Failure²⁹		
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, INTERHEART⁶²), 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 reduc-

tion.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.⁸⁹

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 predic-

tion 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 CVD¹¹¹ 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 individu-

als.^{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 Score¹²⁹; ARIC Risk Score¹³⁰; Health ABC [Health Aging and Body Composition] Heart Failure Score¹³¹), 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 general-

izable 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

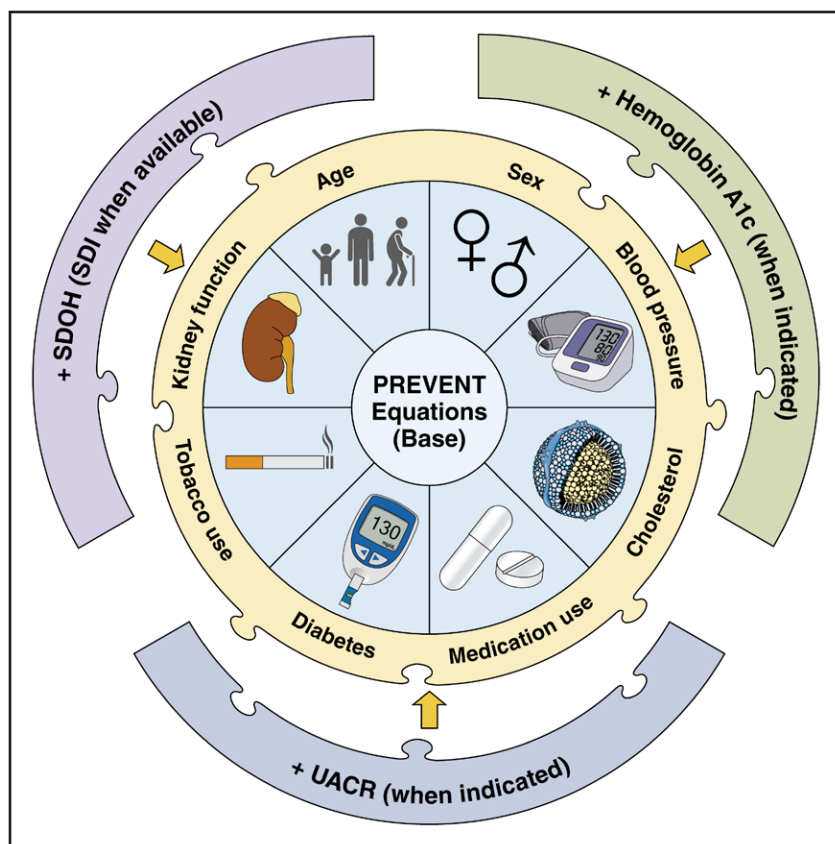


Figure 2. PREVENT base and additional equations.

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.

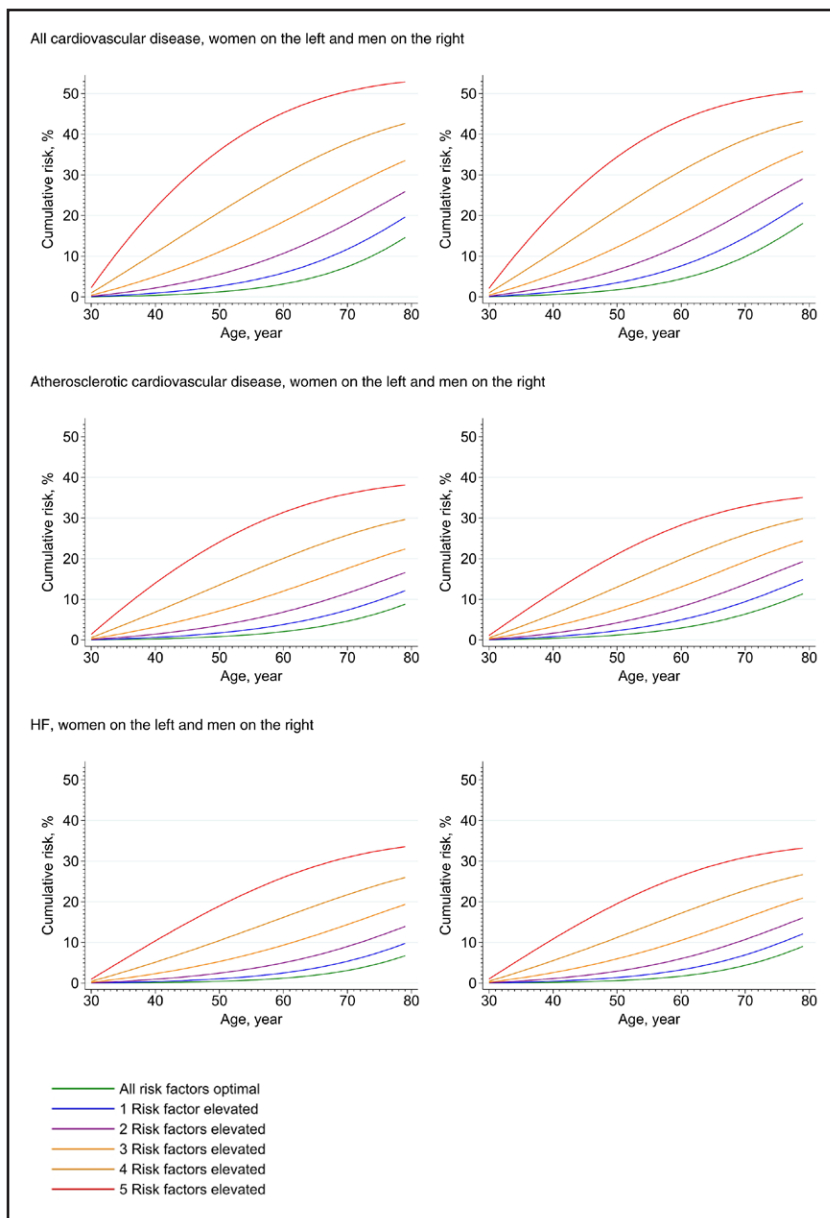


Figure 3. Sex-specific predicted cumulative risk of cardiovascular disease (and subtypes) at index age of 30 years.

Optimal risk factor levels defined as non-high-density lipoprotein cholesterol 3.5 mmol/L or 135 mg/dL; systolic blood pressure 120 mmHg; 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 mmHg, 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 advisory⁸ (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

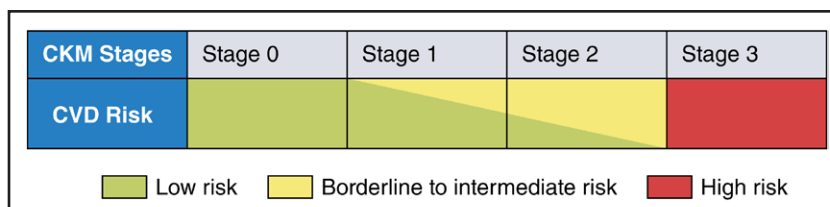


Figure 4. Spectrum of absolute CVD risk across the CKM stages.

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/m² compared with White adults at a BMI of 24.9 kg/m². South Asian ethnicity, which is a social construct, is specifically highlighted in the CKM presidential advisory⁸ and scientific statement⁹ 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.

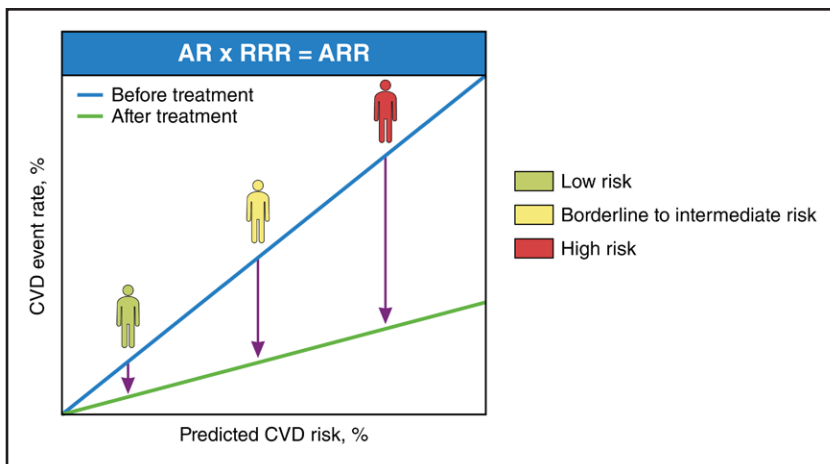


Figure 5. Estimating the expected treatment benefit (absolute risk reduction) on the basis of absolute risk and relative risk reduction of treatment.

