Use of Risk Assessment Tools to Guide Decision-Making in the Primary Prevention of Atherosclerotic Cardiovascular Disease

A Special Report From the American Heart Association and American College of Cardiology

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ABSTRACT

Risk assessment is a critical step in the current approach to primary prevention of atherosclerotic cardiovascular disease. Knowledge of the 10-year risk for atherosclerotic cardiovascular disease identifies patients in higher-risk groups who are likely to have greater net benefit and lower number needed to treat for both statins and antihypertensive therapy. Current U.S. prevention guidelines for blood pressure and cholesterol management recommend use of the pooled cohort equations to start a process of shared decision-making between clinicians and patients in primary prevention. The pooled cohort equations have been widely validated and are broadly useful for the general U.S. clinical population. But, they may systematically underestimate risk in patients from certain racial/ethnic groups, those with lower socioeconomic status or with chronic inflammatory diseases, and overestimate risk in patients with higher socioeconomic status or who have been closely engaged with preventive healthcare services. If uncertainty remains for patients at borderline or intermediate risk, or if the patient is undecided after a patient–clinician discussion with consideration of risk enhancing factors (e.g., family history), additional testing with measurement of coronary artery calcium can be useful to reclassify risk estimates and improve selection of patients for use or avoidance of statin therapy. This special report summarizes the rationale and evidence base for quantitative risk assessment, reviews strengths and limitations of existing risk scores, discusses approaches for refining individual risk estimates for patients, and provides practical advice regarding implementation of risk assessment and decision-making strategies in clinical practice.

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INTRODUCTION

For >2 decades, the paradigm in primary prevention of atherosclerotic cardiovascular disease (ASCVD) has focused on the principle that the intensity of prevention efforts should match the absolute risk of the patient (1,2). For all patients, regardless of absolute risk, appropriate lifestyle modification (i.e., smoking cessation, weight modification, a healthy dietary pattern, and participation in physical activity) should be recommended (3,4). In patients at higher absolute predicted risk for ASCVD (typically, a 10-year estimated risk) for whom the benefits of medical therapy are likely to outweigh potential for harm, more intensive lifestyle efforts and consideration of evidence-based preventive pharmacotherapy have been recommended (1,2,5-7) Thus, quantitative absolute risk assessment in clinical practice has assumed a prominent role in U.S. and international guidelines to facilitate decision-making in primary prevention (1,5-9).

This special report summarizes the rationale and evidence base for quantitative risk assessment, reviews strengths and limitations of existing risk scores, discusses approaches for refining individual risk estimates for patients, and provides practical advice regarding implementation of risk assessment and decision-making strategies in clinical practice. This document is intended to serve as a companion to the "2018 ACC/AHA/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol" (2018 Cholesterol Clinical Practice Guidelines) (10) and the "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" (2017 Hypertension Clinical Practice Guidelines) (7).

QUANTITATIVE RISK ASSESSMENT IN PRIMARY PREVENTION

Rationale

Estimation of the absolute risk of developing an incident cardiovascular disease (CVD) event is the foundation of current approaches to primary prevention of CVD. Relative risk estimates for disease incidence are of limited clinical utility given the uncertainty regarding the incidence rate in the referent group. A relative risk of 10 may seem high but, if the incidence rate in the referent group is near zero, a relative risk of 10 is still a very low absolute risk. Absolute risk estimation allows direct understanding of prognosis and identification of patients at sufficient risk to merit treatment with higher likelihood of net individual and societal benefit. Furthermore, absolute risk estimation allows for assessment of potential benefits from intensive lifestyle and direct comparison of potential benefits and harms from preventive pharmacotherapies to assist clinicians and patients in informed decision-making. There is substantial observational evidence to support this approach in terms of appropriate patient selection for medical therapy (maximizing net benefit and minimizing number-needed-to-treat to prevent one event in 5 to 10 years) with both statins and antihypertensive therapy (11,12). Estimation of absolute risk can be performed rapidly in clinical practice with widely available tools that are increasingly embedded in electronic health record platforms with decision support, facilitating ease of use and implementation.

Evidence Base

A recent comprehensive Cochrane systematic review (13) identified 41 randomized controlled trials that examined the use of short-term CVD risk estimation scores in primary prevention. The authors found significant heterogeneity and low-quality evidence for all of the trial results. Overall, compared with usual care, providing quantitative CVD risk score data to clinicians and patients had statistically significant but modest effects on levels of CVD risk factors (including total cholesterol and systolic blood pressure [SBP]) and on patients' subsequent estimated 10-year CVD risk at follow-up. Providing risk information was also associated with increased initiation or intensification of lipid-lowering and antihypertensive medications. There was also evidence that harm from quantitative risk assessment is very unlikely (13).

Because there are presently no outcomes trials, uncertainty remains as to whether current strategies for providing quantitative CVD risk information will directly reduce near-term CVD event rates. A very large cluster-randomized trial is currently assessing the impact of CVD risk score-based decision-making on CVD event rates in very-high-risk Medicare beneficiaries (14). Further study of clinical outcomes and new models for implementing and optimizing delivery of CVD risk scores in clinical practice are still needed to define their ultimate role in primary prevention of CVD. In the meantime, the use of validated, quantitative risk assessment scores appears to be appropriate, safe, and moderately efficacious in helping to control risk factors, with no additional incurred costs (assuming risk factors would be measured anyway) and the potential for additional value to improve decision-making, as described below.

Use of Quantitative Risk Estimation in Current Prevention Guidelines

The 2018 Cholesterol Clinical Practice Guidelines (10) recommend the use of quantitative 10-year risk assessment, based on measurement of traditional ASCVD risk factors and with use of a validated risk prediction tool, as the first step in considering treatment options for primary

prevention. Results of 10-year risk estimation should be communicated through a clinician-patient risk discussion to decide on the intensity of preventive measures, especially whether to initiate medical therapy. In present guidelines, patients with estimated 10-year ASCVD risk of 5% to <7.5% are considered to be at "borderline" risk and may be considered for drug therapy with a statin under certain circumstances; those with "intermediate" 10-year risk (7.5% to <20%) should be considered for initiation of moderate- to high-intensity statin therapy; and those with "high" 10-year risk (≥20%) should be considered for initiation of high-intensity statin therapy (10). The clinical flow for quantifying and classifying risk, considering risk-enhancing factors, discussing treatment options, and potentially reclassifying risk using coronary artery calcium (CAC) measurement, is detailed below.

