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REVIEW

Evaluating Cardiovascular Disease Risk

Rodney C Richie, MD, FACP, FCCP, DBIM

There was a steady decrease in cardiovascular disease (CVD ischemic heart disease and stroke) mortality from 1960 to 2020, but since then, this decline has reversed. There have been over 228,000 excess CVD deaths through 2022,[1] undoubtedly partially due to the COVID-19 pandemic, but the mortality rate continues to rise (arguably due to the rising epidemic of obesity and diabetes). CVD remains the leading cause of death in developed countries, accounting for over 30% of deaths, and risk estimation is a cornerstone approach to guiding CVD prevention in clinical medicine. Data from the CDC reveal that 36% of US adults have no CVD risk factors, 35% have 1, and 29% have 2 or more risk factors. The age-adjusted percentage of adults with 2 or more CVD risk factors has increased between 2013-2014 to August 2021-August 2023, especially in older age groups.[2] Assessing the risk for CVD mortality is essential for the disability and life insurance industry required to assess that risk at a single point in time (at the issuance of an insurance policy). Evaluating this risk requires careful attention to modifiable and non-modifiable factors, including hypertension and other co-morbidities, abnormal lipid profiles, and lifestyle inequalities. The goal of this treatise is to evaluate the various CVD calculators, but also to review other risk factors that may not be routinely sought in estimating CVD risk. The importance of apolipoproteinB (apoB) and lipoprotein A (LpA) as better risk predictors than just elevated LDL levels will be emphasized, and evidence of systemic inflammation and insulin resistance will be proposed as essential early indicators of future cardiovascular disease.

Author of Correspondence:
Rodney C Richie, MD, FACP, FCCP, DBIM; Editor-in-Chief, Journal of Insurance Medicine;
journal.ins.med@gmail.com

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The Framingham Risk Score,[3] commissioned by the US Congress in 1948, and its derivatives[4,5] were the earliest US guideline-recommended tools for assessing risk of coronary heart disease. Its major limitation included the lack of generalizability to modern populations because the Framingham cohort was composed of homogeneous, geographically limited, predominantly White participants with higher smoking rates and lower use of preventive therapies compared to contemporary US populations. Nevertheless, the study identified key risk factors such as cigarette smoking, high blood pressure, and high cholesterol, and it developed risk scores to predict an individual's 10-year risk of developing heart disease.

In 2013, the American Heart Association (AHA) and the American College of Cardiology (ACC) developed an atherosclerotic

Table 1. 2013 ASCVD Risk Calculator from AHA/ACC

Age	Diabetes (yes, no)
Sex (male, female)	Smoker (yes, no)
Total Cholesterol (mg/dL or mmol/L)	HDL Cholesterol (mg/dL or mmol/L)
Systolic Blood Pressure	Treatment for Hypertension (yes, no)

Table 2. Million Hearts Longitudinal ASCVD Risk Assessment Tool 2016

Sex (male or female)	Age (years)
Race (White/Hispanic or Black)	Total Cholesterol
LDL-Cholesterol	HDL-Cholesterol
Treatment with Statin	Systolic Blood Pressure
Treatment for Hypertension	History of Diabetes
Current Smoker (within last year)	Aspirin Therapy

cardiovascular disease (ASCVD) risk score, expanding prediction beyond coronary heart disease to include stroke, using pooled cohort equations (PCEs) to predict 10-year and lifetime risk of ASCVD.[6] The PCEs were derived from five racially and geographically diverse prospective cohort studies (N=24,626) and used the same traditional risk factors as the original Framingham Risk Score but additionally offered separate equations for White and Black persons. The 2013 ACC/AHA Blood Cholesterol Guideline[7] indicated a clear net absolute benefit of moderate- to high-intensity statin therapy at an estimated 10-year ASCVD risk ≥7.5%. The parameters evaluated are seen in Table 1.