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

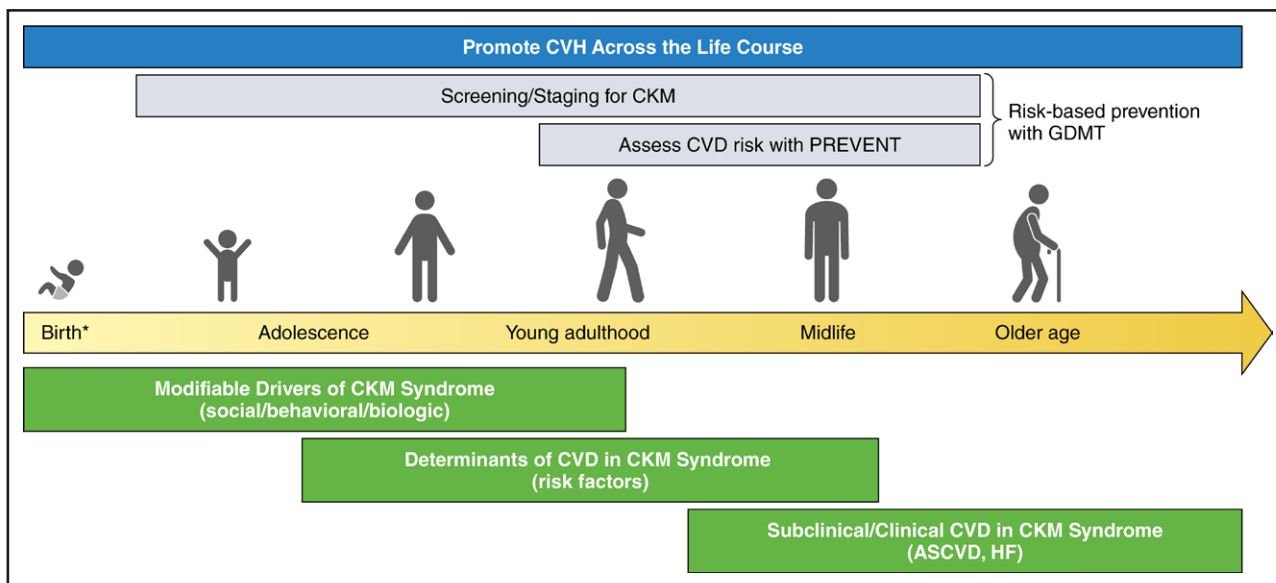


Figure 6. A life course approach to the promotion of CVH, staging of CKM health, and risk assessment: drivers, determinants, and disease.

*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 (pregnancy, 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 $\geq 40\%$ 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

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Disclosures

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*Modest.

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REFERENCES

- Powell-Wiley TM, Poirier P, Burke LE, Després J-P, Gordon-Larsen P, Lavie CJ, Lear SA, Ndumele CE, Neeland IJ, Sanders P, et al; on behalf of the American Heart Association Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Epidemiology and Prevention; and Stroke Council. Obesity and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2021;143:e984–e1010. doi: 10.1161/CIR.0000000000000973
- Rawshani A, Rawshani A, Franzén S, Sattar N, Eliasson B, Svensson A-M, Zethelius B, Miftaraj M, McGuire DK, Rosengren A, et al. Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2018;379:633–644. doi: 10.1056/NEJMoa1800256
- Wright AK, Suarez-Ortegon MF, Read SH, Kontopantelis E, Buchan I, Emsley R, Sattar N, Ashcroft DM, Wild SH, Rutter MK. Risk factor control and cardiovascular event risk in people with type 2 diabetes in primary and secondary prevention settings. *Circulation*. 2020;142:1925–1936. doi: 10.1161/CIRCULATIONAHA.120.046783
- Rangaswami J, Bhalla V, Blair JE, Chang TI, Costa S, Lentine KL, Lerma EV, Mezue K, Molitch M, Mullens W, et al; on behalf of the American Heart Association Council on the Kidney in Cardiovascular Disease and Council on Clinical Cardiology. Cardiorenal syndrome: classification, pathophysiology, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. *Circulation*. 2019;139:e840–e878. doi: 10.1161/CIR.0000000000000664
- Rangaswami J, Bhalla V, De Boer IH, Staruschenko A, Sharp JA, Singh RR, Lo KB, Tuttle K, Vaduganathan M, Ventura H, et al; on behalf of the American Heart Association Council on the Kidney in Cardiovascular Disease; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; and Council on Lifestyle and Cardiometabolic Health. Cardiorenal protection with the newer antidiabetic agents in patients with diabetes and chronic kidney disease: a scientific statement from the American Heart Association. *Circulation*. 2020;142:e265–e286. doi: 10.1161/CIR.0000000000000920
- Reiter-Brennan C, Dzaye O, Davis D, Blaha M, Eckel RH. Comprehensive care models for cardiometabolic disease. *Curr Cardiol Rep*. 2021;23:22. doi: 10.1007/s11886-021-01450-1
- Soroosh GP, Dzaye O, Reiter-Brennan C, Blaha MJ. Cardiometabolic medicine: a review of the current proposed approaches to revamped training in the United States. *Cardiovasc Endocrinol Metab*. 2021;10:168–174. doi: 10.1097/XCE.0000000000000243
- Ndumele CE, Rangaswami J, Chow SL, Neeland IJ, Tuttle KR, Khan SS, Coresh J, Mathew RO, Baker-Smith CM, Camethon MR, et al; on behalf of the American Heart Association. Cardiovascular-kidney-metabolic health: a presidential advisory from the American Heart Association. *Circulation*. Published online October 9, 2023. doi: 10.1161/CIR.0000000000001184
- Ndumele CE, Neeland IJ, Tuttle KR, Chow SL, Mathew RO, Khan SS, Coresh J, Baker-Smith CM, Camethon MR, Després J-P, et al; on behalf of the American Heart Association. A synopsis of the evidence for the science and clinical management of cardiovascular-kidney-metabolic (CKM) syndrome: a scientific statement from the American Heart Association. *Circulation*. Published online October 9, 2023. doi: 10.1161/CIR.0000000000001186