In the 2017 Hypertension Clinical Practice Guidelines (7), quantitative risk estimation is recommended to guide the intensity of initial therapy for patients with stage 1 hypertension (SBP 130-139 mm Hg or diastolic blood pressure [DBP] 80-89 mm Hg). Patients with stage 1 hy-pertension and a 10-year ASCVD risk estimate <10%should be managed initially with nonpharmacological therapy, whereas those with 10-year risk ≥10% are rec-ommended for initial management with both non-pharmacological approaches and antihypertensive drug therapy (7).

EXISTING U.S.-DERIVED RISK SCORES FOR CVD RISK PREDICTION

Pooled Cohort Equations

The 2018 Cholesterol Clinical Practice Guidelines (10) and the 2017 Hypertension Clinical Practice Guidelines (7) recommend use of the U.S.-derived pooled cohort equations (PCE) (5) to estimate 10-year risk for hard ASCVD events (defined as coronary death, nonfatal myocardial infarction, fatal or nonfatal stroke). The PCE are designed to be sex- and race-specific for whites and blacks, and they include stroke (not just coronary heart disease) as an endpoint to better identify modifiable risk in women and blacks. Numerous investigators have examined their performance in external validation samples (15-39). Findings from a systematic review conducted for the 2018 Cholesterol Clinical Practice Guidelines are included in the online data supplement for those guidelines (10).

In general, the PCE are well calibrated near decision thresholds (e.g., 7.5% to 10% 10-year ASCVD risk or equivalent) for individuals from the broad U.S. population, and similarly for men and women. Performance of the PCE in diverse racial/ethnic groups from outside the United States is highly variable, as would be expected given the heterogeneous nature of the populations, differences in prevalence of risk factors, and differences in underlying hazards for ASCVD (15-39).

Clinical risk prediction scores attempt to predict natural history of disease incidence in individuals based on population levels of risk factors and underlying hazards. As such, they are less ideal for accurate risk prediction in patients already receiving intensive preventive efforts. In this context, the PCE have been noted to be well calibrated near decision thresholds in large U.S. general populations and unselected clinical samples (20,30,34,37) and, as with all other CVD risk scores, to overpredict or underpredict risk in other samples (see 2018 Cholesterol Clinical Practice Guidelines Online Data Supplement [10]). These findings of mismatch between predicted and observed events (i.e, miscalibration) are expected among homogeneous subgroups with restricted risk distributions (e.g., white women health professionals or patients with HIV), and should be considered in use of the PCE or any other CVD risk score for an individual patient.

Available data suggest that clinicians should consider that the PCE may overestimate risk in groups with predicted 10-year risk >10% or higher socioeconomic status, or those receiving consistent screening and preventive care (15,17,18,21,26,31-35,37). In general, overprediction of observed event rates has been documented in situations in which the validation sample is more affluent or more likely to receive preventive drug therapy (e.g., statins, aspirin, antihypertensive therapy) and longitudinal follow-up with other preventive services. Consistent overprediction is also observed among high predicted risk strata, particularly predicted 10-year risks >10%, which may be of lesser clinical importance because such groups would likely benefit from preventive medications, so precision of the risk estimate is less essential. A number of explanations for overprediction have been advanced (40,41), including inadequate event capture in validation cohorts, as well as the use of older population-based natural history cohorts for derivation of the PCE, leading to overprediction in more contemporary cohorts who may have been exposed to a lower burden of CVD risk factors before—and certainly to more intensive preventive efforts after—initial risk assessment.

Likewise, the PCE tend to underpredict observed events in samples with lower socioeconomic status or with chronic inflammatory diseases, such as HIV, rheumatoid arthritis, or sarcoidosis (17,20,23,36). Thus, in the context of a clinician-patient discussion (see below), clinicians should consider that the PCE may underestimate risk in individuals with lower socioeconomic status, or with chronic inflammatory conditions. Further work is needed to define additional conditions in which risk may be underestimated. Other risk-enhancing factors, including race/ethnicity, that may modify 10-year risk estimates are described below.

TABLE 1 Features of Current U.S.-Based Cardiovascular Risk Assessment Tools

Risk Assessment Tool	Variables Included	Outcomes Predicted	Derivation Sample	Features	Comments About Implementation
Pooled cohort equations http://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/ (42) https://professional.heart.org/professional/GuidelinesStatements/PreventionGuidelines/UCM_457698_ASCVD-Risk-Calculator.jsp (43)	■ Age ■ Sex ■ Race ■ Total cholesterol ■ HDL-C ■ SBP ■ Antihypertensive therapy ■ History of diabetes mellitus ■ Current smoking	Hard ASCVD (CHD death, nonfatal MI, fatal or nonfatal stroke)	5 community-based cohorts of white and black participants	Sex- and race-specific equations for 4 groups: white men, white women, black men, black women	■ Available in apps/online and in some electronic health record platforms ■ Uncertain utility in other racial/ethnic groups ■ Data available for reclassification by CAC score
Framingham General CVD Risk Profile https://reference.medscape.com/calculator/framingham-cardiovascular-disease-risk (44)	■ Age ■ Sex ■ Total cholesterol ■ HDL-C ■ SBP ■ Antihypertensive therapy ■ History of diabetes mellitus ■ Current smoking	Total CVD (CHD death, MI, coronary insufficiency, angina, ischemic stroke, hemorrhagic stroke, transient ischemic attack, intermittent claudication, and heart failure)	Single community-based cohort of 2 generations	Sex-specific equations for whites	■ Available online ■ Uncertain utility in other racial/ethnic groups ■ Uncertain calibration to hard ASCVD endpoint ■ Uncertain reclassification by CAC score
Reynolds Risk Score http://www.reynoldsriskscore.org/ (45,46)	■ Age ■ Sex ■ Total cholesterol ■ HDL-C ■ SBP ■ Current smoking ■ hsCRP level ■ Parental history of MI before age 60 y	Expanded ASCVD (CHD death, nonfatal MI, fatal or nonfatal stroke, coronary revascularization)	Largely white health professionals enrolled in clinical trials	Sex-specific equations	■ Available online ■ Uncertain utility in other racial/ethnic groups ■ Uncertain calibration to hard ASCVD endpoint ■ Uncertain reclassification by CAC score

ASCVD indicates atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CHD, coronary heart disease; hsCRP, high-sensitivity C-reactive protein; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; MI, myocardial infarction; and SBP, systolic blood pressure.

