Biomarkers, Putative Surrogates, Surrogates, and Decision Making

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The development of new therapies is slow, expensive, and frustrating. The failure rate for new molecular entities exceeds 90%, and total research and development costs per successful new molecular entity are currently estimated to be nearly $2 billion.1 Consternation about the complexity of therapeutic development recently prompted a major report by the President’s Council of Advisors on Science and Technology,2 recommending significant changes to how the development system is regulated and encouraging new methods that will guide better decision making about the potential value of therapies at an earlier point in the development process.

One temptation when developing a new therapy is to rely on surrogate outcomes that can shorten the time to drug development and reduce costs. The article by Peters et al3 in this issue of Circulation: Cardiovascular Imaging provides a systematic examination of one such surrogate outcome. The authors explore the possible value of using carotid intima-media thickness (CIMT) measurement when evaluating new drugs with the potential to prevent atherosclerosis and to reduce the risk of cardiovascular events. Using Medline, the authors identified 48 blinded, controlled trials evaluating therapies that lowered lipid, blood pressure, or glucose levels or that evaluated other vascular prevention modalities in the context of a definitive clinical outcome trial. They then calculated predictive statistics using the clinical outcome findings as the truth, making the case that the use of CIMT as a surrogate offers a good tool for sorting through potential therapies before investing resources in large and expensive outcomes trials.

The quest for surrogate end points for clinical trials is chronicled by a rich literature of failure, and a number of excellent reviews have dissected the problems of relying on such measures.4,5 The accepted nomenclature in this arena is carefully constructed to avoid misleading conclusions. A biomarker is a measure of biological process that informs about health or disease. A clinical outcome is a measure of longevity, functional status, or feeling that reflects something tangible to the patient. A surrogate is a biomarker that can substitute for clinical outcome. Prentice6 defined the operating characteristics needed for a biomarker to be validated as a surrogate, and they are daunting. Association with a clinical outcome is not enough to make a biomarker a surrogate. Instead, the change in the putative surrogate measure must explain a large proportion of the change in a clinical outcome in the context of clinical trials; ideally, it should do so across a variety of interventions. For this reason, most purported surrogates are really putative surrogates, meaning that whereas preliminary evidence exists, results are either contradictory or inconclusive.

Biomarker studies require careful scrutiny before being accepted for the purposes of guiding treatment or for the development of novel therapies. Most notably, whereas the reductions in sample sizes enabled by substituting biomarkers for clinical end points are alluring for various pragmatic reasons, the issue of missing data poses a difficult and perhaps insurmountable problem. Often, those patients with the greatest degree of change in the biomarker of interest are unavailable for follow-up studies because they are either dead or sick. Such informative censoring can distort results in ways that cannot be fully understood, even with increasingly sophisticated biostatistical analysis.

The present article by Peters et al3 provides a valuable compilation of published data, and the authors have done an excellent job of discussing the 5 limitations of the study. However, it falls short of being totally convincing for 2 main reasons. First, the authors relied on the published literature and could not estimate verification bias, limitations that they candidly acknowledged in their discussion. The effects of publication bias are well known and have contributed to the growing use of the National Institute of Medicine’s www.ClinicalTrials.gov registry as a source for more comprehensive evaluation of trials than is possible with the published literature alone.7,8 How many discongruent studies using CIMT were never published and therefore are not available for this review? No one can say.

Second, if the authors had had access to data from individual trial participants, a much more convincing case could be made that the criteria for a true surrogate were met: Is there a strong relationship between change in CIMT and change in clinical events compared with placebo in large outcomes trials?

These limitations do not diminish the service that Peters et al3 have done in conducting this analysis. Given the enormous costs of creating novel therapies, drug developers will seek to hedge their bets in some manner, and CIMT remains a...
rational choice for a drug development pathway in cardiovascular therapeutics. We will be much smarter about surrogates once data transparency from human studies advances to the point that all such data are available for analysis, enabling complete overviews of all relevant studies, so that truly generalizable conclusions can be drawn.

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References

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