Editorial

Biomarkers in Clinical Trials
Can We Move From Fortune Telling to Disease Profiling?

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In contemporary cardiovascular practice, the most common and useful applications of biomarkers focus on disease diagnosis, with troponins for myocardial infarction and natriuretic peptides for heart failure representing the most notable examples. Identification of additional cardiovascular diagnostic markers has proved challenging, however, because high quality studies for diagnostic indications are difficult to perform, and most putative cardiovascular biomarkers demonstrate inadequate cardiac specificity. Cardiovascular biomarker research has increasingly focused on the lower-hanging fruit of risk assessment, at least in part because prognostic biomarker studies are relatively easy to embed within ongoing clinical trials or epidemiology studies. Here also, success has been mixed; although numerous biomarkers have been associated with adverse outcomes across a variety of cardiovascular disease states, few meet appropriately rigorous criteria to support routine measurement for risk prediction in clinical practice.1 Moreover, risk assessment alone is of limited value to clinicians. To move beyond simple fortune telling and to take advantage of the potential value of circulating biomarkers as modifiable indices of specific biological pathways, additional applications have been investigated. These emerging roles include the use of biomarkers to guide therapeutic selection and the profiling of chronic disease course or response to treatment with individual biomarkers or panels of distinct markers. If biomarkers are selected that provide a reliable representation of a biological pathway mediating disease risk, it remains possible that the measurement of changes in these biomarkers will yield useful insight into the expected effects of different therapies.

Article see p 695

In the current issue of Circulation, Sobel et al report findings from a combination of 2 large biomarker substudies of the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) trial, in which they consider several of these potential applications for cardiovascular biomarkers.2 In an ambitious study in which they performed serial measurements of multiple biomarkers reflecting insulin exposure and resistance, glucose control, inflammation, thrombosis, and fibrinolysis, the authors evaluated the potential role of several selected biomarkers to improve risk assessment and to profile the biological actions of the insulin-sensitizing (IS) or insulin-providing (IP) therapies. This latter role implicitly suggests the possibility that these biomarker profiles could function as surrogates to predict differences in clinical efficacy between the therapies.

How well do these biomarkers perform for these purposes? The authors report “striking predictive power” for baseline levels of fibrinogen, D-dimer, and C-reactive protein (CRP) in terms of subsequent mortality and the composite outcome of death, myocardial infarction, or stroke, whereas plasminogen activator inhibitor type-1 (PAI-1) antigen and activity, tissue-type plasminogen activator (tPA) antigen, and fibrinopeptide A did not associate with subsequent events. A closer look, however, raises questions about the robustness of this conclusion. Although statistically significant, the positive associations observed were quantitatively very modest, with only a 2% relative increase in risk per 10% increase in CRP or D-dimer. Associations in this range will not improve the discrimination of prediction models and are likely to result in only trivial (if any) improvements in risk classification. Because measures of association with clinical outcomes provide a potentially misleading overestimation of the clinical value of biomarkers for risk prediction, it is now recommended that studies report more complete risk prediction metrics, including improvement in the receiver-operating characteristic curve, calibration, and reclassification; these analyses were not reported in the present publication. In addition, the authors did not consider these biomarkers in the context of established biomarkers that provide more robust prognostic value in patients with stable coronary artery disease, including natriuretic peptides3 and cardiac troponins,4 as well as emerging biomarkers, such as growth differentiating factor-15, each of which provide substantially more robust prognostic information than the biomarkers reported here. Certainly, a complete evaluation of the prognostic value of new biomarkers requires demonstration of incremental value over the best available competition.

The larger and more novel goal of the study was to capitalize on serial measurements of the biomarkers to compare the impact of IS and IP therapies on biological pathways leading to atherosclerosis progression and complications in patients with diabetes mellitus. Circulating tPA and PAI-1 increased modestly in the IP arm over time but fell significantly in the IS arm, paralleling changes in plasma insulin. Fibrinogen and CRP levels fell in both arms but to a greater extent with IS therapy. The authors conclude that “an insulin-sensitizing as opposed to an insulin-providing strategy led to changes in biomarker profiles indicative of a
profibrinolytic, antithrombotic, and antiinflammatory state.”

Although this conclusion leads us to consider that IS therapy might be preferable to IP therapy in patients with coronary artery disease, we should consider the implications of these findings very critically because the comparisons between IS and IP therapy in BARI 2D were null with regard to important major adverse cardiovascular clinical events. Moreover, the thiazolidinedione used in BARI 2D was almost exclusively rosiglitazone, the drug that led to the greatest magnitude of change in almost all biomarkers assessed in the trial yet has been associated with increased coronary artery disease risk, leading to its withdrawal from the market in Europe and severely restricted use in the United States.