ACC/AHA clinical practice guidelines (7,10) recommend the use of the PCE as an important starting point, not as the final arbiter, for decision-making in primary prevention of ASCVD. After quantitative risk assessment, clinical judgment that is based on the individual patient's preferences, presence of other risk enhancers, and the selective use of CAC scoring, described below, can help to overcome most issues of miscalibration for any risk prediction equations. This approach will help to reclassify risk appropriately and assist in improved decision-making regarding use of lipid-lowering drug therapy for ASCVD risk reduction; however, data regarding the appropriate tools (e.g., echocardiography) for risk reclassification of patients being considered for antihypertensive drug therapy are needed.

Use of Other Risk Scores

ACC/AHA clinical practice guidelines recommend the use of quantitative risk assessment tools as an important step in decision-making for primary prevention of ASCVD. Whereas the guidelines recommend using the PCE for most primary prevention patients (except those with familial hypercholesterolemia or low-density lipoprotein-cholesterol ≥190 mg/dL), other risk assessment tools are available. Most of these other tools have not been validated as broadly as the PCE, but they generally also perform moderately well in discrimination and calibration of the endpoints for which they were specifically designed. Table 1 presents features of available US-based risk assessment tools that include ASCVD as at least part of their outcome.

The Framingham General CVD Risk Profile (44) appears to have similar utility as the PCE for its very broad outcome that includes ASCVD events as well as unstable angina/coronary insufficiency, transient ischemic attack, claudication, and heart failure (which may not be directly preventable with lipid-lowering therapy). The Reynolds Risk Score (45,46) appears to perform somewhat better than the PCE in some higher socioeconomic and lower-risk samples and includes coronary revascularization as an endpoint. Some features of the Framingham and Reynolds risk assessment tools may limit their implementation in clinical practice with regard to alignment with recommendations in ACC/AHA clinical practice guidelines, including uncertainty regarding use in nonwhite patients, calibration to the hard ASCVD endpoint, and reclassification by CAC scoring. The European SCORE (Systematic Coronary Risk Evaluation) algorithm (9) is less applicable to the general U.S. population because it was derived in European samples, and given its endpoint of CVD death (only), with poor representation of and unpredictable calibration for nonfatal CVD events (47).

The QRISK (an algorithm for predicting cardiovascular risk) score (8) is calibrated to the general clinical popu-lation of Great Britain, and is of uncertain value in U.S. samples. If reliable data are available specific to a health system or local population with 10-year follow up, reca-libration may be considered as a means for improving the accuracy of risk equations for that population.

Special Populations

Quantitative risk assessment with current risk scores should not be performed for patients with clinical ASCVD that requires secondary prevention, or for those with confirmed familial hypercholesterolemia or baseline low-density lipoprotein-cholesterol of ≥190 mg/dL. These groups require intensive preventive efforts with lipid-lowering drug therapy (given their considerable risk for future ASCVD events). Similarly, most patients with established diabetes mellitus should be considered for statin therapy and for antihypertensive drug therapy (if blood pressure is elevated) regardless of predicted 10-year risk. However, 10-year risk estimation may still be useful in patients with diabetes mellitus to inform thresholds for initiation of antihypertensive drug therapy and intensity of statin dosing.

Because the PCE and most other risk scores apply only to adults 40 to 75 years of age, there are limited data on the performance and use of quantitative 10-year risk scores among adults <40 years of age. Because of their young age, such individuals would be very unlikely to exceed 10-year risk thresholds for which preventive drug therapy is recommended (48). As discussed below, it is reasonable to consider 30-year or lifetime risk estimation (5) in these younger adults to inform the intensity of prevention efforts. For adults >75 years of age, existing risk scores perform poorly in 10-year risk prediction because of weaker associations of traditional risk factors with events at these older ages and competing risks of noncardiovascular mortality.

For individuals from racial/ethnic groups other than non-Hispanic whites and non-Hispanic blacks, the ACC/AHA clinical practice guidelines recommend use of the PCE versions for whites of the same sex (3,7). In the context of a risk discussion, clinicians should consider that the PCE may overestimate risk in East Asian (e.g., Chinese or Japanese) and Hispanic white populations (16,21,25,28,39), because these groups appear to be at somewhat lower ASCVD risk than their non-Hispanic white counterparts. Data are sparse for other subgroups, but South Asian (e.g., Indian, Pakistani) populations appear to be somewhat higher risk (49). These issues, in the context of the clinician-patient discussion, should be considered unless the patient has very low (<2.5%) or high (>20%) predicted risk by the PCE, in which case any miscalibration is unlikely to affect clinical decision-making. For the 45% of adults 40 to 75 years of age who have 10-year ASCVD risk estimates between 5% and 20% (5), consideration of individual circumstances (e.g., family history), lifetime risk, or measurement of CAC score, as described below, may be useful to refine the initial risk estimate.

Long-Term or Lifetime Risk Assessment

Guidelines (5,6,10) have also promulgated use of tools for long-term or lifetime risk assessment (available at: http://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/ [42] and https://professional.heart.org/professional/GuidelinesStatements/ASCVDRiskCalculator/UCM_457698_ASCVD-Risk-Calculator.jsp [43]) to provide further perspective on the long-term consequences of single elevated clinical risk factors and the aggregate burden of risk factor levels over a longer time horizon. Therefore, lifetime risk assessment appears to be particularly useful for describing and communicating ASCVD risk in younger individuals (<50 years of age) who may have high lifetime risk, but in whom 10-year risk may be low even when significant risk factors are present, because of their young age and the 10-year risk prediction window (50–54). For example, more than half of the U.S. adult population has a 10-year risk estimate <10% and a lifetime risk estimate ≥39% (53). To date, lifetime risk estimates have generally been recommended to promote therapeutic lifestyle change in younger individuals (5,10) rather than as a means for patient selection for drug therapy. However, indirect evidence of benefit for initiation of statin therapy in individuals with lower 10-year risk (mean <10%) and high lifetime risk (based on inclusion criteria requiring at least 1 additional CVD risk factor (50,52)) was seen in the HOPE-3 (Heart Outcomes Prevention Evaluation-3) trial. In this trial, 10 mg of rosuvastatin reduced CVD events compared with placebo (3.7% versus 4.8%; hazard ratio: 0.76; 95% confidence interval: 0.64-0.91) over a median of 5.6 years of follow-up (55). A trial of statin versus placebo among younger individuals with low short-term and high lifetime risk is ongoing (56) and may inform the potential use of using lifetime risk assessment for selection of younger patients for lipid-lowering drug therapy. Simultaneous assessment of 10-year and lifetime risks is therefore reasonable for the purposes of the clinician-patient discussion with an individual patient.