10. Schauer PR, Mingrone G, Ikramuddin S, Wolfe B. Clinical outcomes of metabolic surgery: efficacy of glycemic control, weight loss, and remission of diabetes. *Diabetes Care*. 2016;39:902–911. doi: 10.2337/dc16-0382
11. Lloyd-Jones DM, Allen NB, Anderson CA, Black T, Brewer LC, Foraker RE, Grandner MA, Lavretsky H, Perak AM, Sharma G, et al. Life's Essential 8: updating and enhancing the American Heart Association's construct of cardiovascular health: a presidential advisory from the American Heart Association. *Circulation*. 2022;146:e18–e43. doi: 10.1161/CIR.0000000000001078
12. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenland K, Daniels S, Nichol G, Tomaselli GF, et al; American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's Strategic Impact Goal through 2020 and beyond. *Circulation*. 2010;121:586–613. doi: 10.1161/CIRCULATIONAHA.109.192703
13. Aung K, Lorenzo C, Hinojosa MA, Haffner SM. Risk of developing diabetes and cardiovascular disease in metabolically unhealthy normal-weight and metabolically healthy obese individuals. *J Clin Endocrinol Metab*. 2014;99:462–468. doi: 10.1210/jc.2013-2832
14. Carnethon MR, De Chavez PJD, Biggs ML, Lewis CE, Pankow JS, Bertoni AG, Golden SH, Liu K, Mukamal KJ, Campbell-Jenkins B, et al. Association of weight status with mortality in adults with incident diabetes. *JAMA*. 2012;308:581–590. doi: 10.1001/jama.2012.9282
15. Xu W, Shubina M, Goldberg SL, Turchin A. Body mass index and all-cause mortality in patients with hypertension. *Obesity (Silver Spring)*. 2015;23:1712–1720. doi: 10.1002/oby.21129
16. Califf R, Armstrong P, Carver J, D'agostino R, Strauss W. 27th Bethesda Conference: matching the intensity of risk factor management with the hazard for coronary disease events Task Force 5. Stratification of patients into high, medium and low risk subgroups for purposes of risk factor management. *J Am Coll Cardiol*. 1996;27:1007–1019. doi: 10.1016/0735-1097(96)87733-3
17. Akam EY, Nuako AA, Daniel AK, Stanford FC. Racial disparities and cardiovascular metabolic risk: new horizons of intervention and prevention. *Curr Diab Rep*. 2022;22:129–136. doi: 10.1007/s11892-022-01451-6
- 17a. Khan SS, Matsushita K, Sang Y, Ballew SH, Grams ME, Surapaneni A, Blaha MJ, Carson AP, Chang AR, Ciemins E, et al; for the Chronic Kidney Disease Prognosis Consortium and the American Heart Association Cardiovascular-Kidney-Metabolic Science Advisory Group. Development and validation of the American Heart Association Predicting Risk of Cardiovascular Disease EVENTS (PREVENT) equations. *Circulation*. Published online November 10, 2023. doi: 10.1161/CIRCULATIONAHA.123.067626
18. Virani SS, Newby LK, Arnold SV, Bittner V, Brewer LC, Demeter SH, Dixon DL, Fearon WF, Hess B, Johnson HM, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA guideline for the management of patients with chronic coronary disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation*. 2023;148:e9–e119. doi: 10.1161/CIR.0000000000001168
19. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, et al; European Heart Rhythm Association, European Association for Cardio-Thoracic Surgery. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J*. 2010;31:2369–2429. doi: 10.1093/eurheartj/ehq278
20. Gulati M, Levy PD, Mukherjee D, Amsterdam E, Bhatt DL, Birtcher KK, Blankstein R, Boyd J, Bullock-Palmer RP, Conejo T, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2021;144:e368–e454. doi: 10.1161/CIR.0000000000001029
21. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, De Ferranti S, Faiella-Tommasino J, Forman DE, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139:e1082–e1143. doi: 10.1161/CIR.0000000000000625
22. Ommen SR, Mital S, Burke MA, Day SM, Deswal A, Elliott P, Evanovich LL, Hung J, Joglar JA, Kanto P, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2020;142:e558–e631. doi: 10.1161/CIR.0000000000000937
23. Grundy SM, Balady GJ, Criqui MH, Fletcher G, Greenland P, Hiratzka LF, Houston-Miller N, Kris-Etherton P, Krumholz HM, LaRosa J, et al. Guide to primary prevention of cardiovascular diseases. A statement for health-care professionals from the Task Force on Risk Reduction. American Heart Association Science Advisory and Coordinating Committee. *Circulation*. 1997;95:2329–2331. doi: 10.1161/01.cir.95.9.2329
24. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:S49–S73. doi: 10.1161/01.cir.0000437741.48606.98
25. Lloyd-Jones DM, Wilson PW, Larson MG, Beiser A, Leip EP, D'Agostino RB, Levy D. Framingham risk score and prediction of lifetime risk for coronary heart disease. *Am J Cardiol*. 2004;94:20–24. doi: 10.1016/j.amjcard.2004.03.023
26. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, 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. *Circulation*. 2014;129:S1–S45. doi: 10.1161/01.cir.0000437738.63853.7a
27. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APHA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71:e13–e115. doi: 10.1161/HYP.0000000000000065
28. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberg ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140:e596–e646. doi: 10.1161/CIR.0000000000000678
29. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145:e895–e1032. doi: 10.1161/CIR.0000000000001063
30. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, Collins BS, Das SR, Hilliard ME, Isaacs D, et al; on behalf of the American Diabetes Association. 10. Cardiovascular disease and risk management: standards of care in diabetes—2023. *Diabetes Care*. 2023;46:S158–S190. doi: 10.2337/dc23-S010
31. Cook NR, Ridker PM. Calibration of the pooled cohort equations for atherosclerotic cardiovascular disease: an update. *Ann Intern Med*. 2016;165:786–794. doi: 10.7326/M16-1739
32. Go AS, Tabada G, Reynolds K, Fortmann SP, Garg A, Scott RD, Young J, Lo JC, Solomon MD, Wei R. A new ASCVD risk estimator is more accurate than the ACC/AHA pooled cohort equation in four diverse community-based populations in the U.S. and Canada. *Circulation*. 2018;138:A12623.
33. Mora S, Wenger NK, Cook NR, Liu J, Howard BV, Limacher MC, Liu S, Margolis KL, Martin LW, Paynter NP, et al. Evaluation of the pooled cohort risk equations for cardiovascular risk prediction in a multiethnic cohort from the Women's Health Initiative. *JAMA Intern Med*. 2018;178:1231–1240. doi: 10.1001/jamainternmed.2018.2875
34. Khera R, Pandey A, Ayers CR, Carnethon MR, Greenland P, Ndumele CE, Nambi V, Seliger SL, Chaves PH, Safford MM. Performance of the pooled cohort equations to estimate atherosclerotic cardiovascular disease risk by body mass index. *JAMA Netw Open*. 2020;3:e2023242. doi: 10.1001/jamanetworkopen.2020.23242
35. Kang S-H, Baek H, Cho J, Kim S, Hwang H, Lee W, Park JJ, Yoon YE, Yoon C-H, Cho Y-S, et al. Management of cardiovascular disease using an mHealth tool: a randomized clinical trial. *NPJ Digital Med*. 2021;4:165. doi: 10.1038/s41746-021-00535-z
36. Karmali KN, Brown T, Sanchez T, Long T, Persell SD. Point-of-care testing to promote cardiovascular disease risk assessment: a proof of concept study. *Prev Med Rep*. 2017;7:136–139. doi: 10.1016/j.pmedr.2017.05.016
37. Blood AJ, Cannon CP, Gordon WJ, Mailly C, MacLean T, Subramaniam S, Tucci M, Crossen J, Nichols H, Wagholikar KB, et al. Results of a remotely delivered hypertension and lipid program in more than 10 000 patients