The Million Hearts Longitudinal ASCVD Risk Assessment tool was published in 2016 by the AHA/ACC to estimate the long-term risk of ASCVD incorporating the effects of therapies like statins and blood pressure-lowering medications, thereby guiding personalized treatment decisions.[8] The parameters of this newer calculator are seen in Table 2.

A follow-up ASCVD risk calculator named ASCVD Risk Estimator Plus 2018 combined the functionality of the 2013 tool, the Million Hearts tool, and the updated 2018 AHA/ACC guidelines, with minor changes in the parameters measured. The parameters measured are seen in Table 3.

However, the PCEs were concerning for overestimation of cardiovascular risk by as high as 86%.[9] Potential reasons for overestimation included the changing profile of risk factors between historical and modern cohorts, more effective therapies for preventing ASCVD events in the presence of risk factors, cohort participants being healthier than the general population, and incomplete capture of cardiovascular events.

The AHA convened a science advisory group to address the now growing burden of CVD, both ASCVD and HF, related to cardiovascular-kidney-metabolic (CKM) conditions (obesity, diabetes, and chronic kidney disease that often cluster together). Poor CKM health, increasing in prevalence, is associated with earlier onset of CVD and disproportionately affects racial and ethnic minoritized individuals who experience a greater burden of adverse social factors (residing in neighborhoods with high social deprivation). As such, optimal risk prediction equations were needed that incorporate the prediction of total CVD (ASCVD and HF) and integrate predictors relevant to CKM risk that may be addressed by novel cardiovascular and kidney-protective glucose-lowering therapies such as GLP-1 RAs (glucagon-like peptide-1 receptor agonists) and SGLT-2i (sodium glucose cotransporter-2 inhibitors).

Table 3. ASCVD Risk Estimator Plus 2018

Age	Sex (male, female)
Race (White, Black, Other)	Systolic BP (mm Hg)
Diastolic BP (mm Hg)	Total Cholesterol
LDL Cholesterol	History of Diabetes (yes/no)
Smoker (current, former, never)	On Hypertension Treatment (yes/no)
On a Statin (yes/no)	On Aspirin (yes/no)

Responding to this need, the Predicting Risk of CardioVascular Disease Events (PREVENT) equations were introduced by the AHA in 2023, intended only for persons without existing CVD disease. The PREVENT calculator provides separate 10-year and 30-year estimates for PREVENT-CVD, the most comprehensive tool providing an overall picture of an individual's cardiovascular risk and heart failure, PREVENT-ASCVD, which focuses specifically on atherosclerotic cardiovascular disease, and PREVENT-HF, which focuses just on heart failure risk. The default display is PREVENT-CVD, but each outcome can be selected individually. Because ASCVD and HF are modeled independently, their combined risk may exceed the total CVD estimate. This author, reviewing all three PREVENT options, finds little difference that would justify using anything other than PREVENT-CVD for a comprehensive risk assessment in an insurance applicant population.

The PREVENT calculator recognizes other health factors influencing cardiovascular health, including new variables such as kidney function (estimated GFR), body-mass index (BMI), and glycosylated hemoglobin and urinary albumin-to-creatine ratio (UACR), whereas the 2013 calculator focused on standard measures such as cholesterol and blood pressure. The 2013 calculator included race in its risk calculations, a feature that was intentionally omitted in the PREVENT calculator, with the argument that race is a social construct rather than a biological one.[10,11]

In its place, PREVENT allows the inclusion of a person's zip code as an indicator of social deprivation, highlighting environmental and social factors impacting cardiovascular risk. PREVENT provides risk estimates for overall cardiovascular disease, not just ASCVD, and also predicts heart failure risk, which had increased in importance since 2013. PREVENT provides both 10-year risk estimates for individuals ages 30 to 79 and 30-year risk estimates for those aged 30 to 59.

