Biomarkers to Predict Risk in Apparently Well Populations

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The past 2 decades have brought a surge in interest regarding circulating biomarkers across a wide range of patients and cardiovascular diseases. Indeed, testing of circulating biomarkers has become an integral part of everyday clinical and translational research, with studies leading to substantial insights regarding prediction of incident cardiovascular disease and better understanding of mechanisms of disease.

Population studies, such as the Framingham Heart Study,1 the Cardiovascular Health Study (CHS),2 and the Atherosclerosis Risk in Communities (ARIC) Study,3 have been important sources for biomarker-based analyses. Such community-based analyses have provided critical data regarding the value of biomarkers for prediction of incident cardiovascular events, including seminal data regarding the ability of several important biomarkers, such as aminoterminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTnT), to predict cardiovascular disease onset above and beyond clinical variables. For example, the Framingham Heart Study investigators recently reported the ability of a multiple biomarker score to accurately presage onset of multiple cardiovascular outcomes during a mean follow-up of 11 years: those with scores in the highest quartile had a 2-fold risk of cardiovascular events, a 3-fold risk of death, and most notably a 6-fold risk of incident heart failure (HF); biomarker testing in this analysis not only provided significant discrimination for events but also reclassified risk above and beyond clinical variables.1

Another important study2 was performed by the CHS investigators, who established the knowledge base regarding the importance of serial biomarker testing to predict incident cardiovascular disease. In an elderly population, the CHS investigators found that adding another measurement for NT-proBNP or hs-cTnT a mean age of 56 years who were free of cardiovascular diseases at baseline. In this biracial population, after baseline blood sampling for hs-cTnT, another measurement was made from blood drawn a mean of 6 years later, at ARIC Study visit 4. Patients were then followed up for 16 years for coronary heart disease (CHD), HF, and death. During this long follow-up period, there were nearly 1200 CHD events, nearly 1000 HF events, and more than 1800 deaths.

Between blood sampling time points, development of detectable hs-cTnT (>0.005 ng/mL), occurring in 24.3% of the study participants, improved discrimination for CHD (hazard ratio [HR], 1.4; 95% CI, 1.2-1.6) and death (HR, 1.5; 95% CI, 1.3-1.7); notably, HF was most robustly predicted (HR, 2.0; 95% CI, 1.6-2.4) by an increase in hs-cTnT concentration. Importantly, those with incident development of hs-cTnT concentrations above 0.014 ng/mL (the usual decision limit for acute myocardial infarction) had remarkably robust adjusted HRs for each outcome measure, with a HR approaching 8 for incident HF events during follow-up. This finding leads to the inevitable question: why would a population of patients ostensibly free of cardiovascular disease have circulating evidence for presumably asymptomatic incident cardiac injury, not infrequently exceeding the conventional thresholds for acute myocardial infarction?

To attempt to understand the meaning of an increasing hs-cTnT concentration in a patient without prevalent CHD or HF, one may scrutinize the data in the report by McEvoy et al.3 In the characteristics of the study population at ARIC Study visit 4 (at the time of follow-up blood draw), those with an incident increase in hs-cTnT had a more deleterious cardiovascular phenotype, consistent with reported predictors of hs-cTnT concentrations in the community, such as coronary artery calcium, left ventricular hypertrophy and worse renal function,4 and hyperglycemia.5 McEvoy et al repeated refer to myocardial damage as the cause for the increase in hs-cTnT, but this is a broad term; circulating hs-cTnT may be determined by the presence and severity of CHD, but mechanisms other than necrosis of cardiomyocytes likely lead to measurable change in circulating concentrations of troponin as well.6

Although McEvoy et al also reported change in NT-proBNP—it too increased rather significantly by 6 years in those destined for cardiovascular events—we unfortunately do not know whether the combination of hs-cTnT and NT-proBNP would have been even better for predicting events; intuition would suggest so, particularly for incident HF events. Analysis of whether change in these 2 markers provides incremental prognostic value in the ARIC Study would be an important next step for the investigators to explore. In addition, 44.0% had hs-cTnT concentrations below the limit of detection at both time points, suggesting that healthy individuals may in fact have no circulating evidence of cardiomyocyte damage with this assay. With even more sensitive troponin methods, however, the
percentage with measurable concentrations is higher; whether this would have undermined results of the present study is dubious, however.

To the extent prevention is ultimately the Holy Grail for defeating the global pandemic of CHD, stroke, and HF, the main reason to do a biomarker study such as this would be to set the stage for a biomarker-guided strategy to improve medical care for those patients at highest risk, as has been recently done with NT-proBNP. Critical questions remain:

• Is it possible to lower the risk in someone with measurable hs-cTnT? Possibly. Those individuals with a reduction in hs-cTnT concentrations in the present analysis had somewhat lower risk than would have been predicted by their baseline measurement; these findings echo those from the CHS.

• Which outcome should we attempt to reduce? Although hs-cTnT measurement appears robust for predicting CHD events and death, the strongest and most consistent signal predicted by this biomarker is that for risk of incident HF. Thus, either alone or together with NT-proBNP, this might be the most obvious target.

• How might one intervene to reduce risk associated with an elevated hs-cTnT concentration? Given multiple causes of incident hs-cTnT increase, this is not likely to be a one-size-fits-all approach, but to the extent that recent randomized data from HF clinical trials suggest that it is possible to reduce hs-cTnT concentrations with drug therapies, the logical approach would be to optimize treatment for medical conditions associated with hs-cTnT elevation, while applying therapies that may provide cardioprotection.

• Who will do such a trial? Such a study would require substantial commitment because it would be a long-term trial with a large sample size. It is imperative that discussions regarding such trials begin now, however, convening clinical trialists, biomarker experts, population scientists, governmental agencies, and industry members to develop the most robust strategies for reducing the global pandemic of cardiovascular disease.

Currently, it seems irrefutable that biomarkers can predict risk in population-based cohorts. The excellent data from McEvoy et al and others regarding biomarkers to predict such outcomes have provided plenty of evidence. Although interesting, studies report that inexorably downwardly directed Kaplan-Meier curves predicted by biomarkers do not improve the health of our patients. What is needed now are efforts toward developing strategies to upwardly bend the survival curves of those with a biomarker signature of risk, leveraging the knowledge gained from studies such as the report by McEvoy et al to improve public health.