- across a diverse health care network. *JAMA Cardiol.* 2023;8:12–21. doi: 10.1001/jamacardio.2022.4018
38. Takamine L, Forman J, Damschroder LJ, Youles B, Sussman J. Understanding providers' attitudes and key concerns toward incorporating CVD risk prediction into clinical practice: a qualitative study. *BMC Health Serv Res.* 2021;21:561. doi: 10.1186/s12913-021-06540-y
 39. Patel N, Bhargava A, Kalra R, Parcha V, Arora G, Muntner P, Arora P. Trends in lipid, lipoproteins, and statin use among U.S. adults: impact of 2013 cholesterol guidelines. *J Am Coll Cardiol.* 2019;74:2525–2528. doi: 10.1016/j.jacc.2019.09.026
 40. Perak AM, Ning H, KitBK, DeFerranti SD, Van Horn LV, Wilkins JT, Lloyd-Jones DM. Trends in levels of lipids and lipoprotein B in US youths aged 6 to 19 years, 1999–2016. *JAMA.* 2019;321:1895–1905. doi: 10.1001/jama.2019.4984
 41. Yadlowsky S, Hayward RA, Sussman JB, McClelland RL, Min Y-L, Basu S. Clinical implications of revised pooled cohort equations for estimating atherosclerotic cardiovascular disease risk. *Ann Intern Med.* 2018;169:20–29. doi: 10.7326/M17-3011
 42. Engelhard MM, Navar AM, Pencina MJ. Incremental benefits of machine learning: when do we need a better mousetrap? *JAMA Cardiol.* 2021;6:621–623. doi: 10.1001/jamacardio.2021.0139
 43. Lynam AL, Dennis JM, Owen KR, Oram RA, Jones AG, Shields BM, Ferrat LA. Logistic regression has similar performance to optimised machine learning algorithms in a clinical setting: application to the discrimination between type 1 and type 2 diabetes in young adults. *Diagn Progn Res.* 2020;4:6. doi: 10.1186/s41512-020-00075-2
 44. Hong C, Pencina MJ, Wojdyla DM, Hall JL, Judd SE, Cary M, Engelhard MM, Berchuck S, Xian Y, D'Agostino R, et al. Predictive accuracy of stroke risk prediction models across Black and White race, sex, and age groups. *JAMA.* 2023;329:306–317. doi: 10.1001/jama.2022.24683
 45. Christodoulou E, Ma J, Collins GS, Steyerberg EW, Verbakel JY, Van Calster B. A systematic review shows no performance benefit of machine learning over logistic regression for clinical prediction models. *J Clin Epidemiol.* 2019;110:12–22. doi: 10.1016/j.jclinepi.2019.02.004
 46. Dean BB, Lam J, Natoli JL, Butler Q, Aguilar D, Nordyke RJ. Use of electronic medical records for health outcomes research: a literature review. *Med Care Res Rev.* 2009;66:611–638. doi: 10.1177/1077558709332440
 47. Goldstein BA, Navar AM, Pencina MJ. Risk prediction with electronic health records: the importance of model validation and clinical context. *JAMA Cardiol.* 2016;1:976–977. doi: 10.1001/jamacardio.2016.3826
 48. Rodriguez F, Chung S, Blum MR, Coulet A, Basu S, Palaniappan LP. Atherosclerotic cardiovascular disease risk prediction in disaggregated Asian and Hispanic subgroups using electronic health records. *J Am Heart Assoc.* 2019;8:e011874. doi: 10.1161/JAHA.118.011874
 49. Jeon-Slaughter H, Chen X, Tsai S, Ramanan B, Ebrahimi R. Developing an internally validated Veterans Affairs women cardiovascular disease risk score using Veterans Affairs National Electronic Health Records. *J Am Heart Assoc.* 2021;10:e019217. doi: 10.1161/JAHA.120.019217
 50. Vassy JL, Lu B, Ho Y-L, Galloway A, Raghavan S, Honerlaw J, Tarko L, Russo J, Qazi S, Orkaby AR, et al. Estimation of atherosclerotic cardiovascular disease risk among patients in the Veterans Affairs Health Care System. *JAMA Netw Open.* 2020;3:e2028236. doi: 10.1001/jamanetworkopen.2020.8236
 51. Pencina MJ, Goldstein BA, D'Agostino RB. Prediction models: development, evaluation, and clinical application. *N Engl J Med.* 2020;382:1583–1586. doi: 10.1056/NEJMp2000589
 52. Goldstein BA, Navar AM, Pencina MJ, Ioannidis JP. Opportunities and challenges in developing risk prediction models with electronic health records data: a systematic review. *J Am Med Inform Assoc.* 2017;24:198–208. doi: 10.1093/jamia/ocw042
 53. Mahmoudi E, Kamdar N, Kim N, Gonzales G, Singh K, Waljee AK. Use of electronic medical records in development and validation of risk prediction models of hospital readmission: systematic review. *BMJ.* 2020;369:m958. doi: 10.1136/bmj.m958
 54. Mayo KR, Basford MA, Carroll RJ, Dillon M, Fullen H, Leung J, Master H, Rura S, Sulieman L, Kennedy N, et al. The All of Us Data and Research Center: creating a secure, scalable, and sustainable ecosystem for biomedical research. *Annu Rev Biomed Data Sci.* 2023;6:443–464. doi: 10.1146/annurev-biodatasci-122120-104825
 55. Perry AS, Annis JS, Master H, Naylor M, Hughes A, Kouame A, Natarajan K, Marginean K, Murthy V, Roden DM, et al. Association of longitudinal activity measures and diabetes risk: an analysis from the National Institutes of Health All of Us Research Program. *J Clin Endocrinol Metab.* 2023;108:1101–1109. doi: 10.1210/clinem/dgac695
 56. Glynn P, Greenland P. Contributions of the UK biobank high impact papers in the era of precision medicine. *Eur J Epidemiol.* 2020;35:5–10. doi: 10.1007/s10654-020-00606-7
 57. Pencina MJ, Navar AM, Wojdyla D, Sanchez RJ, Khan I, Ellassal J, D'Agostino RB Sr, Peterson ED, Sniderman AD. Quantifying importance of major risk factors for coronary heart disease. *Circulation.* 2019;139:1603–1611. doi: 10.1161/CIRCULATIONAHA.117.031855
 58. Yusuf S, Joseph P, Rangarajan S, Islam S, Mentz A, Hystad P, Brauer M, Kutty VR, Gupta R, Wielgosz A, et al. Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. *Lancet.* 2020;395:795–808. doi: 10.1016/s0140-6736(19)32008-2
 59. Miura K, Daviglius ML, Dyer AR, Liu K, Garside DB, Stamler J, Greenland P. Relationship of blood pressure to 25-year mortality due to coronary heart disease, cardiovascular diseases, and all causes in young adult men: the Chicago Heart Association Detection Project in Industry. *Arch Intern Med.* 2001;161:1501–1508. doi: 10.1001/archinte.161.12.1501
 60. Stamler J, Daviglius ML, Garside DB, Dyer AR, Greenland P, Neaton JD. Relationship of baseline serum cholesterol levels in 3 large cohorts of younger men to long-term coronary, cardiovascular, and all-cause mortality and to longevity. *JAMA.* 2000;284:311–318. doi: 10.1001/jama.284.3.311
 61. Greenland P, Knoll MD, Stamler J, Neaton JD, Dyer AR, Garside DB, Wilson PW. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. *JAMA.* 2003;290:891–897. doi: 10.1001/jama.290.7.891
 62. Anand SS, Islam S, Rosengren A, Franzosi MG, Steyn K, Yusufali AH, Keltai M, Diaz R, Rangarajan S, Yusuf S; INTERHEART Investigators. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. *Eur Heart J.* 2008;29:932–940. doi: 10.1093/eurheartj/ehn018
 63. Pandey A, Mehta A, Paluch A, Ning H, Carnethon MR, Allen NB, Michos ED, Berry JD, Lloyd-Jones DM, Wilkins JT. Performance of the American Heart Association/American College of Cardiology pooled cohort equations to estimate atherosclerotic cardiovascular disease risk by self-reported physical activity levels. *JAMA Cardiol.* 2021;6:690–696. doi: 10.1001/jamacardio.2021.0948
 64. Jeong SY, Wee CC, Kovell LC, Plante TB, Miller ER 3rd, Appel LJ, Mukamal KJ, Juraschek SP. Effects of diet on 10-year atherosclerotic cardiovascular disease risk (from the DASH Trial). *Am J Cardiol.* 2023;187:10–17. doi: 10.1016/j.amjcard.2022.10.019
 65. Shah RV, Murthy VL, Colangelo LA, Reis J, Venkatesh BA, Sharma R, Abbasi SA, Goff DC, Carr JJ, Rana JS, et al. Association of fitness in young adulthood with survival and cardiovascular risk: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *JAMA Intern Med.* 2016;176:87–95. doi: 10.1001/jamainternmed.2015.6309
 66. Ross R, Blair SN, Arena R, Church TS, Després J-P, Franklin BA, Haskell WL, Kaminsky LA, Levine BD, Lavie CJ, et al; on behalf of the American Heart Association Physical Activity Committee of the Council on Lifestyle and Cardiometabolic Health. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American Heart Association. *Circulation.* 2016;134:e653–e699. doi: 10.1161/CIR.0000000000000461
 67. Naylor M, Shah RV, Tanguay M, Blodgett JB, Chernofsky A, Miller PE, Xanthakis V, Malhotra R, Houstis NE, Velagaleti RS, et al. Feasibility, methodology, and interpretation of broad-scale assessment of cardiorespiratory fitness in a large community-based sample. *Am J Cardiol.* 2021;157:56–63. doi: 10.1016/j.amjcard.2021.07.020
 68. Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raji L, Spinosa DJ, Wilson PW. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation.* 2003;108:2154–2169. doi: 10.1161/01.CIR.00000095676.90936.80
 69. Kannel WB, McGee DL. Diabetes and cardiovascular disease: the Framingham study. *JAMA.* 1979;241:2035–2038. doi: 10.1001/jama.241.19.2035
 70. Sinha A, Ning H, Ahmad FS, Bancks MP, Carnethon MR, O'Brien MJ, Allen NB, Wilkins JT, Lloyd-Jones DM, Khan SS. Association of fasting glucose with lifetime risk of incident heart failure: the Lifetime Risk Pooling Project. *Cardiovasc Diabetol.* 2021;20:66. doi: 10.1186/s12933-021-01265-y
 71. Sinha A, Ning H, Cameron N, Bancks M, Carnethon MR, Allen NB, Wilkins JT, Lloyd-Jones DM, Khan SS. Atherosclerotic cardiovascular disease or heart failure: first cardiovascular event in adults with prediabetes and diabetes. *J Card Fail.* 2023;29:246–254. doi: 10.1016/j.cardfail.2022.10.426
 72. Sinha A, Ning H, Carnethon MR, Allen NB, Wilkins JT, Lloyd-Jones DM, Khan SS. Race- and sex-specific population attributable fractions of incident heart failure: a population-based cohort study from the Lifetime Risk Pooling Project. *Circ Heart Fail.* 2021;14:e008113. doi: 10.1161/CIRCHEARTFAILURE.120.008113
 73. Imai Y, Sakurai M, Nakagawa H, Hirata A, Murakami Y, Kiyohara Y, Ninomiya T, Ishikawa S, Saitoh S, Irie F, et al. Impact of proteinuria and low