A total of 25 observational cohort studies and electronic medical record datasets (N=3,281,919) were used in model development. As noted, the PREVENT equations include traditional risk factors and measures of metabolic and kidney health and social determinants of health to predict 10- and 30-year risk of ASCVD, heart failure, and total cardiovascular disease events. In a separate validation population of 3,330,085 individuals, PREVENT ASCVD risk estimates observed ASCVD event rates with calibration ratios of observed-to-predicted ratios of approximately 1, compared with prior calibration ratios of approximately 0.5 to 0.54 for the PCEs, with the latter representing overestimation of risk by roughly 50%.[12,13]

The model's estimated glomerular filtration rate (eGFR) predictor offers a set of optional add-on predictors of kidney and metabolic health (urinary albumin/creatine ratio, hemoglobin A1C), offering the opportunity to comprehensively assess risk in the context of co-occurring comorbidities in persons with obesity, diabetes, or CKD who are at higher risk for CVD.

The parameters measured in PREVENT are seen in Table 4.

Importantly, all available cholesterol levels were used in the analysis, as clinical practice guidelines no longer recommend fasting for measurement of non-HDL-C, given that TC and HDL-C are minimally affected by fasting status, and the prognostic value of fasting and nonfasting values are similar.[14,15]

To date, no comprehensive treatment guidelines based on the 2023 PREVENT risk categories have been published by the AHA/ACC. The following interim guidance can be used with the new PREVENT risk assessment: for patients with Stage 1 hypertension (systolic BP 130-139 mmHg or diastolic BP 80-89 mmHg) and a 10-year PREVENT-CVD risk of ≥7.5%, antihypertensive medication can be considered after a 3-to-6-month trial of lifestyle modification. For those with Stage 2 hypertension (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg, anti-hypertensive medications are to be started regardless of their PREVENT score. For

Table 4. 2023 PREVENT CVD Risk Calculations

Sex (male, female)	Age (30-79)
Total Cholesterol	HDL Cholesterol
Systolic Blood Pressure	Body Mass Index (BMI)
eGFR (estimated glomerular filtration rate)	Diabetes (yes, no)
Current Smoking (yes/no)	Anti-hypertensive medication (yes/no)
Lipid-lowering medication (yes/no)	Urine Albumin-Creatine Ratio*
HbA1C*	Zip Code* (for social deprivation index)

* Optional predictors for personalization of risk assessment.

cholesterol management (PREVENT-ASCVD) and heart failure prevention (PREVENT-HF), physicians are to use the 2019 Primary prevention Guidelines regarding statin initiation.

As valuable as the PREVENT risk assessment may prove to be, several Harvard researchers cautioned that there might be a downside to this risk scoring.[16] These authors compared the PREVENT equations with the PCEs using existing AHA/ACC guidelines for the differences in predicted 10-year ASCVD risk, AHA/ACC risk categorization based on current thresholds, eligibility for statin or antihypertensive therapy, and projected potential increased occurrences of myocardial infarction or stroke. The main findings of their study include:

1. Approximately half of US adults would be reclassified to a lower AHA/ACC risk category (53%).
2. The estimated number of US adults receiving or recommended for preventive treatment would decrease by an estimated 14.3 million for statin therapy and 2.62 million for antihypertensive therapy.
3. Over 10 years, decreases in treatment eligibility could result in 107,000 additional occurrences of myocardial infarction or stroke.
4. These changes would affect twice as many men as women (−9.93 million vs −4.34 million for statin therapy and −1.84 million versus −0.78 million for antihypertensive therapy) and a greater proportion of Black adults than White adults (−9.89% versus −8.00% for statin therapy and −2.20 vs −1.39% for antihypertensive therapy). Importantly, this analysis focuses on ASCVD risk prediction, not total CVD prediction. Risk estimates for PREVENT-CVD more closely approximate those from the PCEs, but it is not yet known how future AHA/ACC treatment guidelines will factor PREVENT-CVD risk into recommendations.

