

Warning About Shortcuts in Drug Development

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Throughout history, cures and symptomatic treatments have been touted based on extrapolations from poorly understood measures and theories. At best, this has been attributed to naïve believers advocating for proposed therapies without awareness of the accompanying uncertainties and risks. At worst, “snake-oil salesmen” have promoted therapies to unsuspecting audiences with full knowledge of the possibility of doing more harm than good. After multiple public health disasters resulting from unsafe or adulterated drugs and devices, a series of US laws were enacted to require that therapeutic products meet criteria for a positive balance of benefit and risk for their intended use before marketing. Other countries have followed suit, codifying into law the need for demonstration of safety and effectiveness before widespread marketing of drugs and high-risk devices. But recent public discussions predicated on the assumption that safety can be assured without evidence for effectiveness,¹ or that effects on unsubstantiated biomarkers provide enough evidence for large-scale marketing of drugs, raise concerns that hard-learned lessons are being forgotten.

In this issue of *JAHA*, Bikdeli et al provide documentation from an examination of the literature that shows that building cardiovascular clinical therapeutics from trials based solely on unvalidated biomarkers would be folly.² The authors extracted information from 3 prominent medical journals, focusing on clinical trials that used biomarkers as primary outcome measures. As previous reports would suggest, they found that the majority of these studies either were not followed by trials measuring a clinical outcome as a primary endpoint, or, when

such trials were done, they found that the positive biomarker findings were not associated with better clinical outcomes.

Although their findings justifiably cast a shadow on the use of biomarkers as evidence to allow marketing of new drugs, it is nevertheless critical to understand that the careful and appropriate use of biological measures is integral to the development and assessment of medical products. As candidate drugs are winnowed during clinical evaluation, it is essential to demonstrate that the treatment engages a biological target and has an effect on the proposed mechanism.³ However, human biology is complex and putative therapies usually have “off target” effects that are difficult to anticipate. The result is that human therapeutic development is a treacherous enterprise: Even with recent trends toward improvement, roughly 90% of drugs that enter phase 1 trials do not reach marketing approval because of failure to improve clinical outcomes or because of unexpected toxicity.⁴

A pivotal element in the appropriate use of biological measures in therapeutic development hinges on the interpretation of the terms “biomarker” and “surrogate.” Confusion about terminology in this field has persisted for decades. The US Food and Drug Administration (FDA) and National Institutes of Health (NIH) are working to reduce this confusion by collaborating with relevant communities to create a continuously updated resource that provides agreed-upon definitions and examples.⁵ Within this framework, a biomarker is understood as “a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.” Molecular, histological, radiographical, or physiological characteristics are types of biomarkers; an assessment of how an individual feels, functions, or survives is not a biomarker. These measures of feeling or functioning better or surviving longer comprise key criteria for assessing the benefits of a therapy in human terms, thereby forming the basis for regulatory approval for marketing. Although biomarkers cannot be directly equated with these major clinical outcomes, they can be used for a variety of purposes, including risk/susceptibility, diagnostic, monitoring, prognostic, predictive, pharmacodynamics, and safety applications. Interestingly, any biomarker can be excellent for 1 purpose, but useless for another. High-density lipoprotein (HDL) cholesterol is 1 example of a good

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prognostic biomarker that has failed as a surrogate because multiple therapies that increase levels of HDL cholesterol have not reduced cardiovascular events.⁶

In distinction to a biomarker, a *surrogate* is an endpoint used in clinical trials as a substitute for a direct measure of how a patient feels, functions, or survives. A surrogate endpoint does not measure the clinical benefit of primary interest in and of itself, but rather is expected to predict that clinical benefit or harm based on epidemiological, therapeutic, pathophysiological, or other scientific evidence. From a US regulatory standpoint, surrogate endpoints and potential surrogate endpoints can be characterized by their level of clinical validation: validated, reasonably likely, and candidate. However, a widespread lack of understanding about the criteria for validating a candidate surrogate has caused major disappointments when clinicians, investors, patients, and industry leaders have assumed that a change in an unvalidated biomarker will result in an improvement in clinical outcomes.

Perhaps more than any other therapeutic area, cardiovascular medicine has suffered from misguided biomarker use. The CAST (Cardiac Arrhythmia Suppression Trial) is the prototypical example: After widespread acceptance of the hypothesis that suppressing premature ventricular contractions (PVCs) would prevent sudden cardiac death, the NIH launched a trial intended to confirm the concept. However, both CAST and the following CAST II trial were stopped early for excess mortality in the group treated with antiarrhythmics, despite evidence of PVC suppression.^{7,8} Numerous subsequent examples involving proposed heart failure and chronic ischemic heart disease treatments have accrued since then. But this problem is hardly limited to cardiovascular medicine—the FDA recently posted a white paper examining 22 examples of products from multiple therapeutic areas that had promising early-phase results, but were found to be ineffective or dangerous when clinical outcome trials attempted to confirm clinical benefit.⁹

Recent reviews point to declining investment in cardiovascular drug development.¹⁰ There is a commonly held view that regulatory requirements for appropriately sized clinical outcomes trials have suppressed investment in the field. Some have argued that the solution to this decline is to allow a putative therapy to be approved for market based on positive biomarker data, thereby reducing the expensive requirement to measure its effect on clinical outcomes. However, given these examples from cardiovascular medicine, as well as the recent FDA report noted above, one must question the simplistic approach to reducing standards for evidence across the board advocated by some—particularly when the FDA's existing accelerated approval programs show that it is possible to create working pathways for streamlined drug development while maintaining standards that ensure ample empirical evidence.¹¹

An alternative approach would be to conduct the appropriate outcome trials using innovative methods that have recently evolved. Both the NIH's Health Care Systems Collaboratory¹² and the National Patient-Centered Clinical Research Network¹³ are showing how major outcomes trials can be done at a much lower cost by using existing digital data from electronic health records and claims records, leveraging integrated health systems to accelerate patient recruitment, and building on insights from patients and their advocates to streamline and accelerate evidence generation.

Given the findings described above as they relate to cardiovascular disease, one must wonder about other fields of medicine. Our goal should be to accelerate access to, and uptake of, *effective* therapies. Bikdeli et al have demonstrated that an approach based on unvalidated biomarkers would almost certainly lead to dangerous or ineffective drugs reaching the market. A better alternative would be to develop streamlined approaches to clinical outcomes trials¹⁴ that could enable them to be completed much more quickly and at a much lower cost.

Disclosures

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