- eGFR on lifetime risk of cardiovascular disease death: a pooled analysis of data from the Evidence for Cardiovascular Prevention From Observational Cohorts in the Japan Study. *Eur J Prev Cardiol*. 2021;28:zwab061. doi: 10.1093/eurjpc/zwab061.179
74. Østergaard HB, Read SH, Sattar N, Franzén S, Halbesma N, Dorresteijn JA, Westerink J, Visseren FL, Wild SH, Eliasson B, et al. Development and validation of a lifetime risk model for kidney failure and treatment benefit in type 2 diabetes: 10-year and lifetime risk prediction models. *Clin J Am Soc Nephrol*. 2022;17:1783–1791. doi: 10.2215/cjn.05020422
 75. Turin TC, Tonelli M, Manns BJ, Ahmed SB, Ravani P, James M, Hemmelgarn BR. Lifetime risk of ESRD. *J Am Soc Nephrol*. 2012;23:1569–1578. doi: 10.1681/ASN.2012020164
 76. Ahmad FS, Ning H, Rich JD, Yancy CW, Lloyd-Jones DM, Wilkins JT. Hypertension, obesity, diabetes, and heart failure-free survival: the Cardiovascular Disease Lifetime Risk Pooling Project. *JACC Heart Fail*. 2016;4:911–919. doi: 10.1016/j.jchf.2016.08.001
 77. Fox CS, Pencina MJ, Wilson PW, Paynter NP, Vasan RS, D'Agostino RB Sr. Lifetime risk of cardiovascular disease among individuals with and without diabetes stratified by obesity status in the Framingham Heart Study. *Diabetes Care*. 2008;31:1582–1584. doi: 10.2337/dc08-0025
 78. Khan SS, Krefman AE, Zhao L, Liu L, Chorniy A, Daviglius ML, Schiman C, Liu K, Shih T, Garside D, et al. Association of body mass index in midlife with morbidity burden in older adulthood and longevity. *JAMA Netw Open*. 2022;5:e222318. doi: 10.1001/jamanetworkopen.2022.2318
 79. Khan SS, Ning H, Wilkins JT, Allen N, Carnethon M, Berry JD, Sweis RN, Lloyd-Jones DM. Association of body mass index with lifetime risk of cardiovascular disease and compression of morbidity. *JAMA Cardiol*. 2018;3:280–287. doi: 10.1001/jamacardio.2018.0022
 80. Allen NB, Zhao L, Liu L, Daviglius M, Liu K, Fries J, Shih Y-CT, Garside D, Vu T-H, Stamler J, et al. Favorable cardiovascular health, compression of morbidity, and healthcare costs: forty-year follow-up of the CHA study (Chicago Heart Association Detection Project in Industry). *Circulation*. 2017;135:1693–1701. doi: 10.1161/circulationaha.116.026252
 81. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJL, Mann JF, Matsushita K, Wen CP. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet*. 2013;382:339–352. doi: 10.1016/S0140-6736(13)60595-4
 82. Shamseddin MK, Parfrey PS. Sudden cardiac death in chronic kidney disease: epidemiology and prevention. *Nat Rev Nephrol*. 2011;7:145–154. doi: 10.1038/nrneph.2010.191
 83. Matsushita K, Jassal SK, Sang Y, Ballew SH, Grams ME, Surapaneni A, Arnlov J, Bansal N, Bozic M, Brenner H, et al. Incorporating kidney disease measures into cardiovascular risk prediction: development and validation in 9 million adults from 72 datasets. *EClinicalMedicine*. 2020;27:100552. doi: 10.1016/j.eclinm.2020.100552
 84. Thomas B, Matsushita K, Abate KH, Al-Aly Z, Ärnlöv J, Asayama K, Atkins R, Badawi A, Ballew SH, Banerjee A, et al. Global Burden of Disease 2013 GFR Collaborators: CKD Prognosis Consortium; Global Burden of Disease Genitourinary Expert Group. Global cardiovascular and renal outcomes of reduced GFR. *J Am Soc Nephrol*. 2017;28:2167–2179. doi: 10.1681/ASN.2016050562
 85. Heerspink HJ, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou F-F, Mann JF, McMurray JJ, Lindberg M, Rossing P. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383:1436–1446. doi: 10.1056/NEJMoa2024816
 86. Fangel MV, Nielsen PB, Kristensen JK, Larsen TB, Overvad TF, Lip GY, Jensen MB. Albuminuria and risk of cardiovascular events and mortality in a general population of patients with type 2 diabetes without cardiovascular disease: a Danish cohort study. *Am J Med*. 2020;133:e269–e279. doi: 10.1016/j.amjmed.2019.10.042
 87. Lees JS, Welsh CE, Celis-Morales CA, Mackay D, Lewsey J, Gray SR, Lyall DM, Cleland JG, Gill JM, Jhund PS. Glomerular filtration rate by differing measures, albuminuria and prediction of cardiovascular disease, mortality and end-stage kidney disease. *Nat Med*. 2019;25:1753–1760. doi: 10.1038/s41591-019-0627-8
 88. Khan MS, Shahid I, Anker SD, Fonarow GC, Fudim M, Hall ME, Hernandez A, Morris AA, Shafi T, Weir MR, et al. Albuminuria and heart failure: JACC state-of-the-art review. *J Am Coll Cardiol*. 2023;81:270–282. doi: 10.1016/j.jacc.2022.10.028
 89. Levey AS, Grams ME, Inker LA. Uses of GFR and albuminuria level in acute and chronic kidney disease. *N Engl J Med*. 2022;386:2120–2128. doi: 10.1056/NEJMra2201153
 90. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, Hallé JP, Young J, Rashkoff A, Joyce C, et al. HOPE Study Investigators. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA*. 2001;286:421–426. doi: 10.1001/jama.286.4.421
 91. Patel RB, Colangelo LA, Reis JP, Lima JA, Shah SJ, Lloyd-Jones DM. Association of longitudinal trajectory of albuminuria in young adulthood with myocardial structure and function in later life: Coronary Artery Risk Development in Young Adults (CARDIA) study. *JAMA Cardiol*. 2020;5:184–192. doi: 10.1001/jamacardio.2019.4867
 92. Goh LG, Dhaliwal SS, Welborn TA, Lee AH, Della PR. Anthropometric measurements of general and central obesity and the prediction of cardiovascular disease risk in women: a cross-sectional study. *BMJ Open*. 2014;4:e004138. doi: 10.1136/bmjopen-2013-004138
 93. Ndumele CE, Matsushita K, Lazo M, Bello N, Blumenthal RS, Gerstenblith G, Nambi V, Ballantyne CM, Solomon SD, Selvin E, et al. Obesity and subtypes of incident cardiovascular disease. *J Am Heart Assoc*. 2016;5:e003921. doi: 10.1161/JAHA.116.003921
 94. Gregg EW, Sattar N, Ali MK. The changing face of diabetes complications. *Lancet Diabetes Endocrinol*. 2016;4:537–547. doi: 10.1016/S2213-8587(16)30010-9
 95. Tancredi M, Rosengren A, Svensson A-M, Kosiborod M, Pivodic A, Gudbjörnsdóttir S, Wedel H, Clements M, Dahlqvist S, Lind M. Excess mortality among persons with type 2 diabetes. *N Engl J Med*. 2015;373:1720–1732. doi: 10.1056/NEJMoa1504347
 96. Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, Coresh J, Brancati FL. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. *N Engl J Med*. 2010;362:800–811. doi: 10.1056/NEJMoa0908359
 97. Cederholm J, Eeg-Olofsson K, Eliasson B, Zethelius B, Nilsson PM, Gudbjörnsdóttir S, Swedish National Diabetes Register. Risk prediction of cardiovascular disease in type 2 diabetes: a risk equation from the Swedish National Diabetes Register. *Diabetes Care*. 2008;31:2038–2043. doi: 10.2337/dc08-0662
 98. Wilkins JT, Li RC, Sniderman A, Chan C, Lloyd-Jones DM. Discordance between apolipoprotein B and LDL-cholesterol in young adults predicts coronary artery calcification: the CARDIA study. *J Am Coll Cardiol*. 2016;67:193–201. doi: 10.1016/j.jacc.2015.10.055
 99. Mehta A, Virani SS, Ayers CR, Sun W, Hoogeveen RC, Rohatgi A, Berry JD, Joshi PH, Ballantyne CM, Khara A. Lipoprotein (a) and family history predict cardiovascular disease risk. *J Am Coll Cardiol*. 2020;76:781–793. doi: 10.1016/j.jacc.2020.06.040
 100. Reyes-Soffer G, Ginsberg HN, Berglund L, Duell PB, Heffron SP, Kamstrup PR, Lloyd-Jones DM, Marcovina SM, Yeang C, Koschinsky ML; on behalf of the American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Radiology and Intervention; and Council on Peripheral Vascular Disease. Lipoprotein (a): a genetically determined, causal, and prevalent risk factor for atherosclerotic cardiovascular disease: a scientific statement from the American Heart Association. *Arterioscler Thromb Vasc Biol*. 2022;42:e48–e60. doi: 10.1161/ATV.000000000000147
 101. Patel AP, Wang M, Pirruccello JP, Ellinor PT, Ng K, Kathiresan S, Khara AV. Lipoprotein (a) concentrations and incident atherosclerotic cardiovascular disease: new insights from a large national biobank. *Arterioscler Thromb Vasc Biol*. 2021;41:465–474. doi: 10.1161/ATVBAHA.120.315291
 102. Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, Carr JJ, Goff DC, Greenland P, Herrington DM. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. *JAMA*. 2012;308:788–795. doi: 10.1001/jama.2012.9624
 103. Wang TJ, Gona P, Larson MG, Tofler GH, Levy D, Newton-Cheh C, Jacques PF, Rifai N, Selhub J, Robins SJ, et al. Multiple biomarkers for the prediction of first major cardiovascular events and death. *N Engl J Med*. 2006;355:2631–2639. doi: 10.1056/NEJMoa055373
 104. Zethelius B, Berglund L, Sundström J, Ingelsson E, Basu S, Larsson A, Venge P, Ärnlöv J. Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. *N Engl J Med*. 2008;358:2107–2116. doi: 10.1056/NEJMoa0707064
 105. Pencina MJ, D'Agostino RB, Pencina KM, Janssens ACJ, Greenland P. Interpreting incremental value of markers added to risk prediction models. *Am J Epidemiol*. 2012;176:473–481. doi: 10.1093/aje/kws207
 106. Yeboah J, Young R, McClelland RL, Delaney JC, Polonsky TS, Dawood FZ, Blaha MJ, Miedema MD, Sibley CT, Carr JJ, et al. Utility of nontraditional risk markers in atherosclerotic cardiovascular disease risk assessment. *J Am Coll Cardiol*. 2016;67:139–147. doi: 10.1016/j.jacc.2015.10.058
 107. Velagaleti RS, Gona P, Larson MG, Wang TJ, Levy D, Benjamin EJ, Selhub J, Jacques PF, Meigs JB, Tofler GH, et al. Multimarker approach for the prediction of heart failure incidence in the community. *Circulation*. 2010;122:1700–1706. doi: 10.1161/CIRCULATIONAHA.109.929661