For additional risk assessment, exploring other risk factors are suggested as well. For instance, persons with moderate COPD are more likely to die of CVD than their respiratory disease,[17] and 90% of adult-onset asthma patients die of CVD.[18,19] The obvious co-morbidities of hypertension, metabolic dysfunction-associated liver diseases (steatohepatitis [MASH], metabolic and alcoholic liver disease [MetALD], alcoholic liver disease [ALD]) and Type 2 DM, all of which have in common cellular inflammation and insulin resistance, should be considered and might be evaluated with high-sensitivity C-reactive protein (hsCRP), the triglyceride-glucose (TyG) Index or the triglyceride/HDL (TG/HDL) ratio.

When cells become resistant to insulin, the breakdown of fat into free fatty acids is less effectively suppressed. The liver is consequently flooded with excess free fatty acids and responds by increasing the production of triglycerides, packaged into very low-density lipoproteins (VLDL). Insulin resistance impairs the normal suppression of hepatic VLDL production. High triglyceride levels lead to an increased exchange of triglycerides from VLDL for cholesterol esters in HDL particles. This process, involving the cholesteryl ester transfer protein (CETP), results in smaller, denser, and less stable HDL particles that are more rapidly cleared from circulation, resulting in lower HDL serum levels. The combined effect of high triglycerides

and low HDL is the classic dyslipidemia seen in people with insulin resistance and metabolic syndrome, and the triglyceride/HDL ratio captures this imbalance. A TG/HDL ratio >3.0 in mg/dL units, or >1.3 mmol/L, suggests the presence of insulin resistance and increased risk of both cardiovascular disease and prediabetes or type 2 diabetes. A thorough description of the triglyceride-glucose (TyG) index is found in an accompanying article in this issue of the *Journal of Insurance Medicine*.

LDL, the most abundant cholesterol-rich lipoprotein in plasma, is causally linked to atherosclerosis. LDL enters the artery wall via apoproteinB (apoB). A maladaptive response ensues. This response involves modification of LDL particles, which promotes LDL retention and the release of bioactive lipid products that trigger inflammatory responses in vascular cells, as well as adaptive immune responses. Resident and recruited macrophages take up modified LDL, leading to foam cell formation and ultimately cell death due to inadequate cellular lipid handling. Accumulation of dead cells and cholesterol crystallization are hallmarks of the necrotic core of atherosclerotic plaques.

A review of basic physiology helps clarify the dyslipidemias. Cholesterol is a lipid and, as such, is not water-soluble. To be carried in our circulation, it needs to be encased in a protein shell, hence the name "lipoprotein." These protein shells carry cholesterol, triglycerides, and phospholipids, plus vitamins and other proteins that are needed by body tissues. The density of lipid determines the name of the lipid (ie, HDL carries high-density lipoproteins, and LDL carries low-density lipoproteins). LDLs carry more lipids while HDL carry more protein in relation to fat, explaining why they are denser. It is not the cholesterol per se that causes problems, but the nature of the particle in which it's transported. Each lipoprotein particle is enwrapped by larger molecules, called apolipoproteins, that provide structure, stability, and solubility to the particle. HDL particles are wrapped in lipoprotein A1 (or apoA1). LDL particles are wrapped in apolipoprotein B (or apoB), explaining why apoB is a stronger predictor of cardiovascular risk than apoA1.[20]

In a pooled analysis of 15 randomized primary or mixed primary and secondary prevention trials (N=74,390), compared with placebo or no therapy, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statin therapy) was associated with a 28% lower risk of cardiovascular outcomes (3.5% to 4.9%, RR 0.72.)[21]

HDL particle number and size are more predictive than total HDL cholesterol levels and both abnormally low and especially high HDL levels (women with ≥135 mg/dL and men with ≥97 mg/dL) showed increased HR for all-cause and CVD mortality.[22]

Lipoprotein A [Lp(a)],[23] not to be confused with apoA1, is a specific type of lipoprotein particle composed of a lipid core of cholesteryl esters and triacylglycerols, with an outer shell of phospholipids, free cholesterol and apolipoprotein B-100 (apoB-100) particles. Lp(a) is the entire particle, while apoA1 is the unique "extra" that is attached to the apoB-100 component that gives Lp(a) its distinct, pro-atherogenic and pro-thrombotic properties.