REFINING RISK ASSESSMENT FOR INDIVIDUAL PATIENTS: THE CLINICIAN-PATIENT DISCUSSION

When considering drug therapy for primary prevention of ASCVD, clinicians and patients should begin by calculating the 10-year and lifetime ASCVD risk estimates. The initial estimate can then form the basis for a discussion

TABLE 2 Risk-Enhancing Factors for Clinician–Patient Risk Discussion (10)

Risk-Enhancing Factors
■ **Family history of premature ASCVD** (males, age <55 y; females, age <65 y)
■ **Primary hypercholesterolemia** (LDL-C, 160–189 mg/dL [4.1–4.8 mmol/L); non-HDL-C 190–219 mg/dL [4.9–5.6 mmol/L])*
■ **Metabolic syndrome** (increased waist circumference, elevated triglycerides [>150 mg/dL], elevated blood pressure, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 in women mg/dL] are factors; tally of 3 makes the diagnosis)
■ **Chronic kidney disease** (eGFR 15–59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation)
■ **Chronic inflammatory conditions** such as psoriasis, RA, or HIV/AIDS
■ **History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk such as preeclampsia**
■ **High-risk race/ethnicities** (e.g., South Asian ancestry)
■ **Lipid/biomarkers**: Associated with increased ASCVD risk
■ Persistently* elevated, primary hypertriglyceridemia (≥175 mg/dL);
■ If measured:
■ **Elevated high-sensitivity C-reactive protein** (≥2.0 mg/L)
■ **Elevated Lp(a):** A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor especially at higher levels of Lp(a).
■ **Elevated apoB** ≥130 mg/dL: A relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C ≥160 mg/dL and constitutes a risk-enhancing factor
■ **ABI** <0.9

*Optimally, 3 determinations. Reprinted with permission from Grundy SM, et al. (10).

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

that includes consideration of the burden and severity of CVD risk factors, control of those other risk factors, the presence of risk-enhancing conditions (see below), adherence to healthy lifestyle recommendations, the potential for ASCVD risk-reduction benefits from statins and antihypertensive drug therapy, and the potential for adverse effects and drug-drug interactions, as well as patient preferences regarding the use of medications for primary prevention. In this discussion, patient health literacy and numeracy are important factors determining the depth and breadth of the content. Other important factors include the patient's personal desire to avoid stroke or myocardial infarction and potentially increase their longevity, and the countervailing issues of the desire to avoid "medicalization" of preventable conditions and the burden or disutility of taking daily (or more frequent) medications. Data including the absolute 10-year and lifetime risk estimates, the relative and absolute risk reduction benefit to be expected from drug therapy, and even numbers needed to treat over 5 and 10 years to prevent 1 ASCVD event or death may be useful concepts to address and to put in context for individual patients. Several tools and documents exist that may assist clinicians and patients in this discussion, including:

ACC's ASCVD Risk Estimator Plus tool, which can predict 10-year risk using the PCE and can project expected benefit from different therapy choices (e.g., initiation of statin, aspirin, or antihypertensive therapy, or smoking cessation in primary prevention; https://www.acc.org/ASCVDApp) (57);

Mayo Clinic Shared Decision Making Cardiovascular Primary Prevention Choice tool (https://shareddecisions.mayoclinic.org/decision-aid-information/decision-aids-for-chronic-disease/cardiovascular-prevention/) (58);

- A monograph by Martin et al. (59) describing the conceptual framework and practical implementation of the clinician-patient discussion; or
- Table 7 in the 2018 Cholesterol Clinical Practice Guidelines (10), which provides a framework and tips for the clinician-patient discussion.

In using these tools, it is important to recognize that quantitative 10-year risk assessment provides estimates of risk based on group means from large-scale population studies. There is, of course, uncertainty around these estimated probabilities, creating a distribution of risk for patients with a given risk estimate. Where an individual patient falls within the distribution around the estimated 10-year risk depends in large part on other factors, not included in the PCE, that may be considered by the clinician and patient. For example, a 45-year-old patient with a strong family history of premature-onset ASCVD is likely to be at higher risk than a patient with the same age, sex, race and risk factor profile but without such a family history. Discussion of these concepts may assist in eliciting patient preferences and attitudes toward ASCVD risk and views on drug therapy for prevention.

The 2018 Cholesterol Clinical Practice Guidelines (10) identify risk-enhancing factors, or comorbidities, that should be considered to affect the 10-year risk estimate for individual patients (**Table 2**). However, it is difficult to determine how much a risk-enhancing factor or comorbidity may change the 10-year risk estimate quantitatively for an individual patient. Therefore, clinician judgment is crucial to determine whether the presence of a risk-enhancing factor is significant enough to reclassify an individual to a higher (or lower) risk category that may cross a treatment decision threshold for consideration of drug therapy. If, after the clinician-patient discussion, the

benefits of statin medication for the individual patient remain unclear, the patient has important risk-modifying factors that suggest a better or worse risk than the original estimate, or if the patient is undecided regarding drug therapy, additional testing to help with the decision in patients at borderline (5% to <7.5%) or intermediate 10-year risk (7.5% to <20% 10-year risk) is reasonable. Some patients may also desire more specific personal information to guide their decision through demonstration of the presence or absence of the condition of interest (i.e. advanced atherosclerosis). Presently, the best additional test to help reclassify ASCVD risk in these situations is measurement of a CAC score for decision-making regarding statin therapy. Additional testing for decision-making for antihypertensive therapy may have lower clinical utility (60).