108. Wells QS, Gupta DK, Smith JG, Collins SP, Storrow AB, Ferguson J, Smith ML, Pulley JM, Collier S, Wang X, et al. Accelerating biomarker discovery through electronic health records, automated biobanking, and proteomics. *J Am Coll Cardiol*. 2019;73:2195–2205. doi: 10.1016/j.jacc.2019.01.074
109. Segar MW, Khan MS, Patel KV, Vaduganathan M, Kannan V, Willett D, Peterson E, Tang WW, Butler J, Everett BM. Incorporation of natriuretic peptides with clinical risk scores to predict heart failure among individuals with dysglycaemia. *Eur J Heart Fail*. 2022;24:169–180. doi: 10.1002/ehf.2375
110. Pop-Busui R, Januzzi JL, Bruemmer D, Butalia S, Green JB, Horton WB, Knight C, Levi M, Rasouli N, Richardson CR. Heart failure: an underappreciated complication of diabetes. A consensus report of the American Diabetes Association. *Diabetes Care*. 2022;45:1670–1690. doi: 10.2337/dci22-0014
111. Lee DS, Pencina MJ, Benjamin EJ, Wang TJ, Levy D, O'Donnell CJ, Nam B-H, Larson MG, D'Agostino RB, Vasan RS. Association of parental heart failure with risk of heart failure in offspring. *N Engl J Med*. 2006;355:138–147. doi: 10.1056/NEJMoa052948
112. Helgason H, Eiriksdottir T, Ulfarsson MO, Choudhary A, Lund SH, Ivarsdottir EV, Eldjarn GH, Einarsson G, Ferkingstad E, Moore KH. Evaluation of large-scale proteomics for prediction of cardiovascular events. *JAMA*. 2023;330:725–735. doi: 10.1001/jama.2023.13258
113. Shemesh E, Chevli PA, Islam T, German CA, Otvos J, Yeboah J, Rodriguez F, deFilippi C, Lima JA, Blaha M. Circulating ketone bodies and cardiovascular outcomes: the MESA study. *Eur Heart J*. 2023;44:1636–1646. doi: 10.1093/eurheartj/ehad087
114. Mosley JD, Gupta DK, Tan J, Yao J, Wells QS, Shaffer CM, Kundu S, Robinson-Cohen C, Psaty BM, Rich SS, et al. Predictive accuracy of a polygenic risk score compared with a clinical risk score for incident coronary heart disease. *JAMA*. 2020;323:627–635. doi: 10.1001/jama.2019.21782
115. Groenendyk JW, Greenland P, Khan SS. Incremental value of polygenic risk scores in primary prevention of coronary heart disease: a review. *JAMA Intern Med*. 2022;182:1082–1088. doi: 10.1001/jamainternmed.2022.3171
116. Khan SS, Page C, Wojdyla DM, Schwartz YY, Greenland P, Pencina MJ. Predictive utility of a validated polygenic risk score for long-term risk of coronary heart disease in young and middle-aged adults. *Circulation*. 2022;146:587–596. doi: 10.1161/CIRCULATIONAHA.121.058426
117. Khan SS, Post WS, Guo X, Tan J, Zhu F, Bos D, Sedaghati-Khayat B, Van Rooij J, Aday A, Allen NB, et al. Coronary artery calcium score and polygenic risk score for the prediction of coronary heart disease events. *JAMA*. 2023;329:1768–1777. doi: 10.1001/jama.2023.7575
118. Tsao CW, Aday AW, Almarazooq ZI, Anderson CA, Arora P, Avery CL, Baker-Smith CM, Beaton AZ, Boehme AK, Buxton AE, et al; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2023 update: a report from the American Heart Association. *Circulation*. 2023;147:e93–e621. doi: 10.1161/CIR.0000000000001123
119. Aggarwal R, Yeh RW, Maddox KEJ, Wadhera RK. Cardiovascular risk factor prevalence, treatment, and control in US adults aged 20 to 44 years, 2009 to March 2020. *JAMA*. 2023;329:899–909. doi: 10.1001/jama.2023.2307
120. Shah NS, Palaniappan LP, Khan SS. Proportional mortality from ischemic heart disease among Asian American subgroups, from 2018 to 2020. *JAMA Intern Med*. 2022;182:1101–1103. doi: 10.1001/jamainternmed.2022.3616
121. Kobo O, Abramov D, Fudim M, Sharma G, Bang V, Deshpande A, Wadhera RK, Mamas MA. Has the first year of the COVID-19 pandemic reversed the trends in CV mortality between 1999 and 2019 in the United States? *Eur Heart J Qual Care Clin Outcomes*. 2023;9:367–376. doi: 10.1093/ehjqcc/qcac080
122. Goff DC Jr, Khan SS, Lloyd-Jones D, Arnett DK, Carnethon MR, Labarthe DR, Loop MS, Luepker RV, McConnell MV, Mensah GA, et al. Bending the curve in cardiovascular disease mortality: Bethesda+ 40 and beyond. *Circulation*. 2021;143:837–851. doi: 10.1161/CIRCULATIONAHA.120.046501
123. Shah NS, Molsberry R, Rana JS, Sidney S, Capewell S, O'Flaherty M, Carnethon M, Lloyd-Jones DM, Khan SS. Heterogeneous trends in burden of heart disease mortality by subtypes in the United States, 1999–2018: observational analysis of vital statistics. *BMJ*. 2020;370:m2688. doi: 10.1136/bmj.m2688
124. Sidney S, Go AS, Jaffe MG, Solomon MD, Ambrosy AP, Rana JS. Association between aging of the US population and heart disease mortality from 2011 to 2017. *JAMA Cardiol*. 2019;4:1280–1286. doi: 10.1001/jamacardio.2019.4187
125. Agarwal MA, Fonarow GC, Ziaeian B. National trends in heart failure hospitalizations and readmissions from 2010 to 2017. *JAMA Cardiol*. 2021;6:952–956. doi: 10.1001/jamacardio.2020.7472
126. Huffman MD, Berry JD, Ning H, Dyer AR, Garside DB, Cai X, Daviglus ML, Lloyd-Jones DM. Lifetime risk for heart failure among White and Black Americans: cardiovascular lifetime risk pooling project. *J Am Coll Cardiol*. 2013;61:1510–1517. doi: 10.1016/j.jacc.2013.01.022
127. Sattar N, McMurray J, Boren J, Rawshani A, Omerovic E, Berg N, Halminen J, Skoglund K, Eliasson B, Gerstein HC, et al. Twenty years of cardiovascular complications and risk factors in patients with type 2 diabetes: a nationwide Swedish cohort study. *Circulation*. 2023;147:1872–1886. doi: 10.1161/CIRCULATIONAHA.122.063374
128. Khan SS, Ning H, Shah SJ, Yancy CW, Carnethon M, Berry JD, Mentz RJ, O'Brien E, Correa A, Suthahar N, et al. 10-year risk equations for incident heart failure in the general population. *J Am Coll Cardiol*. 2019;73:2388–2397. doi: 10.1016/j.jacc.2019.02.057
129. Kannel WB, D'Agostino RB, Silbershatz H, Belanger AJ, Wilson PW, Levy D. Profile for estimating risk of heart failure. *Arch Intern Med*. 1999;159:1197–1204. doi: 10.1001/archinte.159.11.1197
130. Agarwal SK, Chambless LE, Ballantyne CM, Astor B, Bertoni AG, Chang PP, Folsom AR, He M, Hoogeveen RC, Ni H, et al. Prediction of incident heart failure in general practice: the Atherosclerosis Risk in Communities (ARIC) Study. *Circ Heart Fail*. 2012;5:422–429. doi: 10.1161/CIRCHEARTFAILURE.111.964841
131. Butler J, Kalogeropoulos A, Georgiopoulou V, Belue R, Rodondi N, Garcia M, Bauer DC, Satterfield S, Smith AL, Vaccarino V, et al; Health ABC Study. Incident heart failure prediction in the elderly: the health ABC heart failure score. *Circ Heart Fail*. 2008;1:125–133. doi: 10.1161/CIRCHEARTFAILURE.108.768457
132. Tromp J, Paniagua SM, Lau ES, Allen NB, Blaha MJ, Gansevoort RT, Hillege HL, Lee DE, Levy D, Vasan RS. Age dependent associations of risk factors with heart failure: pooled population based cohort study. *BMJ*. 2021;372:n461. doi: 10.1136/bmj.n461
133. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117:743–753. doi: 10.1161/CIRCULATIONAHA.107.699579
134. McClelland RL, Jorgensen NW, Budoff M, Blaha MJ, Post WS, Kronmal RA, Bild DE, Shea S, Liu K, Watson KE. 10-year coronary heart disease risk prediction using coronary artery calcium and traditional risk factors: derivation in the MESA (Multi-Ethnic Study of Atherosclerosis) with validation in the HNR (Heinz Nixdorf Recall) study and the DHS (Dallas Heart Study). *J Am Coll Cardiol*. 2015;66:1643–1653. doi: 10.1016/j.jacc.2015.08.035
135. Khera A, Budoff MJ, O'Donnell CJ, Ayers CA, Locke J, de Lemos JA, Massaro JM, McClelland RL, Taylor A, Levine BD. Astronaut cardiovascular health and risk modification (Astro-CHARM) coronary calcium atherosclerotic cardiovascular disease risk calculator. *Circulation*. 2018;138:1819–1827. doi: 10.1161/CIRCULATIONAHA.118.033505
136. Stenvinkel P. Chronic kidney disease: a public health priority and harbinger of premature cardiovascular disease. *J Intern Med*. 2010;268:456–467. doi: 10.1111/j.1365-2796.2010.02269.x
137. Shah NS, Ning H, Petito LC, Kershaw KN, Bancks MP, Reis JP, Rana JS, Sidney S, Jacobs DR Jr, Kiefe CI, et al. Associations of clinical and social risk factors with racial differences in premature cardiovascular disease. *Circulation*. 2022;146:201–210. doi: 10.1161/CIRCULATIONAHA.121.058311
138. Hughes ZH, Ning H, Shah SJ, Yancy CW, Wilkins JT, Lloyd-Jones DM, Khan SS, Shah NS. Distribution of 10- and 30-year predicted risks for heart failure in the US population: National Health and Nutrition Examination Surveys 2015 to 2018. *Circ Heart Fail*. 2022;15:e009351. doi: 10.1161/CIRCHEARTFAILURE.121.009351
139. Marma AK, Berry JD, Ning H, Persell SD, Lloyd-Jones DM. Distribution of 10-year and lifetime predicted risks for cardiovascular disease in US adults: findings from the National Health and Nutrition Examination Survey 2003 to 2006. *Circ Cardiovasc Qual Outcomes*. 2010;3:8–14. doi: 10.1161/CIRCOUTCOMES.109.869727
140. Lloyd-Jones DM, Larson MG, Beiser A, Levy D. Lifetime risk of developing coronary heart disease. *Lancet*. 1999;353:89–92. doi: 10.1016/S0140-6736(98)10279-9
141. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, Murabito JM, Vasan RS, Benjamin EJ, Levy D; Framingham Heart Study. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation*. 2002;106:3068–3072. doi: 10.1161/01.cir.0000039105.49749.6f
142. Lloyd-Jones DM, Leip EP, Larson MG, D'Agostino RB, Beiser A, Wilson PW, Wolf PA, Levy D. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. *Circulation*. 2006;113:791–798. doi: 10.1161/CIRCULATIONAHA.105.548206

