Editorial

Cardiovascular risk prediction in older adults with the use of biomarkers

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Estimation of cardiovascular disease (CVD) risk is of paramount importance for the design of primary prevention strategies. Several multivariate risk models have been developed for CVD risk calculation in asymptomatic adults based upon assessment of multiple variables that cause a graded increase in risk. In the United States, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines introduced a 10-year CVD risk prediction equation based on adults aged 40 to 79 years old from several cohorts [Atherosclerosis Risk in Communities (ARIC), Cardiovascular Health Study (CHS), Coronary Artery Risk Development in Young Adults (CARDIA), Framingham Original and Offspring cohort] that assesses hard endpoints (fatal and nonfatal MI and stroke) and is utilized to guide initiation of cholesterol-lowering and antihypertensive therapy (1,2). The pooled cohort equation (PCE) has been calibrated in some (3) but not all ethnic cohorts (4). The estimation of CVD risk with the PCE is not without limitations. The equation overestimates the 10-year risk for CVD by an average of 20% across all risk groups (3-7), does not have substantially improved discrimination and calibration compared with prior risk models (5), and does not include other important outcomes such as heart failure (HF). Age remains a major determinant of risk in the PCE, and it has been estimated that among individuals with optimal risk factors, a 10-year CVD risk ≥7.5%, which is an indication for statins according to the ACC/AHA guidelines (1), was reached by 65 and 70 years of age in white and African-American males and 75 and 70 years of age in white and African-American females respectively, with optimal risk factors (8). However, PCE is not validated and is inadequate for risk prediction of individuals over age 80. As life expectancy increases, the population of adults over the age 75 with CVD risk factors will expand further and the prevalence of CVD will remain high as ~two thirds of CVD events occur in this age group (9). Among elderly adults, the association between traditional risk factors and CVD risk is attenuated and other age-related comorbid conditions compete with traditional risk factors and should be taken into consideration (10). Also, it's important to note that chronologic age may not be sufficient to determine CVD risk and other parameters such as frailty and functional status should be considered in primary prevention strategies.

In this context, the study by Saeed and colleagues has attempted to fill this gap in the literature, in their article published in the *Journal of American College of Cardiology* (11), utilizing data on individuals aged between 69 and 88 years from the ARIC cohort who participated in ARIC visit 5, conducted between June, 2011, and August, 2013. The purpose of this study was to evaluate short-term CVD event risk including risk for HF hospitalization in older adults with the addition of three biomarkers [N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity cardiac troponin T (hs-cTnT), and high-sensitivity C-reactive protein (hs-CRP)] that were measured once during visit 5. The study population consisted of 4,760 adults with mean age of

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75 years, with the majority being females (62.3%), already treated with antihypertensive and/or cholesterol-lowering medications. Incident HF hospitalizations were the most frequent events (n=193) followed by atherosclerotic CVD events (ASCVD) [fatal and non-fatal myocardial infarction (MI) and stroke] (n=195). hscTnT and NT-proBNP were more robustly associated with outcome, whereas hs-CRP showed was not associated with incident stroke. The addition of each biomarker to PCE increased c-statistic and NT-proBNP improved discrimination the most compared with the other two biomarkers. The complete model of PCE and the three measured biomarkers resulted in the most significant improvement in discrimination and risk classification (measured by C-statistic, category-free net reclassification index, and integrated discrimination index) with delta c-statistic of 0.103. The use of PCE in this cohort, overestimated the risk in low-risk individuals and underestimated the risk in high-risk individuals. The addition of biomarkers to the model improved risk assessment in the high-risk category. Although in aggregate, the findings support the use of widely available biomarkers for risk prediction in older adults, a few limitations need to be acknowledged. The study lacks validation cohort and the biomarkers were measured once in a population with individuals already on preventive strategies. HF events were more frequent than fatal and non-fatal Mis and strokes, hence NT-proBNP and hscTnT improved discrimination and re-classification of PCE. Finally, the risk model was derived from a 4-year follow-up and therefore it cannot be directly compared with the 10-year CVD risk derived from the PCE. Whether a combined risk factor and biomarker model can effectively estimate CVD risk and guide initiation of preventive therapies in elderly, is a hypothesis that requires validation in prospective studies.

The likelihood of less precise PCE-based risk estimation in certain population groups is recognized and the guidelines acknowledge the need for additional biomarker evaluation such as hsCRP ≥2.0 mg/L, coronary artery calcium score ≥300 Agatston units, and ankle-brachial index <0.9 in intermediate risk patients (ASCVD risk score of 5% to <7.5%), in whom cholesterol-lowering therapy is not clearly indicated based on PCE (1). Our group has previously identified 5 biochemical risk markers—hsCRP, homocysteine, albuminuria, NT-proBNP, and troponin T—that predicted 10-year incidence of atherosclerotic CVD risk independent of traditional risk factors included in the PCE, in a multiethnic cohort of healthy adults at baseline (12). We developed an aggregate biomarker score (hs-CRP, Homocysteine and Albuminuria: 1 point, NT-pro BNP: 2 points, Troponin T: 3 points) that improved discrimination and risk classification of PCE and could guide decisions about initiation of cholesterol-lowering therapy. The findings of Saeed and colleagues in conjunction with the results of previous studies on the associations between CVD and commonly available biomarkers, highlight the interplay of metabolic, inflammatory, myocardial and renal pathways in the pathogenesis of CVD.

Although areas of uncertainty in the CVD risk prediction in the elderly remain, the results of the studies described above have important implications. Decision making about initiation of preventive strategies in older adults who are not on cholesterol-lowering or antihypertensive therapy, should not rely only on multivariate risk models of traditional risk factors. Assessment of frailty, socioeconomic and functional status and measurement of widely available biomarkers can affect the risk-benefit ratio of preventive therapies and their utilization in older adults should be validated in randomized, controlled trials.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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