EDITORIAL

Combining Biomarkers and Imaging for Short-Term Assessment of Cardiovascular Disease Risk in Apparently Healthy Adults: A Paradigm-Shifting Approach?

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Cardiovascular disease (CVD) risk prediction remains a critical part of CVD prevention, with several strategies being explored among apparently healthy adults. To facilitate shared patient-physician decision making on initiation of preventive therapies, the American Heart Association and the American College of Cardiology recommend the screening of traditional atherosclerotic CVD (ASCVD) risk factors and application of the race- and sex-specific pooled cohort equations to estimate 10-year risk for asymptomatic adults, aged 40 to 75 years.[1] As stipulated in the guidelines, no single risk calculator is appropriate for all patients, acknowledging that in certain populations, the pooled cohort equation has reasonable calibration but may underestimate or overestimate risk among other populations. In addition, for adults aged 20 to 39 years and those aged 40 to 59 years who are not at elevated (≥7.5%) 10-year risk, a lifetime or 30-year risk of ASCVD may be considered.[1]

See Article by Gore et al.

Long-term risk estimation (≥10 years) is important in decision making on initiation of preventive therapy, but short-term CVD risk prediction (ie, <5 years) is equally relevant to guide evaluation of healthy individuals in critical or high-risk occupations, such as astronauts and aircrew, for whom short-term evaluations may be warranted to maintain flight safety and prevent critical incapacitation or fatalities.[2] Several risk assessment strategies have been considered in this subgroup, but short-term risk assessment has not been extensively studied. However, a critical requirement before adopting a short-term risk prediction model is proof that it is comprehensive, contemporary, generalizable, and cost-effective, and provides meaningful clinical guidance to reinforce adherence to lifestyle recommendations among seemingly healthy adults.

In this issue of the *Journal of the American Heart Association* (*JAHA*), Gore et al[3] evaluate a novel approach that combines biomarkers (NT-proBNP [N-terminal pro-B-type natriuretic peptide]; high-sensitivity cardiac troponin T; and hs-CRP [high-sensitivity C-reactive protein]) and imaging (carotid intimal-medial thickness; plaque; and coronary artery calcium [CAC]) for short-term (3-year) assessment of CVD risk in apparently healthy adults. Pooling data from the ARIC (Atherosclerosis Risk in Communities) study, the MESA (Multi-Ethnic Study of Atherosclerosis), and the DHS (Dallas Heart Study), the authors studied 16 581 participants free of CVD at baseline. The mean age of the pooled cohort was 57.3±10 years, 55.7% were women, and 25.7% were black. Over the 3-year follow-up period, incident global CVD (composite of cardiovascular death, myocardial infarction, stroke, coronary revascularization, incident heart failure, or atrial fibrillation) was observed in 3.3% of the pooled cohort (553 events)

and incident ASCVD (fatal or nonfatal myocardial infarction or stroke) was observed in 1.6% of the pooled cohort (260 events). The authors report that abnormal biomarker and imaging markers were each associated with the primary outcome of global CVD after adjustment for traditional CVD risk factors and body mass index. A simple integer score that incorporates the number of abnormal tests of the 4 biomarkers (hs-CRP, NT-proBNP, high-sensitivity cardiac troponin T, and the composite imaging marker) showed that participants with integer scores of 1, 2, 3, and 4 had ≈2-, 3-, 4.5-, and 8-fold increased global CVD risk, respectively, compared with those with a score of 0, with similar results observed for ASCVD.

Short-term CVD risk prediction may prove useful in evaluating healthy individuals in critical occupations, such as astronauts before prolonged space flight, airline pilots, and certain active-duty military personnel.[3] A question of interest is, what is the clinical utility of short-term CVD risk assessment beyond this small, select population? One may argue that it is important for explaining imminent CVD risk to individuals and fostering adoption of healthy lifestyle changes. However, is there any incremental benefit of short-term CVD risk assessment compared with long-term risk assessment in decision making on the initiation of preventive therapies? The authors suggest that a serial short-term assessment of risk in the same individual may provide a time-updated risk profile. However, this may not be a cost-effective approach compared with long-term risk assessment, considering the multiplicity of screening parameters at each short-term risk assessment visit.

Alternatively, short-term CVD risk assessment may be relevant in uniquely communicating risk among young adults and older adults for whom pooled cohort equation–based risk assessment may not be applicable. However, young adults experience few short-term events. Older individuals have more events. Over a follow-up period of ≈4 years, Saeed et al demonstrated that the addition of biomarkers (NT-proBNP, high-sensitivity cardiac troponin T, and hs-CRP) to the pooled cohort equation improved short-term global CVD (defined as composite of incident coronary heart disease, incident stroke, and incident heart failure hospitalization) risk prediction, which may be relevant in decision making on preventive therapies in older adults (aged 75.4±5.1 years).[4] Whether this model behaves fundamentally differently or better than standard 10-year assessment, however, remains unclear.

