ONLINE EXCLUSIVE

CV risk prediction tools: Imperfect, Yes, but are they serviceable?

CVD risk prediction tools have largely been used to determine the advisability of statin therapy. They might be better used to counsel patients about across-the-board risk factor modification.

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PRACTICE RECOMMENDATIONS

❯ *Avoid the inclination to think that there is 1 best tool for accurately estimating an asymptomatic patient's risk of cardiovascular disease (CVD).* Ⓒ

❯ *Be mindful that 2013 ACC/AHA Pooled Cohort Risk equations can overestimate CVD risk depending on multiple factors, including the population being evaluated (even though the equations might be the most generalizable of available CVD risk calculators).* Ⓒ

❯ *Consider using one of the newer CVD risk markers to further inform treatment recommendations when quantitative risk assessment does not offer information for making a clear treatment decision.* Ⓒ

Strength of recommendation (SOR)

Ⓐ Good-quality patient-oriented evidence

Ⓑ Inconsistent or limited-quality patient-oriented evidence

Ⓒ Consensus, usual practice, opinion, disease-oriented evidence, case series

Prevention of cardiovascular disease (CVD) requires timely identification of people who are at increased risk in order to target effective dietary, lifestyle, or pharmacotherapeutic intervention—or a combination of the 3. Risk factors for CVD are well understood, but the relative impact of each factor on an individual's overall risk is difficult to accurately quantify, making a validated CVD risk calculator an important clinical tool.

Despite numerous available CVD risk calculators, one best tool has yet to emerge. This state of affairs has limited the ability of front-line providers who are tasked with primary prevention of CVD—including family physicians (FPs)—to provide the best evidence-based recommendations to patients.

Implications of CVD risk assessment

Baseline CVD risk assessment is the cornerstone of recommendations for primary prevention of CVD, including aspirin and statin therapy. Interventions to lower CVD risk are of greatest benefit to those at highest risk at initiation of therapy. Overall, statins reduce the risk of a first cardiovascular event in otherwise healthy people by approximately 25% over 10 years.[1] Because relative risk reduction is fairly consistent across different levels of absolute risk, a 25% relative reduction confers more actual benefit if risk starts at, say, 40% than at 10%.[2] In that example, the same 25% reduction in relative risk results in 1) an absolute risk reduction of 10% when risk starts at 40%, compared to an absolute risk reduction of 2.5% when risk starts at 10% and 2) a number needed to treat (NNT) of, respectively, 10 and 40 (over 10 years).

Identifying a person with an elevated risk of developing CVD has multiple implications. Ideally, that patient is moti-

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vated to pursue positive therapeutic lifestyle modifications and make changes that positively affect long-term CVD risk. Conversely, that asymptomatic person identified as at elevated risk also becomes a patient with a medical problem that might adversely affect insurance premiums and self-esteem, and may trigger the use of medications with cost and potential adverse effects. Although the benefit of preventive therapy is greater for a patient at higher risk of disease, the harm of a therapy is relatively constant across all risk groups. Accurately discriminating high and low risk of CVD is, therefore, imperative.

The venerable Framingham risk score

Cardiovascular risk prediction has its roots in the late 1940s, when primary risk factors for CVD were not well-understood, with the inception of the Framingham Heart Study. (A greater understanding of CVD risk today notwithstanding, coronary artery disease [CAD] remains the leading cause of death among American adults.) In the late 1940s, blood pressure (BP) was recognized as the single most useful variable for identifying people at high risk of CVD; other variables were understood to be predictive as well. A composite score—the Framingham Risk Score (FRS)—was thereby developed to calculate the probability that CVD would occur over 8 years in a person who was initially free of such disease.[3]

The original FRS included glucose intolerance and left ventricular hypertrophy (LVH) identified by electrocardiography (EKG) in its algorithm.[3] Other, older algorithms also include a family history of premature CVD. In each risk calculator, these variables are treated as dichotomous (Yes or No), but actual risk associated with each variable is in fact more along a continuum. It is now well-recognized that the sensitivity of EKG for accurately detecting LVH is relatively low; more recent algorithms no longer include this component. A family history of premature CVD variably contributes to an individual's CVD risk; however, its true impact is nearly impossible to accurately quantify, so this variable is also not included in more modern risk calculators.

