Identifying individuals at risk for developing coronary heart disease (CHD) is fundamental to the practice of primary prevention in modern cardiology because it enables clinicians to determine which patients are eligible to receive evidence-based therapies that can prevent or delay the progression of atherosclerotic disease. Several multivariable risk-prediction algorithms are available, and the most widely used in the US is the Framingham cardiovascular disease (CVD) risk profile, from which the Framingham Risk Score (FRS) is derived.

The FRS estimates an individual’s risk of developing nonfatal myocardial infarction or CHD-related death (“hard events”) over a 10-year period, on the basis of what are now considered to be the traditional risk factors of age, total cholesterol concentrations, HDL cholesterol, systolic blood pressure, and cigarette smoking status; the equations are sex specific. Individuals are then stratified into low risk (<10% risk over 10 years), intermediate risk (10% to 20% risk over 10 years), or high-risk (≥20% risk over 10 years) based on their score, and this risk score then guides a clinician’s decision to institute antiplatelet or lipid-lowering therapy or advise intensive lifestyle modification. Several multivariate risk assessment algorithms in addition to the FRS have since been proposed and validated in diverse populations to estimate risk for a period of less than 10 years.

The FRS has been critiqued for its relatively limited view of only a 10-year timeframe, because an individual’s lifetime risk of CHD may be high, but a 10-year risk prediction model sometimes underestimates this risk and can delay efforts to modify that risk. A greater duration of exposure to untreated risk factors allows for continued progression of subclinical atherosclerosis. Examination of the Framingham cohort showed that despite younger individuals in lower risk groups having a very low 10-year CHD risk, they still had a substantial lifetime risk for CHD; 10-year prediction models thus may underestimate disease risk in younger individuals, especially in women in whom stroke is much more common as the initial presentation of cardiovascular disease. The FRS also does not take into account family history of premature CVD, triglycerides, or glucose intolerance.

In the June 2009 issue of Circulation Michael Pencina and colleagues proposed a new tool for estimating the 30-year risk of hard CVD events in individuals free of CVD at baseline. The algorithm is based on 4506 individuals enrolled in 1971 from the Framingham Offspring cohort, who are the children of the original Framingham Heart Study cohort and their spouses. Participants were followed for a maximum of 35 years (median 32 years) and the primary outcome was hard CVD, defined as the composite of hard CHD (coronary death, myocardial infarction) and fatal and nonfatal stroke.

The secondary outcome was “full” CVD (defined as hard CHD plus coronary insufficiency, angina pectoris, stroke plus transient ischemic attack, intermittent claudication, and congestive heart failure). A 5-fold cross-validation was used to account for the fact that the model was evaluated on the same data on which it was developed, and additional internal validation was assessed by randomly developing the function in the first two-thirds of the cohort and evaluating its performance in the remaining third. The competing risk of noncardiovascular causes of mortality was factored into the equation.

As with the traditional FRS, standard CVD risk factors (male sex, age, systolic blood pressure, antihypertensive treatment, total and HDL cholesterol, smoking, and diabetes mellitus) remained highly significant as predictors of CVD over a 30-year period; diastolic blood pressure and triglycerides were not statistically significant, and exchanging LDL in place of total cholesterol did not significantly improve the model’s performance. Body mass index was only weakly significant and was not included in the main risk prediction model, but was used to replace lipids in
a simplified office-based risk model and was highly significant \((P \leq 0.01)\).

A striking finding was the comparison of the 30-year risk of hard CVD with 10-year risks in younger individuals; in their example among 25-year old individuals, especially among women. Although a 10-year model may suggest negligible risk levels \((<5\%\)) of these 30-year models give estimates that are almost 10 times higher. The greater the number of risk factors, the more marked the difference in the 10-year risk vs the 30-year risk profile, suggesting that there is a magnification of the long-term consequence of untreated risk factors acting in concert.

This finding alone has important implications for treatment decisions for the 25-year old female smoker with hypertension and dyslipidemia who would likely remain untreated for many decades until her age, which is weighted heavily in the 10-year prediction models, would reclassify her into the intermediate range. Delayed treatment of this patient would especially be unfortunate if this person has a family history of premature CVD or multiple components of the metabolic syndrome. Thus these findings argue that we must redouble prevention efforts at a young age in individuals with multiple risk factors, in whom unmitigated risks allow for continued atherosclerotic disease progression.

The 30-year risk model has several advantages. It has the potential to be a powerful motivator for clinicians and patients alike. Young patients hearing that they have a 1 in 4 chance of having a heart attack or stroke over 30 years rather than a 1 in 40 chance over 10 years may strengthen their resolve to heed lifestyle modification recommendations. The tool also requires only input that is easily obtained in the office setting without the need for costly tests or exposure to ionizing radiation. It is hoped that the authors will provide an online version of their risk calculator for those providers without subscription and access to Circulation, or a simplified paper calculator that assigns a score, thus facilitating more widespread use and recognition of this risk-assessment method.

The long-term prediction model remains plagued by the same issues as the 10-year model. As the original FRS was limited by its study in a predominantly white, middle-income cohort, so too is the 30-year risk calculator, which limits its generalizability to populations with more ethnic and economic diversity. The 30-year model also does not include family history of premature coronary disease as a risk factor, but this is a well-established risk factor for the development of coronary disease \((4)\).

Because the baseline variables were collected in the 1970s, newer biomarkers of CVD had not yet been evaluated and could potentially add to the tool’s predictive power. The landmark Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) \((5)\) trial demonstrated that including high-sensitivity C-reactive protein testing and treating high-risk asymptomatic individuals \([defined as high-sensitivity C-reactive protein >2.0 mg/L but normal LDL concentrations <3.36 mmol/L (130 mg/dL)]\) decreased incident CVD by 44\% and all-cause mortality by 20\%. Furthermore, noninvasive imaging techniques, such as coronary computed tomography, carotid intima media thickness measurement, and cardiac MRI have yet to be incorporated into risk assessment tools, yet with their ability to detect subclinical atherosclerosis, these techniques could add significant prognostic weight to risk assessment algorithms. The detection of subclinical atherosclerosis that is advanced for age in a 45-year old patient with a family history of premature CVD may not lead to a clinically significant cardiovascular event over a 10-year period, but portends a significant lifetime risk.

The 30-year prediction tool proposed by Pencina et al. now provides clinicians with a tool to assess longer-term risk of CVD and may lead to the introduction of earlier prevention strategies in asymptomatic individuals. The availability of a longer-term risk prediction algorithm does not answer the question of whether and when to treat younger asymptomatic individuals. The focus of the shorter-term prediction tools is a presumed direct benefit to individuals in the short run, whereas lifetime risk carries broader implications for public health and the need for the individual to adopt lifestyle changes to lower risk in the long run \((6)\). It remains to be seen whether the use of the algorithm will translate into an increase in the number of younger individuals receiving aspirin and lipid-lowering therapies vs a more aggressive lifestyle modification approach owing to clinician’s unease with prescribing medications to asymptomatic, seemingly healthy individuals.

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References