CAC MEASUREMENT TO RECLASSIFY RISK

Recognizing the imprecision of multivariable CVD risk prediction scores—as well as the uncertainty clinicians and patients may encounter regarding the potential benefits of drug therapy for an individual patient at borderline or intermediate 10-year ASCVD risk—additional testing for assessment of the presence of subclinical atherosclerosis is reasonable. In such cases, additional testing should only be used if it can provide sufficient information to modify the decision. In general, identification of subclinical atherosclerosis rather than use of serum biomarkers is preferred, because of the extensive body of evidence demonstrating the superior utility of atherosclerosis disease assessment, particularly with CAC measurement, over any serum biomarker for the prediction of future ASCVD events, including both coronary heart disease and stroke (61-63). Other modalities for assessing subclinical atherosclerosis, including carotid intima-media thickness and carotid plaque burden assessment, are weaker predictors of overall ASCVD events compared with the CAC score (5,62,63).

Presently, CAC measurement is not typically covered by insurers; therefore, patients should be informed that testing will incur direct out-of-pocket costs (typically between $50 and $350 [64]). With modern computed tomographic (CT) scanners, CAC scoring confers minimal additional risk from radiation exposure (~1 millisievert, which is comparable to a bilateral mammogram) (65,66). The potential for observing incidental findings of uncertain clinical significance (e.g., incidentally observed lung nodules, requiring further testing) also exists; studies suggest that incidental findings may be observed in ≥10% of asymptomatic individuals undergoing cardiac CT imaging. These findings are overwhelmingly, but not exclusively, benign in nature but often require follow up imaging to assess their potential health impact (67,68).

The costs and anxiety potentially caused by these findings can be mitigated by limiting the window of imaging/reading to just the cardiac region, or by focused follow-up. Recommendations have been published for managing these incidental findings based on size, cancer risk categories, and other features (69,70). Because CAC scores do not decrease, and may in fact increase, with plaque stabilization as a result of statins (71), repeat CAC scoring in patients taking statins is of limited clinical utility, and it cannot be used to assess the efficacy of statin therapy.

Reclassification of Risk Using CAC Scores

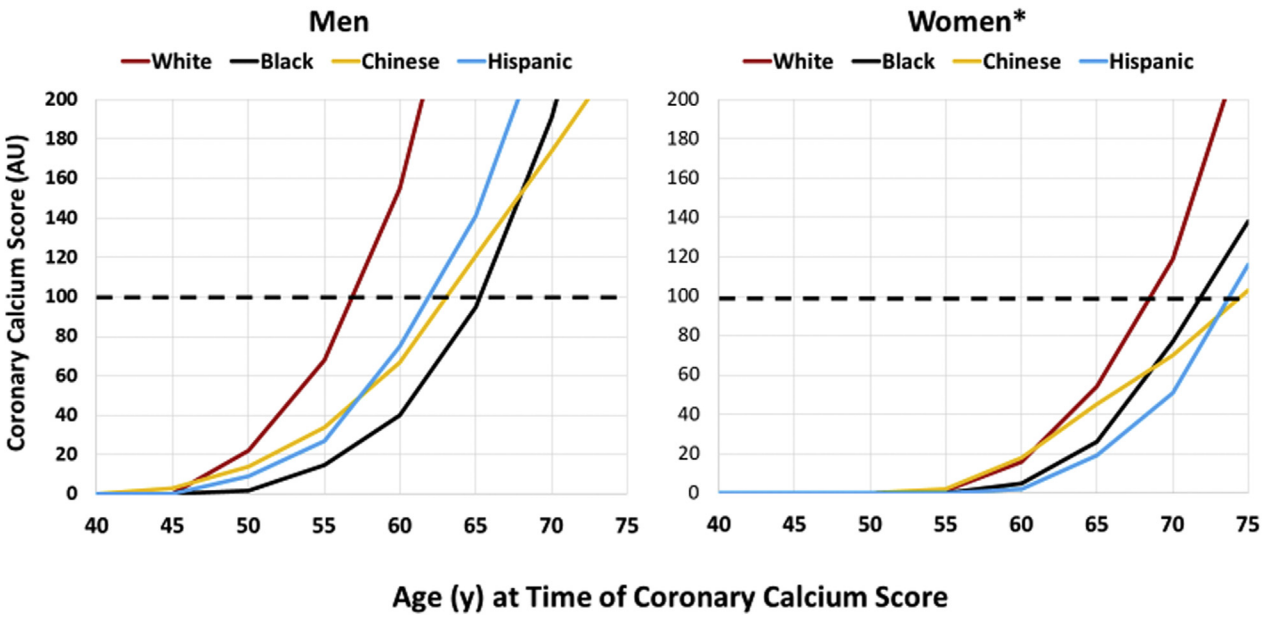
Since the publication of the "2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk" and the "2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults" (5,6), a substantial amount of evidence has been published demonstrating the utility of CAC measurement to reclassify risk specifically in the context of the PCE (32,62,63,72-76). Data demonstrate the important improvements in discrimination, calibration, and net reclassification that can occur for intermediate-risk patients with measurement of CAC after quantitative risk assessment, as is frequently seen in sequential Bayesian testing strategies using effective secondary tests with reasonable sensitivity and specificity for prognosis.

Reclassification of borderline and intermediate-risk patients with demonstration of a CAC score of ≥100 Agatston units (AU) (or ≥75th percentile for age, sex, and race/ethnicity; see the MESA [Multi-Ethnic Study of Atherosclerosis] CAC tools website, https://www.mesa-nhlbi.org/Calcium/input.aspx) (77) identifies patients who have a 10-year event rate ≥7.5%, who would be expected to have greater benefit from statin therapy ("up-risking") (32,62,63,72-76). **Figure 1** shows the CAC score values indicating the 75th percentile for age/sex/race/ethnicity. Men <50 years of age and women <60 years of age with any CAC will nearly always exceed the 75th percentile. Similarly, men <60 years of age and women <70 years of age with CAC measurement of ≥100 AU will nearly always exceed the 75th percentile. Conversely, reclassification of intermediate-risk patients who have a CAC score of 0 AU identifies patients with low observed 10-year event rates that fall below the range where statins may provide net benefit ("derisking" or "downrisking") (32,62,63,72-76,78).