Caution: The FRS has meaningful limitations

Although the original Framingham cohort has been expanded multiple times since its inception, clinicians and researchers continue to express concern that the predominantly white, middle-class Framingham, Massachusetts, population might not be representative of the United States in general—which would limit the accuracy of the FRS predictive tool when it is applied to a more diverse population. Furthermore, cholesterol-lowering medications were not available when the FRS was first developed. The FRS, therefore, might not accurately estimate risk in more modern populations, in whom aggressive modification of CVD risk factors has resulted in a lower overall rate of atherosclerotic CVD than when the FRS was developed.[4]

Although demographic changes have increasingly led to an extension of primary prevention strategies for CAD to elderly people, the FRS has been demonstrated to perform less well in patients older than 70 years, particularly men.[5] An ideal CAD prediction model for elderly people should take into account that, with growing age and frailty, CAD events may be increasingly preempted by death from competing non-coronary causes. In addition, the predictive association of typical CVD risk factors diminishes with increasing age.[6,7] Koller and colleagues developed a CAD risk prediction model that accounted for death from non-coronary causes and was validated specifically in patients 65 years and older. Koller's prediction model provided well-calibrated risk estimates, but it was still not substantially more accurate than the FRS—illustrating the overall difficulty in predicting CAD risk in elderly people.[8]

Alternative risk calculators have come on the scene

Over the past 2 decades, numerous models have been developed in an attempt to overcome the perceived shortcomings of the FRS. A recent systematic review identified 363 prediction models described in the medical literature prior to July 2013.[9] The usefulness of most models remains unclear, however, owing to:

- methodological shortcomings,
- considerable heterogeneity in the definitions of outcomes, and
- lack of external validation.

Even models that are well-validated for a specific population suffer from lack of applicability to a broad multinational population.

In the United Kingdom (UK), electronic health record systems now have the QRISK2 tool embedded to calculate 10-year CVD risk. This algorithm incorporates multiple traditional and nontraditional risk factors (**TABLE**[10]). With the inclusion of additional risk factors and validation performed in a population similar to the one from which the algorithm was derived, QRISK2 predicts CVD risk in the UK population more accurately than the modified FRS does.[10] It is not clear, however, whether the same algorithm can be applied to the general US population.

New tool: 2013 ACC/AHA pooled cohort risk equations

In the context of multiple imperfect CVD risk-prediction algorithms, the American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Practice Guidelines published the 2013 Pooled Cohort Risk (PCR) equations to predict 10-year risk of a first atherosclerotic CVD event. The Task Force acknowledged concern that the FRS is based on a cohort that might not accurately represent the general US population. Accordingly, PCR equations were developed from 5 large National Institutes of Health (NIH)-funded cohorts: the Framingham Heart Study, the Framingham Offspring Study, the Atherosclerosis Risk in Communities study, the Cardiovascular Health Study, and the Coronary Artery Risk Development in Young Adults Study.

The resulting CVD risk calculator incorporates 4 risk equations: 1 each for African-American and non-Hispanic white males and females.[11] Of note, PCR equations are typically used to estimate 10-year CVD risk, but they can be modified to estimate risk over any period. The associated Guideline on the Assessment of Cardiovascular Risk recommends statin therapy for primary prevention of CVD in patients with a predicted 10-year

risk ≥7.5% and consideration of statin therapy for patients with a predicted 10-year risk between 5% and 7.5%.[12]

In late 2016, the US Preventive Services Task Force (USPSTF) recommended low- to moderate-dosage statin therapy in adults 40 to 75 years of age without a history of CVD but with at least 1 CVD risk factor (dyslipidemia, diabetes, hypertension, or smoking), and a PCR-calculated 10-year CVD risk of ≥10%. For people with a PCR-calculated risk of 7.5% to 10%, the USPSTF recommended that clinicians "selectively offer" low- to moderate-dosage statin therapy, noting a smaller likelihood of benefit and uncertainty in an individual's risk prediction.[13]

Pooled cohort risk equations have predictive validity

Estimates are that nearly 50% of US adults and as many as 65% of European adults would be candidates for statin therapy if, using PCR equations, the 2013 ACC/AHA guidelines were broadly applied.[14] Since PCR equations were released, multiple groups have attempted to evaluate the predictive validity of the algorithm in various populations, with mixed findings.

Data from the 1999-2010 NHANES—the National Health and Nutrition Examination Survey—were used to calculate estimated CVD risk for patients free of atherosclerotic CVD at baseline. Risk prediction using PCR equations was compared to true all-cause and CVD mortality using the National Center for Health Statistics National Death Index. In this large, US adult population without CVD at baseline, PCR-estimated CVD risk was significantly associated with all-cause and CVD-specific mortality risk.[15]

In a community-based primary prevention cohort, 39% of participants were found statin-eligible—ie, they had an estimated 10-year CVD risk ≥7.5%—by ACC/AHA guidelines, compared with 14% found statin-eligible by the guidelines of the National Cholesterol Education Program's 2004 updated "Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III)." Despite the larger percentage, participants who were statin-eligible by ACC/AHA guidelines

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TABLE

Examples of variables considered in the QRISK2 calculation of 10-year CVD risk[10]

Age	Renal disease
Atrial fibrillation	Rheumatoid arthritis
Body mass index	Self-assigned ethnicity
Family history of coronary artery disease in a first-degree relative younger than 60 years	Sex
	Smoking status
Hypertension (treated)	Systolic blood pressure
Ratio of total cholesterol to high-density lipoprotein	Townsend deprivation index*
	Type 2 diabetes

*Relative lack of economic resources within a population; typically, based on census-derived data that are linked to postal code.

