Biomarkers, Risk Factors, and Risk
Clarifying the Controversy About Surrogate End Points and Clinical Outcomes

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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 to qualify biomarkers for use in the evaluation of drugs for chronic disease. We were challenged in applying a uniform standard because of our uncertainty about whether an intervention that influenced biomarkers would affect people. It was clear that a simple set of biomarkers could not capture the full effect of any drug. The panel ultimately provided some guidance to the FDA, but I voiced support for an emphasis on limitations of what we can know about a drug’s effect based on biomarkers. I saw value in the use of biomarkers, but also the need to be realistic about what information they can convey.

Meta-analyses of statin trials have shown a relationship between the degree of lowering of LDL cholesterol and reduction in risk. This precise relationship has been questioned by investigators who revealed concerns about plotting a line from the control group of one study to an intervention group of another study conducted more than a decade later, even as they acknowledged that statins can lower risk. Nevertheless, even if this relationship is true for statins, it cannot be generalized. Although statins can lower LDL cholesterol and lower risk, all drugs that lower LDL cholesterol do not have the same effect. Moreover, the paucity of head-to-head comparison makes it difficult to determine whether the slope of the line that defines this relationship varies by drugs within the class, and evidence exists for within-class variation in risk profile.

The recent literature is replete with studies that sought and failed to validate practices based on surrogate end points. Examples include Action to Veterans Affairs Diabetes Trial (VA-DT), Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE), Dalteparin in Stable Coronary Heart Disease Patients With Recent Acute Coronary Syndrome (Dal-OUTCOMES), Control Cardiovascular Risk in Diabetes (ACCORD), and Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH). In each case, the outcome expected by the change in the surrogate outcome was not what was observed in the trial.

In addition, disasters have been averted because a company conducted an outcomes trial before obtaining approval based on surrogate end points. By all accounts, Pfizer anticipated that torcetrapib would be a blockbuster drug based on its salutary effects on raising high-density lipoprotein cholesterol and markedly reducing LDL cholesterol. In the company-sponsored Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial, the drug increased high-density lipoprotein cholesterol by 72% and reduced LDL cholesterol by 25%, and the trial was terminated early because the drug increased mortality by 58%.

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 levels. Moreover, they emphasized that treatments without outcomes trials should be relegated to last-line agents, with unclear utility.

The opinions expressed in this article are not necessarily those of the American Heart Association.

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(Circ Cardiovasc Qual Outcomes. 2015;8:00-00.
DOI: 10.1161/CIRCOUTCOMES.115.002245.)
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Circ Cardiovasc Qual Outcomes is available at http://circoutcomes.ahajournals.org
DOI: 10.1161/CIRCOUTCOMES.115.002245
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.\textsuperscript{12,16} There seem to be many mechanisms by which these drugs improve the lipid profile.\textsuperscript{17} 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.\textsuperscript{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 presentation of the results at the Scientific Sessions of the AHA, the investigators went beyond the boundaries of their 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%.

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,\textsuperscript{21} a multidisciplinary, integrated approach to understanding complex systems, is teaching us to be humble as we observe emergent phenomena 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.

Sources of Funding

Dr Krumholz is supported by grant U01 HL105270-05 (Center for Cardiovascular Outcomes Research at Yale University) from the National Heart, Lung, and Blood Institute.

Disclosures

Dr Krumholz is the recipient of research agreements from Medtronic and from Johnson & Johnson, through Yale University, to develop methods of clinical trial data sharing and chairs a cardiac scientific advisory board for United Healthcare.

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