

Fixing the Prevention Gap Using Imaging-Guided Risk Estimates



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For nearly 2 decades, coronary artery calcium (CAC) has been considered a vital component of screening programs, with abundant prognostic evidence supporting its utility for an accurate long-term prediction of all-cause mortality, stroke, coronary artery disease, and many other clinical outcomes (1). In comparative analysis, CAC uniformly outperforms other traditional as well as nontraditional biomarkers, including high-sensitivity C-reactive protein (2). Despite the multitude of peer-reviewed papers on CAC, current guidelines rely on global risk scores alone to determine treatment eligibility for cholesterol management (3). In fact, the American College of Cardiology (ACC) and American Heart Association (AHA) revised clinical practice guidelines for cholesterol treatment identify patients eligible for statin therapy on the basis of a pooled cohort equation (PCE), derived using population registries enrolling from 1968 to 1990 (e.g., the Framingham study cohorts, the ARIC [Atherosclerosis Risk in Communities] study, the CHS [Cardiovascular Health Study], and the CARDIA [Coronary Artery Risk Development in Young Adults] study). The PCE is notable for expanding prior endpoint risk estimates to include stroke as also predictive estimates for black Americans (3). Using the PCE, statin therapy is indicated for patients 40 to 75 years of age who have risk scores $\geq 7.5\%$ and low-density lipoprotein cholesterol levels of 70 to 189 mg/dl (3). The use of the PCE to guide statin therapy use has been criticized for overestimation of atherosclerotic

cardiovascular disease (ASCVD) risk (4). In fact, a recent report from the National Institutes of Health-sponsored MESA (Multi-Ethnic Study of Atherosclerosis) calculated $>90\%$ discordance between observed and predicted PCE risk estimates (5). Moreover, a recent review by Cook and Ridker (4) revealed that the PCE has been externally validated in 15 contemporary cohorts and reported that the average risk overestimation was between 60% and 90%.

In this issue of *iJACC*, Mahabadi et al. (6) report that more than one-half of enrollees in the Heinz-Nixdorf Recall cohort met indications for statin therapy on the basis of the ACC/AHA clinical practice guideline for cholesterol treatment (3). Similar analyses have been published by Blaha et al. (7) and Nasir et al. (8). In the present report, among patients with statin indications, nearly 19% and 40% had CAC scores of 0 and 1 to 99. Similar findings were reported when applying the European Society of Cardiology risk categories. Among those with statin indications but with CAC scores <100 , the 10-year observed ASCVD risk estimate was less than one-half that of patients with CAC scores ≥ 100 (7.0% vs. 14.4%). A potential recommended management strategy on the basis of a PCE plus CAC scoring would eliminate uniform statin use for nearly two-thirds of the eligible cohort with CAC scores <100 . By targeting higher risk patients with CAC scores ≥ 100 , the number needed to treat was markedly reduced to 19 to 23, depending on the guideline applied. These results support prior findings of the imprecision of the PCE and that risk is variable among those with statin indications.

This report extends prior work that PCE risk overestimation leads to overtreatment with statin therapy. But in this case, the Heinz Nixdorf investigators suggest that the premise of risk-guided

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care to influence risk reduction is flawed on the basis of the PCE. Moreover, it also suggests that the incorporation of novel biomarkers, as recently suggested by Cook and Ridker (4), remains a vital means to refine risk strata to improve precision in guided treatment strategies. Additionally, the finding of Mahabadi et al. (6) is 1 of more than a dozen reports that misguided risk estimates have dramatic implications for population management. Findings such as these further contribute to the controversies and limitations of the PCE. There are several solutions, including a recalibration of the PCE risk estimates, for which data were collected from the 1960 through the 1980s, using contemporary cohorts, but this will remain an open-ended strategy that necessitates continuous recalibration with changes in population risk and emerging data. In the meantime, a more practical strategy might be to consider including novel biomarkers to improve risk reclassification (4). One could even argue that these kinds of data provide clues that, if a randomized trial was performed, the PCE-alone strategy would fail compared with PCE plus CAC scoring (or some other effective biomarker discovered in the future). Improved refinement in risk estimation can avert the overtreatment that hinders the PCE, reduce treatment side effects (e.g., higher rates of diabetes), and improve patient satisfaction and adherence to preventive care. Clinical trial data are available demonstrating that CAC assessment improves adherence to preventive therapies and life-style-modifying behaviors (9-12).

The PCE was devised using decades-old data from when atherosclerotic cardiovascular risk was more prevalent. Today, secular shifts in risk factor prevalence have resulted in marked reductions in morbidity and fatal outcomes related to ASCVD risk, possibly rendering the PCE somewhat outdated (13). Recent

technology evaluations, including that of the U.S. Preventive Services Task Force, have long held screening to a high standard of improved clinical outcomes based on randomized clinical trial evidence. Without such data, technology assessments rely on the status quo or, in this case, the PCE. However, the inaccuracies of the PCE are common to other global risk scores and reflect the indirect association of risk factors with atherosclerotic disease. The benefit of global risk scores lies in their ability to aggregate risk across diverse risk factor patterns and measurements but not in risk precision. Therefore, it is time to strongly consider offering patients a more refined approach to targeting risk factor management on the basis of the precise hazard for cardiovascular events using novel biomarkers, such as CAC scoring (14). Novel systemic or imaging biomarkers, such as CAC, provide direct visualization of atherosclerotic disease, and an improvement in risk detection is expected. Given this direct association between imaging atherosclerosis and disease-specific risk, it may be postulated that targeting patients with disease would improve the therapeutic risk reduction on the basis of a higher relative hazard and greater pool of at-risk patients. On the basis of substantive evidence that the PCE remains ineffective at stratifying risk with lingering subsets of diverse low to high relative hazards for future ASCVD risk, it remains time for a serious discussion of the need for supplemental imaging strategies to improve targeted preventive therapies.

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