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Multiple Biomarker Panels for Cardiovascular Risk Assessment

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Guidelines for the assessment of cardiovascular risk remain focused squarely on established risk factors. Although it is known that tools based on these risk factors, such as the Framingham Risk Score, have a number of limitations when applied in clinical practice — performing reasonably well for groups but not necessarily for individuals and underestimating long-term risk among younger persons — it has proved surprisingly difficult to improve on established risk factors for the prediction of cardiovascular disease. Of the many strategies that have been proposed to improve risk stratification, the measurement of plasma biomarkers is particularly attractive as compared with alternatives such as cardiovascular imaging.

Numerous biomarkers have been proposed to have mechanistically plausible links to clinical cardiovascular disease, with many reported to identify people at an increased risk for future cardiovascular events independently of the presence of established risk factors. Typically, however, the risk increment captured by elevated levels of these markers is modest, and little improvement is seen in traditional measures of discrimination such as the C statistic or the area under the receiver-operating-characteristic curve. Much of the recent debate over emerging biomarkers focuses on the questions of how much incremental value is provided and what the best metrics are to quantify improvements in screening performance.

One strategy that has been proposed to improve on the limitations of individual biomarkers is to combine multiple biomarkers into an integrated score or algorithm. However, an evaluation of 3209 participants from the Framingham Heart Study failed to validate this approach. Although persons with high biomarker scores had an increased risk of death as compared with those with low scores, the increment in the C statistic over the model with traditional risk factors was small. Similarly, in the Cardiovascular Health Study, which included 5808 older Americans, the addition of six novel biomarkers did not improve discrimination beyond established risk factors among subjects with or without chronic kidney disease. Thus, despite decades of research and the introduction of numerous candidate biomarkers and putative risk factors, risk prediction for cardiovascular disease in the population appears to have progressed only marginally.

An article in this issue of the Journal suggests that measurable progress with the use of biomarkers could be possible. Zethelius et al. report data from an evaluation of multiple biomarkers in a community cohort of elderly men. Among 1135 men with a mean age of 71 years at study entry (661 of whom were free of cardiovascular...
disease at baseline), troponin I, N-terminal pro–brain natriuretic peptide, cystatin C, and C-reactive protein were each associated with death from cardiovascular and all causes over a 10-year follow-up period after adjustment for established cardiac risk factors. When the markers were combined, the risk of death increased by a factor of more than 16 across categories that were defined by the number of biomarkers that were above prespecified threshold values, after adjustment for risk factors. It is particularly notable, given the advanced age of the study cohort, that only 26 deaths from cardiovascular causes occurred over 10 years among the 486 men who did not have an elevation in any of the biomarkers. The C statistic increased from 0.66 for the risk factor model alone to 0.77 when the four biomarkers were added and from 0.69 to 0.75, in the subgroup that was free of cardiovascular disease at baseline. Statistical measures of model calibration, risk reclassification, and global fit all supported the incremental value of the multiple biomarkers over established risk factors.

Why are the results of this study so strikingly different from those of previous studies? First, the biomarkers that were evaluated in the current study were better than those that were measured in previous studies. The authors included three markers that clearly reflect existing cardiac or renal damage. Cystatin C has emerged as a more accurate estimator of glomerular filtration rate than serum creatinine and demonstrates a linear association with cardiovascular disease. In population studies, N-terminal pro–brain natriuretic peptide is associated with multiple pathological cardiovascular phenotypes and predicts the risk of death and cardiac events. Perhaps the most intriguing marker included is troponin I, a marker of myocardial injury that is not intuitively attractive for population screening because of the low prevalence of elevated levels among healthy people. However, when detected in the general population, troponins are strongly associated with cardiac abnormalities such as left ventricular hypertrophy or systolic dysfunction and major risk factors such as renal insufficiency and diabetes. Troponins are highly specific for myocardial damage, and although current assays offer suboptimal sensitivity for population screening, sensitivity may be augmented by combining troponin with other biomarkers and will be further enhanced with the introduction of high-sensitivity troponin assays. In the present study, troponin I and N-terminal pro–brain natriuretic peptide appeared to contribute more than C-reactive protein and cystatin C to the multimarker panel.

A second important difference between the current study and previous studies is the restriction of the Zethelius study cohort to lean white men who were all the same age at study entry. The use of this restricted cohort may decrease the observed C statistic for established risk factors and inflate the increment in the C statistic over what would be expected in a more diverse cohort with a wider age range. This restriction mitigates the powerful influence of age in the established risk factor model; moreover, some established risk factors are less predictive of events from cardiovascular disease among older people. In addition to age, race, sex, and body composition also contribute in important ways to variability in the levels of C-reactive protein and N-terminal pro–brain natriuretic peptide, and the influence of these factors could not be evaluated in the homogeneous cohort that was studied. It will be critical to fully understand important noncardiac sources of variation in each biomarker under consideration as a screening test for cardiovascular disease, because the cardiac signal being screened for may be subtle among the asymptomatic target population.

Third, the inclusion of patients with prevalent cardiovascular disease distinguishes the present study from a pure evaluation of population screening. Among persons with prevalent cardiovascular disease, established risk factors are less powerful predictors of outcome than are markers of atherosclerosis burden and ventricular function, factors that were not considered in the present study. The data for those without prevalent cardiovascular disease in this study are of greatest interest for biomarker screening, since secondary approaches to prevention should be implemented aggressively among people with established cardiovascular disease regardless of biomarker levels.

A fourth issue relates to the statistical metrics that were used to evaluate the novel biomarkers. To their credit, Zethelius et al. use state-of-the-art tools to assess multiple measures of the predictive utility of their Cox-based models for the prediction of risk. If Cox models are to remain the statistical method of choice for risk prediction and discrimination, future authors should
Intracerebral Hemorrhage — Improving Outcome by Reducing Volume?

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Intracerebral hemorrhage accounts for 10 to 15% of all strokes. It is the type of stroke with the highest mortality, with a 1-year survival rate of less than 50%.1 Most intracerebral hemorrhages occur in patients who have hypertension, which is the major modifiable risk factor for the occurrence of intracerebral hemorrhage.2 Although improvements in the early recognition and general intensive care of patients with intracerebral hemorrhage have been associated


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