143. Wilkins JT, Ning H, Berry J, Zhao L, Dyer AR, Lloyd-Jones DM. Lifetime risk and years lived free of total cardiovascular disease. *JAMA*. 2012;308:1795–1801. doi: 10.1001/jama.2012.14312
144. Stone NJ, Smith SC Jr, Orringer CE, Rigotti NA, Navar AM, Khan SS, Jones DW, Goldberg R, Mora S, Blaha M, et al. Managing atherosclerotic cardiovascular risk in young adults: JACC state-of-the-art review. *J Am Coll Cardiol*. 2022;79:819–836. doi: 10.1016/j.jacc.2021.12.016
145. Gooding HC, Gidding SS, Moran AE, Redmond N, Allen NB, Bacha F, Burns TL, Catov JM, Grandner MA, Harris KM, et al. Challenges and opportunities for the prevention and treatment of cardiovascular disease among young adults: report from a National Heart, Lung, and Blood Institute Working Group. *J Am Heart Assoc*. 2020;9:e016115. doi: 10.1161/JAHA.120.016115
146. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, Crews DC, Doria A, Estrella MM, Froissart M. New creatinine-and cystatin C–based equations to estimate GFR without race. *N Engl J Med*. 2021;385:1737–1749. doi: 10.1056/NEJMoa2102953
147. Quaggin SE, Palevsky PM. Removing race from kidney disease diagnosis. *J Am Soc Nephrol*. 2021;32:2987–2989. doi: 10.1681/ASN.2021091284
148. Vyas DA, Eisenstein LG, Jones DS. Hidden in plain sight—reconsidering the use of race correction in clinical algorithms. *N Engl J Med*. 2020;383:874–882. doi: 10.1056/NEJMms2004740
149. Ukoha EP, Snaveley ME, Hahn MU, Steinauer JE, Bryant AS. Toward the elimination of race-based medicine: replace race with racism as pre-eclampsia risk factor. *Am J Obstet Gynecol*. 2022;227:593–596. doi: 10.1016/j.ajog.2022.05.048
150. Vyas DA, James A, Kormos W, Essien UR. Revising the atherosclerotic cardiovascular disease calculator without race. *Lancet Digit Health*. 2022;4:e4–e5. doi: 10.1016/S2589-7500(21)00258-2
151. Vasan RS, Rao S, van den Heuvel E. Race as a component of cardiovascular disease risk prediction algorithms. *Curr Cardiol Rep*. Published online August 14, 2023. doi: 10.1007/s11886-023-01938-y
152. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, May M, Brindle P. Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. *BMJ*. 2007;335:136. doi: 10.1136/bmj.39261.471806.55
153. Breathett K, Spatz ES, Kramer DB, Essien UR, Wadhwa RK, Peterson PN, Ho PM, Nallamothu BK. The groundwater of racial and ethnic disparities research: a statement from *Circulation: Cardiovascular Quality and Outcomes*. *Circ Cardiovasc Qual Outcomes*. 2021;14:e007868. doi: 10.1161/CIRCOUTCOMES.121.007868
154. Frank DA, Johnson AE, Hausmann LR, Gellad WF, Roberts ET, Vajravelu RK. Disparities in guideline-recommended statin use for prevention of atherosclerotic cardiovascular disease by race, ethnicity, and gender: a nationally representative cross-sectional analysis of adults in the United States. *Ann Intern Med*. 2023;176:1057–1066. doi: 10.7326/m23-0720
155. Gregg LP, Ramsey DJ, Akeroyd JM, Jafry SA, Matheny ME, Virani SS, Navaneethan SD. Predictors, disparities, and facility-level variation: SGLT2 inhibitor prescription among US veterans with CKD. *Am J Kidney Dis*. 2023;82:53–62.e1. doi: 10.1053/j.ajkd.2022.11.017
156. Mittman BG, Le P, Payne JY, Ayers G, Rothberg M. Sociodemographic disparities in the use of GLP-1 receptor agonists and SGLT-2 inhibitors among US adults with type 2 diabetes: NHANES 2005– March 2020. *medRxiv*. Published online March 31, 2023. doi: 10.1101/2023.03.30.23287965
157. Cologne J, Hsu W-L, Abbott RD, Ohishi W, Grant EJ, Fujiwara S, Cullings HM. Proportional hazards regression in epidemiologic follow-up studies: an intuitive consideration of primary time scale. *Epidemiology*. 2012;23:565–573. doi: 10.1097/ede.0b013e318253e418
158. Kom EL, Graubard BI, Midthune D. Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. *Am J Epidemiol*. 1997;145:72–80. doi: 10.1093/oxfordjournals.aje.a009034
159. Pencina MJ, Larson MG, D'Agostino RB. Choice of time scale and its effect on significance of predictors in longitudinal studies. *Stat Med*. 2007;26:1343–1359. doi: 10.1002/sim.2699
160. Thiébaud AC, Bénichou J. Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. *Stat Med*. 2004;23:3803–3820. doi: 10.1002/sim.2098
161. Visseren FL, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, Benetos A, Biffi A, Boavida J-M, Capodanno D. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice: developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies with the special contribution of the European Association of Preventive Cardiology (EAPC). *Eur J Prev Cardiol*. 2022;29:5–115. doi: 10.1093/eurjpc/zwab154
162. Stone NJ, Blumenthal RS, Lloyd-Jones D, Grundy SM. Comparing primary prevention recommendations: a focused look at United States and European guidelines on dyslipidemia. *Circulation*. 2020;141:1117–1120. doi: 10.1161/CIRCULATIONAHA.119.044562
163. Wong ND, Glovaci D, Wong K, Malik S, Franklin SS, Wygant G, Iloje U. Global cardiovascular disease risk assessment in United States adults with diabetes. *Diab Vasc Dis Res*. 2012;9:146–152. doi: 10.1177/1479164112436403
164. Zhao Y, Malik S, Budoff MJ, Correa A, Ashley KE, Selvin E, Watson KE, Wong ND. Identification and predictors for cardiovascular disease risk equivalents among adults with diabetes. *Diabetes Care*. 2021;44:2411–2418. doi: 10.2337/dc21-0431
165. Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, Jeppesen OK, Lingvay I, Mosenson O, Pedersen SD, et al; PIONEER 6 Investigators. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2019;381:841–851. doi: 10.1056/NEJMoa1901118
166. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, et al; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375:1834–1844. doi: 10.1056/NEJMoa1607141
167. Sinha B, Ghosal S. Meta-analyses of the effects of DPP-4 inhibitors, SGLT2 inhibitors and GLP1 receptor analogues on cardiovascular death, myocardial infarction, stroke and hospitalization for heart failure. *Diabetes Res Clin Pract*. 2019;150:8–16. doi: 10.1016/j.diabres.2019.02.014
168. Wright AK, Carr MJ, Kontopantelis E, Leelarathna L, Thabit H, Emsley R, Buchan I, Mamas MA, van Staa TP, Sattar N, et al. Primary prevention of cardiovascular and heart failure events with SGLT2 inhibitors, GLP-1 receptor agonists, and their combination in type 2 diabetes. *Diabetes Care*. 2022;45:909–918. doi: 10.2337/dc21-1113
169. Stratton I, Cull C, Adler A, Matthews D, Neil H, Holman R. Additive effects of glycaemia and blood pressure exposure on risk of complications in type 2 diabetes: a prospective observational study (UKPDS 75). *Diabetologia*. 2006;49:1761–1769. doi: 10.1007/s00125-006-0297-1
170. Persell SD, Lloyd-Jones DM, Baker DW. National Cholesterol Education Program risk assessment and potential for risk misclassification. *Prev Med*. 2006;43:368–371. doi: 10.1016/j.ypmed.2006.06.017
171. Havranek EP, Mujahid MS, Barr DA, Blair IV, Cohen MS, Cruz-Flores S, Davey-Smith G, Dennison-Himmelfarb CR, Lauer MS, Lockwood DW, et al; on behalf of the American Heart Association Council on Quality of Care and Outcomes Research, Council on Epidemiology and Prevention, Council on Cardiovascular and Stroke Nursing, Council on Lifestyle and Cardiometabolic Health, and Stroke Council. Social determinants of risk and outcomes for cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2015;132:873–898. doi: 10.1161/CIR.0000000000000228
172. Sims M, Kershaw KN, Breathett K, Jackson EA, Lewis LM, Mujahid MS, Suglia SF; on behalf of the American Heart Association Council on Epidemiology and Prevention and Council on Quality of Care and Outcomes Research. Importance of housing and cardiovascular health and well-being: a scientific statement from the American Heart Association. *Circ Cardiovasc Qual Outcomes*. 2020;13:e000089. doi: 10.1161/HCQ.0000000000000089
173. Lloyd-Jones DM. Cardiovascular risk prediction: basic concepts, current status, and future directions. *Circulation*. 2010;121:1768–1777. doi: 10.1161/CIRCULATIONAHA.109.849166
174. Thanassoulis G, Pencina MJ, Sniderman AD. The benefit model for prevention of cardiovascular disease: an opportunity to harmonize guidelines. *JAMA Cardiol*. 2017;2:1175–1176. doi: 10.1001/jamacardio.2017.2543
175. Thanassoulis G, Sniderman AD, Pencina MJ. A long-term benefit approach vs standard risk-based approaches for statin eligibility in primary prevention. *JAMA Cardiol*. 2018;3:1090–1095. doi: 10.1001/jamacardio.2018.3476
176. Pencina MJ, Pencina KM, Lloyd-Jones D, Catapano AL, Thanassoulis G, Sniderman AD. The expected 30-year benefits of early versus delayed primary prevention of cardiovascular disease by lipid lowering. *Circulation*. 2020;142:827–837. doi: 10.1161/CIRCULATIONAHA.120.045851
177. Patel AP, Wang M, Kartoun U, Ng K, Khera AV. Quantifying and understanding the higher risk of atherosclerotic cardiovascular disease among South Asian individuals: results from the UK Biobank prospective cohort study. *Circulation*. 2021;144:410–422. doi: 10.1161/CIRCULATIONAHA.120.052430
178. Gujral UP, Vittinghoff E, Mongraw-Chaffin M, Vaidya D, Kandula NR, Allison M, Carr J, Liu K, Narayan KV, Kanaya AM. Cardiometabolic abnormalities among normal-weight persons from five racial/ethnic groups in the United States: a cross-sectional analysis of two cohort studies. *Ann Intern Med*. 2017;166:628–636. doi: 10.7326/m16-1895