CAC Scoring in Intermediate-Risk Patients (Predicted 10-Year ASCVD Risk of 7.5% to <20%)

In patients 40 to 75 years of age and at intermediate risk, substantial data indicate that use of CAC measurement can be effective in reclassifying risk meaningfully in a large proportion of individuals (32,61-63,72-76,79-81). In

FIGURE 1 Levels of CAC Score Indicating 75th Percentile for Age, Sex, and Race/Ethnicity (Data From MESA; https://www.mesa-nhlbi.org/Calcium/input.aspx) (77)



*Lines indicate age/sex/race/ethnicity-specific CAC score at 75th percentile. Values for age to the left of these lines indicate CAC score >75th percentile. Dashed line indicates absolute CAC score of 100 AU. AU indicates Agatston units; CAC, coronary artery calcium; and MESA, Multi-Ethnic Study of Atherosclerosis.

this intermediate-risk range, those who also have CAC measurement of ≥100 AU (or 75th percentile for age/sex/race/ethnicity) have event rates in the range where the benefit of statin therapy would clearly exceed any potential for harms. Additionally, such data can inform a patient and clinician regarding higher likelihood of benefit from drug therapy. Conversely, those with intermediate predicted risk and CAC score of 0 AU appear to have lower 10-year event rates (<7.5%) (32,73,75,79,80,82), suggesting that drug therapy could be of limited value.

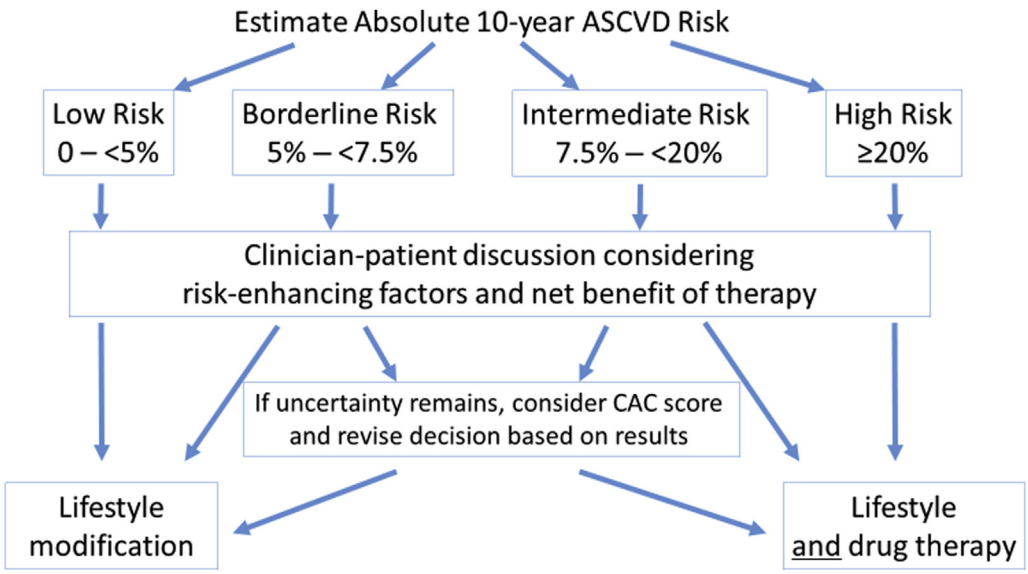
For those with a CAC score of 1 to 99 AU and with CAC <75th percentile for age/sex/race/ethnicity, it is important to note that there is evidence of subclinical atherosclerosis, and observed 10-year event rates largely remain in the intermediate-risk range (32). Reclassification is modest for these individuals, but they remain in a statin benefit group, so clinical judgment and patient preferences should guide decision-making. Therefore, for patients with CAC score of 1 to 99 AU, it is beneficial to extend the clinician-patient discussion regarding the potential net benefit of drug therapy. For untreated patients, repeat CAC measurement in 5 years may have some value to reassess for CAC progression, but data are limited (83,84).

CAC Scoring in Low-Risk and Borderline-Risk Patients

Outside of the intermediate-risk range, the yield of CAC measurement in younger and lower-risk patients (with 10-year predicted risk <5%) to find CAC measurement of ≥100 AU is overall very low (32,85,86). Therefore, universal CAC measurement in this large portion of the population would have low yield for a CAC measurement of ≥100 AU. Some potential benefit has been suggested among low-risk women with a family history of premature ASCVD events (80). For individuals at borderline risk (5% to <7.5%), presence of risk-enhancing factors (**Table 2**) may be useful to improve the yield of CAC scoring and to reclassify risk if a patient in this predicted risk range is considering the use of statin therapy. Data suggest that CAC measurement in individuals at borderline risk may be effective at reclassifying some subgroups of patients (32,62,74-76,79,81,82), but further data are needed to define these groups more clearly.

Carr et al. (79) examined CAC scores in participants of the CARDIA (Coronary Artery Risk Development in Young Adults) study at ages 32 to 46 years and observed that, even at this younger age, having CAC score of >0 AU was associated with ASCVD event rates in the range associated with statin benefit, particularly for those with CAC score of ≥100 AU. The presence of ASCVD risk factors through

FIGURE 2 **Overall Conceptual Approach to Risk Assessment and Decision-Making Regarding the Intensity of Prevention Efforts and Use of Drug Therapy in Primary Prevention of ASCVD**



ASCVD indicates atherosclerotic cardiovascular disease; and CAC, coronary artery calcium.

young adulthood identified those above the median risk for developing CAC in this cohort, which improved the number needed to screen to identify a younger adult with CAC score of >0 AU. These results support the notion that selective CAC measurement in younger adults (<45 years of age), based on the presence of significant and sustained risk factors, may be useful to inform discussions on primary prevention, even in those at borderline predicted risk (5% to <7.5%) (79).

CAC Scoring in High-Risk Patients (≥20% 10-Year Risk)

At the other end of the risk spectrum, the yield among individuals with high-predicted risk (≥20% 10-year risk) for a CAC score of 0 AU becomes small (32,85,86), and the reclassification provided by a CAC score of 0 AU does not result in subgroups with 10-year event rates below 7.5%. This important context frames the recommendations regarding use of CAC measurement after quantitative risk assessment and performance of a clinician-patient discussion with an individual patient.

