How Do We Find the Best Biomarkers for Cardiovascular Disease?

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Conventional cardiovascular risk assessment is based on traditional risk factors such as serum cholesterol concentrations (cholesterol, HDL cholesterol, LDL cholesterol) and blood pressure levels. It is becoming increasingly clear that the newer laboratory measures may help to refine risk estimates in the general population. In a recent publication of the MONICA5 (Monitoring of Trends and Determinants of Cardiovascular Disease) investigators (1), Blankenberg and colleagues evaluated the potential contribution of 30 novel biomarkers to the 10-year cardiovascular disease risk in 2 population cohorts. These biomarkers were part of the MORGAM (MONICA, Risk, Genetics, Archiving, and Monograph) Biomarker Project and were representative of 9 distinct metabolic processes linked to atherosclerosis (2). They include (a) lipid-related biomarkers, (b) renal function markers, (c) metabolic markers representing glucose and obesity pathways, (d) markers of vascular function and neurohumoral activity, (e) inflammation markers, (f) markers of oxidative stress and antioxidants, (g) coagulation markers, (h) angiogenesis markers, and (i) necrosis markers.

In addition to the inclusion of a large number of biomarkers for assessment, this study was based on a highly standardized and comprehensive quality control and assurance program implemented on clinical laboratory instruments. All analyses were performed in the MORGAM Mainz Biomarker Laboratory. The risk estimation was first established with data from participants in the FINRISK97 study of 7915 men and women, of whom 538 (6.8%) had incident cardiovascular events at 10 years (3). The cardiovascular disease risk estimation was subsequently validated with data from participants in the Belfast Prospective Epidemiological Study of Myocardial Infarction (PRIME), which consisted of 2551 men, of whom 260 (10.2%) had cardiovascular events (4).

The baseline characteristics of the male participants from the 2 study cohorts showed minor differences for several of the analytes. Of interest, the risk estimate development cohort (FINRISK97) had a wider age range (SD, 13.6 years) than the risk estimate validation cohort (SD, 2.9 years). Different conclusions have been reported when studies have differed in age range, and studies designed with participants in a narrower age range have been more likely to yield significant results. In addition to the inclusion of more participants of younger ages, the FINRISK97 study also included more participants on high-cholesterol medication (3.0% vs 1.1%) compared with PRIME. Male participants in the FINRISK97 study were also more likely to have hypertension (35.9% vs 15.4%) and diabetes (5.6% vs 1.8%). These differences at baseline and potentially during follow-up may affect the contribution of certain analytes as predictors of vascular disease end points and may affect risk estimation. Another issue that may affect the findings is the fact that the samples from the 2 cohorts were stored at −80 °C for various lengths of time, with a difference of at least 6 years (1991 for the first participant in the PRIME study and 1997 for the first participant in the FINRISK97 study).

How do we find the best biomarkers for cardiovascular disease? Composite end points are often used to increase the number of events in the comparison with persons who do not develop events. Such composite end points might include the development of acute coronary syndrome coronary disease, cardiac failure, cerebrovascular disease, and intermittent claudication. When possible, it is probably best to focus the research interest on discrete events, such as the occurrence of a first coronary heart disease event. Even that approach can be difficult in the modern era. Persons who are relatively asymptomatic at baseline may develop symptoms, undergo a diagnostic evaluation, and then have an elective cardiovascular procedure such as coronary stent placement. Such events are somewhat outside the classic category of “hard coronary heart disease,” which has generally indicated that a myocardial infarction or coronary heart disease death has occurred.
Most of the cardiovascular biomarker studies that test the utility of a large number of laboratory tests are hypothesis-generating in nature, and validation of the results is important. The validation cohort should share many of the characteristics of the development data set, and achieving this criterion may be difficult. Several validations of a new biomarker may be needed to demonstrate that the new test provides information that could help predict risk in the population or in specific subgroups of the population (5). Finally, when the usefulness of a new test for predicting disease is assessed, it is important to bear in mind whether the test adds or replaces information concerning risk or prognosis for a specific clinical or subclinical outcome and whether the test accounts for a substantial proportion of the risk associated with the outcome. The test must also be reproducible, be standardized, have a high diagnostic sensitivity and specificity, and have a high predictive value. In addition, abnormal results must lead to different treatment.

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References