The Cardiovascular Biomarker Conundrum
Challenges and Solutions

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DEFINED BROADLY, A BIOMARKER IS A PHYSIOLOGICAL variable that can be measured objectively and reliably and connotes some biological characteristic about the patient in whom it is measured. As such, biomarkers either can be used as a surrogate for a hard end point, correlating with an important clinical outcome of interest, or can be used to provide prognostic information—predictive of future events and, at their best, a tool to influence treatment strategies. In this commentary, we argue that this latter use is the most appropriate application for biomarkers.

Biomarkers as Surrogates

The use of a biomarker as a surrogate for hard end points, ie, important clinical outcomes, such as morbidity and mortality, remains fraught with challenges and must be used with caution. Cardiovascular medicine has witnessed several notorious examples of well-studied and understood biomarkers in which the predicted conclusions ultimately differed from the clinical end point. Two examples are particularly illustrative: the premature ventricular contraction (PVC) and high-density lipoprotein (HDL).

Sudden cardiac death, particularly after myocardial infarction, was considered a “world wide public health problem” in the latter half of the 20th century. The frequency of PVCs was shown to correlate with and was thought to contribute to these deaths. A new generation of antiarrhythmic drugs, able to suppress PVCs in the vast majority of patients, emerged and was used in widespread practice. In the late 1980s, the Cardiac Antiarrhythmic Suppression Trial (CAST) was conducted to assess the safety and efficacy of a practice that was then commonplace. Recruitment for the trial was hindered by physicians who were reluctant to allow patients to undergo randomization with a 50% chance of not receiving these medications. Ultimately, the trial was completed and showed that these drugs (encainide, flecainide, and later moricizine) conferred greater mortality than placebo, and their use greatly diminished.

Torcetrapib, a cholesterol ester transferase inhibitor, provides another cautionary tale when biomarkers substitute for true end points. The drug reliably increased HDL (without countervailing effects on low-density lipoprotein [LDL]) but ultimately increased cardiovascular mortality. In both cases, whether the results were due to some failure of the biomarker (PVC or HDL) or some deleterious, unintended effect of the drugs, the lesson remains the same. Surrogate end points (no matter how robust) can provide misleading information regarding the true end point.

These examples have necessitated setting a lofty bar for biomarkers as surrogates of major clinical outcomes. Specifically, the marker must track with a hard end point (without any medical intervention), the marker must continue to track the end point (under the influence of an intervention), and the marker must correlate with the end point across several broadly different classes of interventions before any change in the biomarker might be reliably interpreted as implying an improvement in the hard outcome. Despite this, doubt may persist. A novel agent may still harbor a negative unexpected effect. Panels of biomarkers may be used to screen for such effects; however, these arrays may not be error proof (and might require years of validation and testing). For these reasons, the use of biomarkers as surrogate end points remains a difficult and distant goal.

Biomarkers to Augment Existing Risk Models

In clinical practice today biomarkers are being used to convey prognostic information. The challenge of using biomarkers in this capacity is to provide additional information beyond that which is already obtained by assessing clinically available variables.

The Framingham risk score provides a good example. It is one of the most cited models in all of biomedicine and predicts 10-year risk of coronary heart disease or death based on age, blood pressure, total (or LDL) cholesterol level, HDL cholesterol level, smoking (within 6 months), and presence of diabetes mellitus. In a review of 79 publications that cited the original Framingham risk score report and evaluated at least 1 additional prognostic factor, more than 30 articles examined, at least in part, a genetic or serum test and more than 40 articles examined.
what arguably could be called a biomarker.6 Although 63 of 79 articles (80%) made claims of enhanced ability to predict outcome, “most studies had flaws in their design, analyses, and reporting that cast doubt on the reliability of the claims of improved prediction.”6 Common errors included calculating the Framingham risk score suboptimally, not examining coronary heart disease as an outcome, and not providing a recalculation analyses (ie, showing how many patients would be reclassified with the new model). Newer studies of predictors beyond the Framingham risk score are challenged to show meaningful recalculation, and some indeed have met this mark.7

Tailoring Therapy

A predictive test is used to delineate patients who will be good candidates for therapy vs those who will not. In the Surgical Treatment of Ischemic Heart Failure (STICH) trial,8 myocardial viability (assessed by myocardial perfusion imaging or low-dose dobutamine echocardiography) was assessed to determine which patients with coronary artery disease (CAD) and left ventricular dysfunction would benefit from adding coronary artery bypass graft (CABG) surgery to evidence-based medical therapy. Although myocardial viability did offer prognostic value, it did not provide incremental benefit beyond other clinically available data, and myocardial viability assessment did not identify a group of patients receiving aggressive medical therapy who benefited particularly from CABG surgery. The Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial9 attempted to validate a novel predictive biomarker. In that trial, among older patients with “normal” LDL cholesterol and elevated high-sensitivity C-reactive protein (hs-CRP) levels (ie, >2 mg/L), the use of rosuvastatin improved cardiovascular end points and total survival at 2 years. However, for hs-CRP to have been fully confirmed as a biomarker, the trial also would have recruited patients with normal hs-CRP levels (<2 mg/L), randomized them to receive rosuvastatin or placebo, and shown that these patients did not benefit from statin therapy or did so only marginally and at unacceptable cost profiles; however, this analysis was not performed.

Biomarkers hold the greatest promise in this domain, delineating patients who will benefit from a therapy vs those who might not. A meta-analysis10 of trials of statin therapy for primary prevention (excluding patients with known CAD, but including those otherwise at high risk) generated controversy by demonstrating that more than 200 patients would need to be treated with statin therapy for 5 years to save 1 life. If this finding is confirmed, predictive biomarkers would be needed to identify the subset of patients who might benefit at a more reasonable number of patients needed to be treated (<100). Other costly cardiovascular therapies might similarly warrant studies demonstrating improved prediction with novel biomarkers. Rigorous trial design is of paramount importance with biomarker studies, and prospective randomized trials must remain the gold standard for this research. Thus, groups of patients must be defined a priori, those hypothesized as benefiting from a therapy must be identified as such, and limits must be placed on multiple hypotheses testing.

Biomarkers hold tremendous promise in cardiovascular medicine, but this promise has the greatest importance and immediacy when a biomarker is used as a predictive test. The use of biomarkers as surrogates for hard end points involving major clinical outcomes remains a distant goal as the recent history of some cardiovascular clinical trials has clearly demonstrated. The flurry of biomarker research has created a maze of possible uses. Use of biomarkers as predictive tests represents the greatest promise of this technology and the shortest and most effective path out of the maze.

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REFERENCES