The integer score developed by Gore et al[3] that incorporates abnormal tests of the 4 biomarkers is a simple approach that could be useful for clinical evaluations during office visits. However, like any risk score, a concern with its use among individuals in high-risk professions is the translation of its utility from population-level data to an individualized risk

assessment tool that could affect life-changing decisions. In addition, a challenge with this integer scoring system is artificial dichotomization of rich continuous risk factor data and the inability to disentangle the *severity* of abnormal test and how it affects the prediction of global CVD and ASCVD. A scoring system that discriminates extreme biomarker values may have added benefit in guiding intensity of preventive therapies after risk assessment.

Furthermore, the integer score applied a similar weight to the various biomarkers evaluated in the study. Thresholds for defining abnormal biomarkers were a priori selected at hs-CRP ≥3 mg/L, NT-proBNP ≥100 ng/L, and high-sensitivity cardiac troponin T ≥5 ng/L. Abnormal carotid ultrasound was defined as the presence of either carotid plaque or intimal medial thickness ≥75th percentile for age and sex.[3] The threshold for positive CAC was defined as Agatston score >10. The hs-CRP does reclassify 10-year risk on the basis of the pooled cohort equation but not nearly as well as the CAC score.[5] This and many other examples from comparative studies support the argument that a scoring system that assigns different weights to the various biomarkers may perform better, as noted by the authors in the study limitations.[6]

CAC scoring is currently guideline endorsed for shared clinical decision making on preventive therapy allocation in asymptomatic 40- to 75-year-old individuals with 5% to 20% 10-year ASCVD risk. In such individuals, those with CAC ≥100 Agatston Units or CAC ≥75th percentile have ASCVD event rates that may warrant initiation of statins.[1] In addition, those with CAC=0 may derive limited value from statin therapy because of lower 10-year event rates.[1] Therefore, would an alternative initial consideration be to classify participants on the basis of CAC score and its severity (rather than just the cut point of CAC=10), and further reclassify participants according to the other biomarkers examined? In sensitivity analyses in a subset of participants with baseline CAC=0 or normal carotid intima-media thickness, higher integer scores, on the basis of plasma biomarkers, were still significantly associated with higher short-term global CVD risk after adjustment for traditional CVD risk factors.[3] However, the clinical significance of this in an already low short-term risk group is unclear.

The authors further show that despite the different measurement of subclinical atherosclerosis among different cohorts in the study, stratified analyses showed that carotid measurements in the ARIC study had comparable prognostic utility as CAC in DHS and MESA. However, Mortensen et al showed that carotid imaging did not reclassify risk as well as CAC scores.[7] CAC and carotid plaques have different clinical utility. CAC may be optimal in predicting coronary heart disease events compared with carotid plaque, which may

better predict stroke events.[8] In the BioImage study, Mortensen et al showed that CAC was superior to carotid plaque burden in predicting both coronary heart disease events alone and combined ASCVD.[7] Thus, the outcome of a short-term risk assessment model is critical to consider if it is to change clinical decision making: here a global composite outcome makes targeted preventive therapies less straightforward.

In shaping the future of risk prediction, is there a role for serial short-term risk assessments in providing a risk profile that may be relevant for *precision* CVD prevention strategies, as suggested by the authors? Precision medicine appears conceptually important in identifying optimal interventions that are patient specific.[9] As it relies on novel approaches of phenotyping patients, it may be important in truly novel selection of optimal preventive therapies and in revolutionizing cardiovascular care. Combined biomarkers and imaging strategies, as described in this article, are a start, but fundamental disruption is needed. Perhaps the future will bring these tests coupled with measures of vital sign and risk factor variability as well as advanced panomics, including genomic studies that may provide another paradigm in precision CVD prevention.

In conclusion, as the field of CVD risk assessment evolves, and several strategies, ranging from short- to long-term risk prediction models, are being explored, it is important to adopt approaches that improve patient-physician communication, are easy to comprehend, and foster compliance with lifestyle modifications and preventive therapies.[10] Short-term risk assessment that combines biomarkers and imaging is a step forward in the assessment of healthy adults who are involved in high-risk occupations, like astronauts going on space missions. However, it is important to validate these risk prediction models in other external cohorts, confirm their true additive value over 10-year models, and consider utility among populations for whom traditional risk prediction models may not be applicable.

ARTICLE INFORMATION

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