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

James A. de Lemos, MD; Darren K. McGuire, MD, MHSc

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. 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.

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From the Division of Cardiology and Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas.

Correspondence to James A. de Lemos, MD, UT Southwestern Medical Center, 5909 Harry Hines Blvd, HA 9.133, Dallas, TX 75390-9047. E-mail james.delemos@utsouthwestern.edu

(Circulation. 2011;124:663-665.)

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Circulation is available at http://circ.ahajournals.org
DOI: 10.1161/CIRCULATIONAHA.111.044271

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profibrinolytic, antithrombotic, and anti-inflammatory 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 and increases fat expansion and adiposity, 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 2D 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.

Disclosures
Dr de Lemos has received grant support from Roche Diagnostics; consulting income from Tethys Bioscience, AstraZeneca, and Daiichi Sankyo; and lecture honoraria from BMS/Sanofi-Aventis. Dr McGuire has received consulting income from F. Hoffmann LaRo-
che, Genentech, Daiichi Sankyo, Novo Nordisk, Tethys Bioscience, and Ipsen Pharmaceutical.

References

Keywords: Editorials ■ biological markers ■ C-reactive protein ■ diabetes mellitus ■ inflammation
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_Circulation_. 2011;124:663-665
doi: 10.1161/CIRCULATIONAHA.111.044271

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/124/6/663

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