How can the perceived favorable effects on circulating biomarkers be reconciled with the disappointing overall trial result from BARI 2D? Several possible explanations can be posited. First, it is quite possible that changes in the biomarkers that were differentially affected by IS compared with IP therapy may not provide clinically relevant information, even if some of them have been directly implicated in diabetic vascular disease. This possibility is suggested by the absence of association with clinical outcomes for some biomarkers (PAI-1, tPA, and fibrinogen) and weakness of association for others (CRP) that were influenced by therapy. Second, it is possible that although the directional effect on biomarkers was favorable, the magnitude of change, individually and in aggregate, was not sufficient to yield clinically meaningful improvement in outcomes. For mediators that only modestly influence outcomes, a very large change may be required to translate into a reduction in clinical events. Third, favorable effects on pathways reflected by the biomarkers may be counterbalanced by unfavorable effects on other pathways that are not captured with any of the measured biomarkers. Rosiglitazone, for example, causes plasma volume expansion that may adversely affect neurohormonal balance, increases fat expansion and adiposity, and reduces hematocrit, effects that may counterbalance any favorable effects on inflammation and thrombosis that were observed in the present study. Fourth, it is possible that neutral or counterregulatory effects of the therapy on redundant biomarkers (and the pathways they reflect) would counterbalance favorable effects on other related biomarkers. For example, the absence of an effect of IS therapy on D-dimer and fibrinopeptide A may counterbalance favorable changes in PAI-1 and tPA and dilute any effect on thrombotic tendency. Finally, it is possible that methodological issues may have exaggerated the effects of therapies on the biomarkers. For example, several studies, including an earlier report from the BARI 2D investigators, have reported a strong influence of body mass index on tPA, PAI-1, CRP, and fibrinogen. In their analyses of the association of IP and IS drugs with biomarker changes, the authors account for baseline body mass index but not for changes in body mass index. The 0.8-kg/m² difference in body mass index between the IP and IS groups at the end of the study period may explain, at least in part, the differences in biomarkers observed between IS and IP regimens.

We would argue that the present study should once again serve as a cautionary note for the interpretation of biomarker changes in clinical trials and consideration of their use as surrogates of clinical risk, adding to an increasing number of such invalidated cardiovascular risk markers in diabetes mellitus, including hemoglobin A₁c, triglycerides, and most recently high-density lipoprotein cholesterol. Indeed, we interpret the disconnect between the inflammatory and thrombotic biomarker findings and clinical events in BARI 2D to suggest that tPA, PAI-1, CRP, and fibrinogen are not useful indices to predict drug effects on diabetic vascular disease. In contrast, the null findings for fibrinopeptide A and D-dimer might paradoxically be considered more reliable because the findings with these markers track with the null clinical event results; D-dimer merits additional consideration because it also independently, albeit modestly, associates with outcomes. Clearly, embedding biomarker profiling studies within randomized trials is fraught with challenges. At best, when biomarker changes are concordant with effects on clinical events, such studies may propose a mechanism for the success or failure of the randomized therapy. However, when the biomarker findings are contradictory to those for clinical events, confusion regions. Moreover, as illustrated by the present study, it is unlikely that biomarker changes will be uniform either within the same putative biological pathway or between different pathways, and it is not clear how to weigh inconsistent results between biomarkers within or across the various pathways.

A more complete understanding of biomarker/phenotype correlations is needed to fully capitalize on the potential of cardiovascular biomarker profiling studies. Ideally, changes in biomarkers would be validated against precise disease phenotypes, including both imaging-based phenotypes and clinical events, before being tested in large-scale therapeutic studies. Moreover, the profiles must be shown to correlate similarly with disease phenotypes across multiple different therapeutic classes in order to be able to use the profiles to predict drug response. If such criteria are met and validated biomarkers of disease processes are identified, profiling studies may be more appropriately positioned earlier in the drug development process. In this context, circulating biomarkers that provide validated information about disease pathways may improve efficiency when selecting between multiple candidate compounds and/or dosages. Biomarker profiles may play an even more important role in identifying safety signals before large numbers of individuals are exposed to an experimental agent.

The BARI 2 D investigators are to be congratulated for tackling an important research question and highlighting the major challenges ahead before biomarker profiles can be used clinically or even reliably from a research standpoint to compare different therapies. If a stronger foundation is built through translational research, identifying consistent associations between circulating biomarkers and cardiovascular phenotypes, biomarkers may indeed emerge as tools to monitor disease and to predict drug response.

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