The controversy and confusion about surrogate end points have intensified with the recent Food and Drug Administration (FDA) approval of the proprotein convertase subtilisin/kexin type 9 inhibitor drugs based on their ability to lower low-density lipoprotein (LDL) cholesterol. Although these drugs have great potential to reduce the risk of heart disease and stroke, we still await the most critical evidence about their benefit and risk in outcomes trials.

The Institute of Medicine (IOM) defines biomarkers as indicators of normal biological processes, pathogenic processes, or pharmacological responses to an intervention. But even as biomarkers can reflect the influence of an intervention, changes in their levels may not be indicative of changes in risk. When biomarkers are used as proxies for clinical end points, they are referred to as surrogate end points, and facilitate more efficient and timely evaluation of interventions. They are particularly important when the effect of a drug is expected to take extensive time to become manifest.

However, changes in surrogate end points cannot be considered equivalent to changes in risk. People too often confuse the pharmacological modification of risk factors with the safety and effectiveness of drugs. Most drugs have the potential to influence a wide range of biological processes far beyond a single biomarker or even a set of biomarkers.

I participated in a panel of the IOM that was charged with providing the FDA guidance about evaluating biomarkers and surrogate end points. The group was asked for a framework providing the FDA guidance about evaluating biomarkers and beyond a single biomarker or even a set of biomarkers.

The important role of evidence from outcomes trials was a crucial point for the authors of the new ACC/AHA Lipid Guidelines. After years of reviewing the literature, the group found no support in trials for a target level, particularly one that was agnostic to the type of agent used to reduce LDL cholesterol. Moreover, they emphasized that treatments without outcomes trials should be relegated to last-line agents, with unclear utility.
Another instructive example involves fibrates. From a range of metabolic measurements, it would seem that fibrates would be effective in lowering the risk of cardiovascular disease. And yet, clinical trials have yielded mixed results, with a surprising lack of efficacy in the statin era.12,18 There seem to be many mechanisms by which these drugs improve the lipid profile.19 Moreover, they seem to act by affecting transcription at the nuclear level. The key aspect is the possibility that there are important effects on people that are not well reflected by a narrow spectrum of biomarkers.

Adding to the controversy is the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), not because of the results but because of their framing. IMPROVE-IT was a double-blind randomized controlled trial that assessed the clinical benefit and safety of Vytorin (ezetimibe/simvastatin combination) versus simvastatin monotherapy in individuals with an acute coronary syndrome.18 In a study of 18,144 subjects followed for a median of 6 years, the investigators found that the combination drug reduced relative risk by about 6%.

IMPROVE-IT tested a drug combination versus drug monotherapy in a particular group of patients. However, in the presentation of the results at the Scientific Sessions of the AHA, the investigators went beyond the boundaries of their results by concluding that IMPROVE-IT reaffirms the cholesterol hypothesis that reducing LDL cholesterol prevents cardiovascular events.19 The implication was profound, suggesting that all interventions that lower LDL cholesterol can be assumed to reduce risk. Dr Stone,15 the leader of the Lipid Guidelines, countered in his commentary with the evidence that many trials show that you cannot make such a simple assumption. Meanwhile, the related editorial published by the New England Journal of Medicine was titled, “Proof That Lower is Better—LDL Cholesterol and IMPROVE-IT.”20

That changes in lipid values are not a proxy for patient outcomes is supported by several trials that are testing particular drugs known to reduce LDL cholesterol. That companies and investigators are conducting these studies is a testament to the remaining uncertainty even after the drugs have been studied in trials involving surrogate end points, as the outcomes trials would not be ethical if the modification of the lipid profile by a particular agent was already known to reduce risk.

Meanwhile, the FDA has approved proprotein convertase subtilisin/kexin type 9 inhibitors because of their effects on the surrogate end point. Moreover, despite the evidence-based abandonment of target levels by the Lipid Guidelines, the FDA has approved proprotein convertase subtilisin/kexin type 9 inhibitors so that patients can reach target levels, even as those targets are unspecified. In its press release, the FDA maintained a middle position by writing, “Multiple clinical trials have demonstrated that statins lower the risk of having a heart attack or stroke. A trial evaluating the effect of adding Praluent to statins on reducing cardiovascular risk is ongoing.”

It is clear that without direct testing, it is not possible to know whether the modification of a biomarker like LDL cholesterol by a particular drug could modify risk. Absent this testing, it is important that the uncertainty be acknowledged and incorporated into discussions with patients.

Even those of us who view surrogate end points with caution recognize that they are often necessary and are sometimes all that is possible to obtain within a reasonable time frame. Nevertheless, we advocate for specificity in the language surrounding treatment options and for a distinction to be made between strategies that were tested with outcomes trials and those whose effect is currently only understood in the context of surrogate end points.

The biology of humans is complex and we are far from understanding it in a comprehensive way. Systems biology,21 a multidisciplinary, integrated approach to understanding complex systems, is teaching us to be humble as we observe emergent phenomenon in human biology that defy easy prediction. This humility is making its way into clinical medicine, particularly as it applies to the adoption of expensive medications with risks and benefits that are incompletely characterized by outcomes studies. Such caution should not diminish our hopes that certain interventions may have wonderful effects on health; we just need to prove it.

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