Lp(a) is a significant CVD risk. It is a complex lipoprotein particle that combines a low-density lipoprotein (LDL)-like particle with an apoA1 component, which is covalently bonded to apolipoprotein B-100 (apoB-100 is the main protein on LDL particles). Lp(a) is a member of the apoB particle family and therefore more likely to penetrate the cardiac arterial endothelium, with thrombogenic and atherogenic potential. It is the preferential lipoprotein carrier for oxidized phospholipids, and its role adversely affects vascular inflammation, atherosclerotic lesions, and thrombogenicity, leading to CVD. It is genetically determined (Lp(a) gene located on chromosome 6q25.3-q26) and is the most prevalent hereditary risk factor for heart disease. It is the major cause of acute myocardial

infarction and/or sudden cardiac death in younger populations. Diet and environment have no effect on serum concentrations that remain constant over a lifetime.[24-26] Standard antilipidemic therapies such as statins, fibrates, and ezetimibe have a negligible effect on Lp(a) levels; injectable monoclonal PCSK9 inhibitors have been shown to reduce Lp(a) levels by 30% but have not yet been documented to improve survival. A new class of drugs called oligonucleotides show promise to substantially lowering Lp(a) levels. Less than 0.5% of people undergo Lp(a) testing even though high levels constitute a major risk factor for heart disease.

Apolipoprotein B (apoB) typically correlates with LDL cholesterol but is a more accurate predictor of risk than LDL levels.[26] About 20% of people who have a normal LDL cholesterol will have a high apoB, denoting an especially significant cardiovascular risk. It is apoB that carries cholesterol in the blood. This protein encapsulates LDL particles but also intermediate-density lipoproteins (IDL), very low-density lipoprotein cholesterol. A rough proxy for apoB is to determine the non-HDL cholesterol by calculating the Total Cholesterol (TC) minus HDL cholesterol. While nowhere as precise as a direct apoB measurement, this measurement correlates reasonably well.

The Apo B/Apo A-1 ratio is a measurement of the balance between "good" and "bad" cholesterol. A high ratio is considered better for cardiovascular health, indicating a higher level of beneficial Apo A1 in HDL and/or a lower level of harmful Apo B in LDL. Optimal ratios are below 0.7. For men, a ratio above 0.9 may indicate increased risk; for women, a ratio above 0.8 may indicate increased risk.

Finally, it should be recognized that "normal" blood tests are based on a 95% prediction interval, the range in which 95% of values are seen in a bell-shaped curve, excluding the highest 2.5% and the lowest 2.5% of a "normal population." As pointed out earlier, 35% of this "normal population" will have at least one risk factor for ASCVD, and 29% will have two or more risk factors for ASCVD, so simply accepting a lab value for glucose or triglycerides or other predictive measure as being "within normal limits" ignores these risks in a normal population. Obviously, drilling down to specifically identify persons with "low normal" HDLs or "upper limit of normal" LDLs should also be noted and considered in any risk assessment.

SUMMARY

Measuring and addressing the risks for CVD has been an on-going effort for the past 60 years. The dramatic decline in CVD deaths from 1960 to 2020 reflected increased identification of risks and improved therapy for CVD, but the current rise in CVD deaths back to levels seen in 2010 is concerning. The evolution of CVD risk scoring systems may help identify cardiovascular risk, but addressing these risks remains a challenge. Appreciation of the roles of inflammation and insulin resistance are evolving and are now being addressed with the newer sodium-glucose cotransporter 2-inhibitors (SGLT-2 inhibitors) and (glucagon-like peptide-1 receptor-agonist (GLP-1 RA) medicines. Under-testing for the atherogenic particles Lp(a) and apoB remains problematic, as these two measurements provide more prognostic information than levels of LDL and HDL. Rough estimates for apoB may be achieved by subtracting total cholesterol from HDL cholesterol and lacking an apoB measurement should be routinely accessed and included in risk assessment for CVD.

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