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had an increased hazard ratio for incident CVD compared with those who were statin-eligible by ATP III; investigators concluded that ACC/AHA guidelines using PCR equations were associated with greater accuracy and efficiency in identifying increased risk of incident CVD.[16]

Pooled cohort risk equations might overestimate CVD risk

In contrast, a more recent study followed a large, integrated US health-care delivery system population over 5 years, starting in 2008.[17] In this group of adults without diabetes, PCR equations substantially overestimated actual 5-year risk of CVD in both sexes and across multiple socioeconomic strata. Similar overestimation of CVD risk was demonstrated in non-Hispanic white, non-Hispanic black, Asian/Pacific Islander, and Hispanic subjects. The latter 2 ethnic groups are considered "white or other" in the atherosclerotic CVD risk equation, raising additional concern that PCR equations may not be accurate for broad, multiethnic application.[17] The ACC/AHA Cardiovascular Risk Assessment guideline recognizes this concern, as well, noting that PCR equations may overestimate risk for Hispanic and Asian Americans.[12]

Predicted 10-year CVD risk using PCR equations was compared with observed event rates in 3 large-scale primary prevention cohorts: the Women's Health Study, the Physicians' Health Study, and the Women's Health Initiative Observational Study.[18] In each cohort, the ACC/AHA risk prediction algorithm overestimated observed risk by 75% to 150%. The authors concluded that 40% to 50% of the 33 million middle-aged Americans deemed statin-eligible by ACC/AHA guidelines may not have actual CVD risk that exceeds the 7.5% threshold recommended for statin treatment.[18]

Therefore, the discrimination of PCR equations—their ability to differentiate between individuals who are more or less likely to develop clinical CVD—is good. The calibration of the equations—the difference between predicted and observed risk—is not as good, however: PCR equations appear to overestimate actual risk in many groups.[15]

Additional limitations to pooled cohort risk equations

The predictive value of PCR equations is hampered by several factors:

- Despite expansion of the studied cohorts beyond the original Framingham population, the groups still include people screened for study participation or enrolled in clinical trials. The generalizability of this study population to the diverse population treated in a typical clinical practice is, potentially, limited.
- Use of strategies for primary prevention of CVD (eg, statin therapy, antiplatelet therapy, BP control, blood glucose control) continues to increase. Lowering the risk of CVD in the

general population with a broad primary prevention approach effectively widens the gap between observed and equation-predicted CVD risk—and thus strengthens the impression of overestimation of risk by PCR equations.

- Lack of comprehensive surveillance in some studies may result in underassessment of CVD events. In this case, PCR equations would, again, appear to overestimate risk.[19]

Novel tools are available; their use is qualified

First, newer risk markers offer additional options for improving risk prediction offered by the ACC/AHA PCR equations: Coronary artery calcium, ankle-brachial index, high-sensitivity C-reactive protein, and a family history of CAD are all independently associated with incident CAD. ACC/AHA guidelines suggest that assessment of 1 or more of these variables might be considered an adjunct when risk assessment using PCR equations alone does not offer information for making a clear treatment decision.[12]

Of the 4 risk markers, coronary artery calcium provides the most significant increase in discrimination compared to the FRS alone; comparative data using PCR equations is unavailable.[20] ACC/AHA guidelines specifically recommend against routine measurement of carotid intima-media thickness for assessment of risk of a first atherosclerotic event.[12]

Second, a revised set of PCR equations offers improved discrimination and calibration compared to the 2013 PCR equations. A National Institutes of Health (NIH)-sponsored group updated the equations' cohort by 1) eliminating the original Framingham Heart Study (FHS) data, which was first collected in 1948, and 2) adding data from the Jackson Heart Study and the Multi-Ethnic Study of Atherosclerosis (MESA). Both new cohorts include patient data from 2000 to 2012. Additionally, the NIH group modified the statistical methods used to derive PCR equations. Although these revised PCR equations offer a substantially more accurate estimate of CVD risk, they have not yet been validated for routine clinical use.[21]

Bottom line: In prediction there persists imperfection

It is widely held that CVD risk prediction, with subsequent treatment to reduce identified risk, is an important component of an overall strategy to reduce the burden of CVD. Cardiovascular risk factors, such as BP and lipid values, do show limited improvement among populations in which systematic screening is practiced, but the true impact of systematic CVD risk assessment alone for healthy people has yet to be demonstrated in terms of hard clinical outcomes.[22]

CVD risk prediction is most widely used to inform recommendations for statin treatment. However, ACC/AHA PCR equations might substantially overestimate CVD risk and lead to expanded use of statins in patient populations for which such treatment has less potential benefit. Nonetheless, PCR equations do offer good discrimination between higher-risk and lower-risk people.

CVD risk prediction remains an imperfect science—science that is best used as an adjunct to discussion of comprehensive CVD risk factor modification with the individual patient. **JFP**

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