The general approach to the potential use of CAC measurement after quantitative risk assessment is summarized below. If a CAC score is obtained, the results and their interpretation should be shared with the patient. A systematic review and meta-analysis by Gupta et al. (87) indicates that informing patients of their CAC score, when it is >0 AU, is effective for increasing their likelihood of initiating and continuing lifestyle modifications and pursuing drug therapy, with significant, although modest, changes in risk factor levels and predicted risk levels. The potential benefit of CAC scoring for individuals >75 years of age is uncertain. Clinicians should use their judgment regarding the potential use of risk reclassification in this age group. The incidental finding of CAC on thoracic CT imaging, done for other purposes, does indicate the presence of coronary atherosclerosis. When possible, an AU CAC score should be reported for these incidental findings, or a qualitative indication of severity (mild, moderate, heavy/severe) should be provided. In general, findings of moderate or more CAC suggest a CAC score of at least 100 AU (65,70).

PRACTICAL APPROACH TO RISK ASSESSMENT AND CLINICAL DECISION-MAKING

Figure 2 displays the conceptual approach to risk assessment and its role in decision-making regarding the intensity of prevention efforts and use of pharmacotherapy in primary prevention of ASCVD, particularly in the context of decision-making for use of statin medications. Table 3 provides a stepwise approach, in addition to clinical practice guidelines and tools to assist clinicians and patients through this process.

The interpretation and clinical response to a CAC score in borderline- or intermediate-risk patients merits

TABLE 3 Clinical Workflow for Implementing Risk Assessment in Adults for Primary Prevention of ASCVD

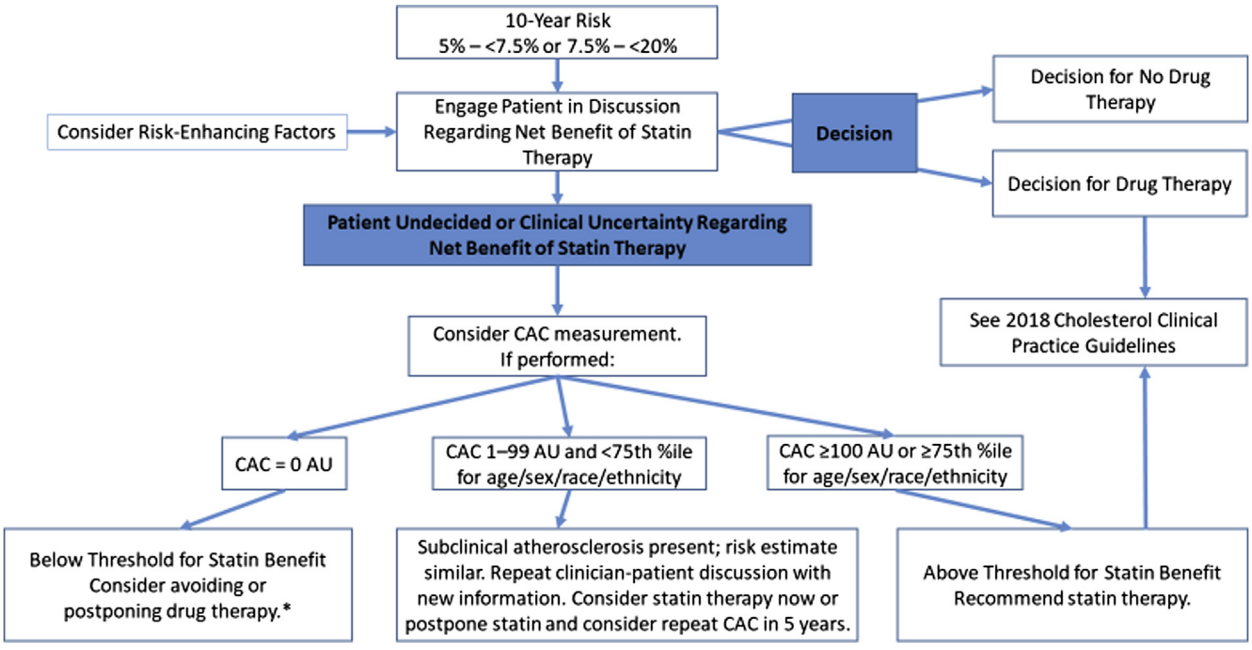
Step	Guidelines	Example Tools
1. Perform routine history and physical examination, assess health behaviors (e.g., smoking, diet, physical activity) measure physiological risk factors (e.g., blood pressure, lipid panel, diabetes mellitus screening as appropriate)	2013 ACC/AHA Risk Assessment Guideline (5) 2013 AHA/ACC Lifestyle Management Guideline (3) 2013 AHA/ACC/TOS Obesity Guideline (4)	…
2. Estimate 10-y (if age 40-75 y) and lifetime (if age 20-59 y) risks for ASCVD and classify 10-y risk as low (<5%), borderline (5% to <7.5%), intermediate (7.5% to <20%), or high (≥20%)	2017 Hypertension Clinical Practice Guidelines (7) 2018 Cholesterol Clinical Practice Guidelines (10)	■ Many EHRs can calculate 10-y ASCVD risk automatically ■ ASCVD Risk Estimator Plus (https://www.acc.org/ASCVDApp) (58)
3. Consider risk-enhancing factors (see **Table 2**) to modify risk classification based on clinical judgment	2017 Hypertension Clinical Practice Guidelines (7) 2018 Cholesterol Clinical Practice Guidelines (10)	…
4. Engage patient in discussion regarding 10-y and lifetime ASCVD risk, importance of controlling risk factors to reduce risk, potential for individual net benefit of drug therapy, potential harms from drug therapy, and individual patient preferences*	2018 Cholesterol Clinical Practice Guidelines (10)	■ ASCVD Risk Estimator Plus (https://www.acc.org/ASCVDApp) (58) ■ Mayo Clinic Shared Decision Making Cardiovascular Primary Prevention Choice tool (https://shareddecisions.mayoclinic.org/decision-aid-information/decision-aids-for-chronic-disease/cardiovascular-prevention/) ■ Monograph by Martin et al. (59) describing the conceptual framework and practical implementation of the clinician-patient discussion ■ Table 7 in the 2018 Cholesterol Clinical Practice Guidelines (10), which provides a framework and tips for the clinician-patient discussion
5. Recommend lifestyle modifications as appropriate to individual patient (e.g., smoking cessation, weight loss, dietary changes, increased physical activity). Consideration of lifetime risk for ASCVD may be particularly useful in reinforcing need for therapeutic lifestyle modification in those with low 10-y but high lifetime estimated risk.	2013 AHA/ACC Lifestyle Management Guideline (3)	…
6. Address control of blood pressure and goals of therapy, as needed	2017 Hypertension Clinical Practice Guidelines (7)	…
7. For borderline-risk (10-y risk 5% to <7.5%) and intermediate-risk (7.5% to <20%) patients who are undecided regarding statin therapy, or when there is clinical uncertainty regarding the net benefit, consider the value of additional testing with measurement of CAC. If CAC is measured, interpret results as follows (see **Figure 3**):	2018 Cholesterol Clinical Practice Guidelines (10)	■ MESA CAC Tools (https://www.mesa-nhlbi.org/Calcium/input.aspx) (77)
7a. CAC score of 0 AU indicates that a borderline- or intermediate-risk individual is reclassified to a 10-y event rate lower than predicted, and below the threshold for benefit from a statin. Consider avoiding or postponing statin therapy unless there is a strong family history of premature ASCVD, history of diabetes mellitus, or heavy cigarette smoking. Consider repeat CAC measurement in 5 ys if patient remains at borderline or intermediate risk.	2018 Cholesterol Clinical Practice Guidelines (10)	■ MESA CAC Tools (https://www.mesa-nhlbi.org/Calcium/input.aspx) (77)
7b. CAC score 1 to 99 AU and <75th percentile for age/sex/race/ethnicity indicates that there is subclinical atherosclerosis present. This may be sufficient information to consider initiating statin therapy, especially in younger individuals, but does not indicate substantial reclassification of the 10-y risk estimate. Consider patient preferences and, if statin decision is postponed, consider repeat CAC scoring in 5 y.	2018 Cholesterol Clinical Practice Guidelines (10)	■ MESA CAC Tools (https://www.mesa-nhlbi.org/Calcium/input.aspx) (77)
7c. CAC score 100 AU or ≥75th percentile for age/sex/race/ethnicity indicates that the individual is reclassified to a higher event rate than predicted, that is above the threshold for statin benefit. Statin therapy is more likely to provide benefit for such patients.	2018 Cholesterol Clinical Practice Guidelines (10)	■ MESA CAC Tools (https://www.mesa-nhlbi.org/Calcium/input.aspx) (77)
8. For high-risk patients (10-y risk ≥20%), recommend statin therapy	2018 Cholesterol Clinical Practice Guidelines (10)	…
9. Monitor indicators of response to therapy routinely (LDL-C levels for statin therapy, blood pressure levels for antihypertensive therapy)	2018 Cholesterol Clinical Practice Guidelines (10) 2017 Hypertension Clinical Practice Guidelines (7)	■ ACC LDL-C Manager (https://www.acc.org/LDLCmanager)