179. Kanaya AM, Kandula NR, Ewing SK, Herrington D, Liu K, Blaha MJ, Srivastava S, Dave SS, Budoff MJ. Comparing coronary artery calcium among U.S. South Asians with four racial/ethnic groups: the MASALA and MESA studies. *Atherosclerosis*. 2014;234:102–107. doi: 10.1016/j.atherosclerosis.2014.02.017
180. Kwan TW, Wong SS, Hong Y, Kanaya AM, Khan SS, Hayman LL, Shah SH, Welty FK, Deedwania PC, Khaliq A, et al; on behalf of the American Heart Association Council on Epidemiology and Prevention; Council on Lifestyle and Cardiometabolic Health; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; and Council on Genomic and Precision Medicine. Epidemiology of diabetes and atherosclerotic cardiovascular disease among Asian American adults: implications, management, and future directions: a scientific statement from the American Heart Association. *Circulation*. 2023;148:74–94. doi: 10.1161/CIR.0000000000001145
181. Powell-Wiley TM, Baumer Y, Baah FO, Baez AS, Farmer N, Mahlobo CT, Pita MA, Potharaju KA, Tamura K, Wallen GR. Social determinants of cardiovascular disease. *Circ Res*. 2022;130:782–799. doi: 10.1161/CIRCRESAHA.121.319811
182. Bancks MP, Kershaw K, Carson AP, Gordon-Larsen P, Schreiner PJ, Carnethon MR. Association of modifiable risk factors in young adulthood with racial disparity in incident type 2 diabetes during middle adulthood. *JAMA*. 2017;318:2457–2465. doi: 10.1001/jama.2017.19546
183. Perak AM, Ning H, Khan SS, Bundy JD, Allen NB, Lewis CE, Jacobs DR Jr, Van Horn LV, Lloyd-Jones DM. Associations of late adolescent or young adult cardiovascular health with premature cardiovascular disease and mortality. *J Am Coll Cardiol*. 2020;76:2695–2707. doi: 10.1016/j.jacc.2020.10.002
184. Perak AM, Baker-Smith C, Hayman LL, Khoury M, Peterson AL, Ware AL, Zachariah JP, Raghuvver G; on behalf of the American Heart Association Council on Hypertension; Council on Cardiovascular and Stroke Nursing; Council on Lifelong Congenital Heart Disease and Heart Health in the Young. Toward a roadmap for best practices in pediatric preventive cardiology: a science advisory from the American Heart Association. *Circ Cardiovasc Qual Outcomes*. 2023;16:e000120. doi: 10.1161/HCQ.0000000000000120
185. Khan SS, Brewer LC, Canobbio MM, Cipolla MJ, Grobman WA, Lewey J, Michos ED, Miller EC, Perak AM, Wei GS, et al; on behalf of the American Heart Association Council on Epidemiology and Prevention; Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Hypertension; Council on Lifestyle and Cardiometabolic Health; Council on Peripheral Vascular Disease; and Stroke Council. Optimizing prepregnancy cardiovascular health to improve outcomes in pregnant and postpartum individuals and offspring: a scientific statement from the American Heart Association. *Circulation*. 2023;147:e76–e91. doi: 10.1161/CIR.0000000000001124
186. Perak AM, Lancki N, Kuang A, Labarthe DR, Allen NB, Shah SH, Lowe LP, Grobman WA, Lawrence JM, Lloyd-Jones DM, et al; HAPO Follow-Up Study Cooperative Research Group. Associations of maternal cardiovascular health in pregnancy with offspring cardiovascular health in early adolescence. *JAMA*. 2021;325:658–668. doi: 10.1001/jama.2021.0247
187. Lloyd-Jones DM, Huffman MD, Karmali KN, Sanghavi DM, Wright JS, Pelser C, Gulati M, Masoudi FA, Goff DC Jr. Estimating longitudinal risks and benefits from cardiovascular preventive therapies among Medicare patients: the Million Hearts Longitudinal ASCVD Risk Assessment Tool: a special report from the American Heart Association and American College of Cardiology. *Circulation*. 2017;135:e793–e813. doi: 10.1161/CIR.0000000000000467
188. Mark PB, Carrero JJ, Matsushita K, Sang Y, Ballew SH, Grams ME, Coresh J, Surapaneni A, Brunskill NJ, Chalmers J, et al. Major cardiovascular events and subsequent risk of kidney failure with replacement therapy: a CKD Prognosis Consortium study. *Eur Heart J*. 2023;44:1157–1166. doi: 10.1093/eurheartj/ehac825
189. Grams ME, Brunskill NJ, Ballew SH, Sang Y, Coresh J, Matsushita K, Surapaneni A, Bell S, Carrero JJ, Chodick G, et al; CKD Prognosis Consortium. Development and validation of prediction models of adverse kidney outcomes in the population with and without diabetes. *Diabetes Care*. 2022;45:2055–2063. doi: 10.2337/dc22-0698
190. Nelson RG, Grams ME, Ballew SH, Sang Y, Azizi F, Chadban SJ, Chaker L, Dunning SC, Fox C, Hirakawa Y, et al; CKD Prognosis Consortium. Development of risk prediction equations for incident chronic kidney disease. *JAMA*. 2019;322:2104–2114. doi: 10.1001/jama.2019.17379
191. Tangri N, Grams ME, Levey AS, Coresh J, Appel LJ, Astor BC, Chodick G, Collins AJ, Djurdjev O, Elley CR, et al; CKD Prognosis Consortium. Multinational assessment of accuracy of equations for predicting risk of kidney failure: a meta-analysis. *JAMA*. 2016;315:164–174. doi: 10.1001/jama.2015.18202
192. Moura FA, Berg DD, Bellavia A, Dwyer JP, Mosenzon O, Scirica BM, Wiviott SD, Bhatt DL, Raz I, Feinberg MW, et al. Risk assessment of kidney disease progression and efficacy of SGLT2 inhibition in patients with type 2 diabetes. *Diabetes Care*. 2023;46:1807–1815. doi: 10.2337/dc23-0492
193. Mehta R, Buzkova P, Patel H, Cheng J, Kizer JR, Gottdiener JS, Psaty B, Khan SS, Ix JH, Isakova T, et al. Cardiac mechanics and kidney function decline in the cardiovascular health study. *Kidney360*. 2023;4:622–630. doi: 10.34067/KID.000000000000100