Ellipses indicate that no example tool is available.

*Some patients or groups may be at somewhat greater risk for hemorrhagic stroke (especially individuals with uncontrolled hypertension, and some race/ethnic groups), which may influence clinical judgment about the relative merits of preventive therapies such as aspirin, or influence decisions about the choice, intensity and timing of prevention efforts; for example, clinicians may choose to focus on antihypertensive therapy and defer decisions regarding statins and aspirin to a later time in such patients.

ACC indicates American College of Cardiology; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; EHR, electronic health record; LDL-C, low-density lipoprotein-cholesterol; MESA, Multi-Ethnic Study of Atherosclerosis; and TOS, The Obesity Society.

FIGURE 3 Algorithm of Clinical Approach to Incorporate CAC Measurement in Risk Assessment for Borderline- and Intermediate-Risk Patients



*Clinicians and patients may not wish to postpone therapy in patients with a CAC score of 0 and diabetes mellitus, heavy current cigarette smoking, or strong family history of premature ASCVD. Blue shading indicates decision node. %ile indicates percentile; ASCVD, atherosclerotic cardiovascular disease; and CAC, coronary artery calcium.

further discussion. **Table 3** provides guidance, and **Figure 3** provides an algorithm of the clinical workflow to incorporate CAC measurement and interpretation. Those with CAC score of 0 AU appear to have 10-year event rates below the range where statins provide net benefit, suggesting that drug therapy may be less beneficial at present. Those with CAC score of ≥100 AU (or ≥75th percentile for age/sex/race/ethnicity) are reclassified to the extent that they have event rates in a range where statin therapy would be even more clearly beneficial. Posttest risk estimates do not differ substantially from pretest estimates for those with CAC scores of 1 to 99 AU and <75th percentile for age/sex/race/ethnicity, so it is recommended to continue the risk discussion to make a decision regarding the use of drug therapy (32,62,73,74,76,79,80,82,88,89). Patient preference may be particularly important to elicit in this scenario. **Figure 2** presents the CAC score thresholds at which the CAC score meets the 75th percentile for age, sex, and racial/ethnic subgroups (based on data from the MESA study; https://www.mesa-nhlbi.org/Calcium/input.aspx) (77). Further data are needed to refine estimates of the potential benefit of repeat CAC testing in 5 years among those with initial CAC score of 0 AU or 1 to 99 AU, and in diverse age and sociodemographic groups.

FUTURE DIRECTIONS

Quantitative ASCVD risk scores will likely be improved in the future by advances in epidemiology, development of additional large and representative cohorts (especially among Hispanics, East Asians, South Asians and patients >75 years of age), consideration of novel risk markers, and advances in data analysis. Such data should allow for better risk estimation in segments of the population, including underrepresented minority groups and those with social deprivation, and may allow for more targeted risk assessment within diverse racial/ethnic groups. For example, there appear to be differential risks among Hispanic/Latino groups of different heritage. Newer models, such as the Million Hearts Model (now incorporated into the ACC's ASCVD Risk Estimator Plus app) (90) may also allow for longitudinal risk assessment, with updating of predicted risk based on initiation of and response to therapies such as aspirin, statins, antihypertensive therapy, and sustained smoking cessation. Of even greater impact than marginal improvements in risk estimation would be improvements in health systems approaches to implementing ASCVD risk assessment and prevention in practice and developing better tools to facilitate clinician-patient discussions and shared clinical decision-making around prevention.

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AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (COMPREHENSIVE)—USE OF RISK ASSESSMENT TOOLS TO GUIDE DECISION-MAKING IN THE PRIMARY PREVENTION OF ATHEROSCLEROTIC CARDIOVASCULAR DISEASE: A SPECIAL REPORT FROM THE AMERICAN HEART ASSOCIATION AND THE AMERICAN COLLEGE OF CARDIOLOGY (AUGUST 2018)

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