



## Redefining Quality — Implications of Recent Clinical Trials

Harlan M. Krumholz, M.D., and Thomas H. Lee, M.D.

Related articles, p. 2545 and 2560

Simple approaches to patient care are better — except when they are not. Recent clinical studies are leading to a reexamination of the paradigm whereby efforts to prevent vascular disease focus

on the achievement of particular levels of risk factors such as low-density lipoprotein (LDL) cholesterol, systolic blood pressure, and glycated hemoglobin. Although these factors and their levels are important determinants of the development and progression of vascular disease, it is increasingly apparent that the specific strategies used to modify them make a critical difference in patient outcomes. This insight has implications for clinical practice, performance measurement, and regulatory requirements.

The conventional wisdom, which emerged from epidemiolog-

ic studies of risk factors and the subsequent successful trials of certain strategies for risk-factor modification, has been that the clinician's key focus ought to be on reducing risk factors below specific levels. This approach, however, neglects the importance of which specific strategies are used to modify these factors. A clinical trial is ultimately a test of a strategy, and we should not be surprised that different strategies may have different effects on patients beyond their effect on risk-factor levels.

Awareness of this issue was boosted on December 2, 2006, the

day Pfizer stopped the study named ILLUMINATE (Investigation to Understand Its Impact in Atherosclerotic Events) and all other trials involving torcetrapib, which until then had been seen as a promising agent that lowered LDL cholesterol levels and raised high-density lipoprotein (HDL) cholesterol levels. ILLUMINATE was halted because patients receiving torcetrapib plus atorvastatin had a higher mortality rate than those receiving atorvastatin alone — despite 72% increases in HDL levels and 25% decreases in LDL levels.<sup>1</sup>

ILLUMINATE is not alone in raising questions about the wisdom of patient care that prioritizes target levels of some risk factors over attention to the way in which those levels are achieved.

The Women's Health Initiative revealed that hormone-replacement therapy, which reduces LDL cholesterol levels, increased the risk of cardiovascular disease.<sup>2</sup> Another study, called ENHANCE (Effect of Combination Ezetimibe and High-Dose Simvastatin versus Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia), showed that ezetimibe did not reduce the progression of arteriosclerosis when combined with simvastatin, as compared with simvastatin alone, even though the combination did result in a greater reduction of LDL cholesterol. Rosiglitazone improves glucose control, but it may also be associated with increased cardiovascular risk.<sup>3</sup> Adding an angiotensin-receptor blocker to an angiotensin-converting-enzyme inhibitor may produce a greater reduction in blood pressure, but it may not reduce cardiovascular risk and it increases the risk of other adverse events.<sup>4</sup>

The importance of understanding clinical trials as tests of strategies has assumed even greater prominence because of two studies being reported on in this issue of the *Journal* — ACCORD (Action to Control Cardiovascular Risk in Diabetes) and ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation). These two studies (pages 2545–2559 and 2560–2572, respectively) tested the hypothesis that specific strategies involving the use of multiple medications to achieve tight glucose control would improve outcomes in patients with type 2 diabetes mellitus. The studies, which used dif-

ferent pharmacologic strategies, found that the tight control achieved did not reduce the risk of macrovascular complications. The ACCORD study's intensive con-

***We are now beginning to appreciate that a strategy's effect on a risk factor may not predict its effect on patient outcomes.***

trol strategy was associated with a higher risk of death, which led to early discontinuation of this part of the study. The ADVANCE study's findings indicate that its strategy may reduce the risk of worsening renal function at the cost of an excess risk of hypoglycemic events.

Thus, the risk–benefit ratio of interventions designed to modify risk factors can vary depending on the type and number of medications and other approaches that are concurrently incorporated. In particular, some medications may have beneficial or harmful effects beyond their effect on a risk factor. Moreover, the strength of the evidence supporting particular strategies varies. Some strategies are known to improve patient outcomes, whereas others are known to affect only risk-factor levels or other intermediate outcomes. We are now beginning to appreciate that a

strategy's effect on a risk factor may not predict its effect on patient outcomes.

Clearly, the way in which risk factors are modified really does matter. Lifestyle interventions may have few risks, but we cannot assume the same for drugs — and drug-related risks are not always known or appreciated. For example, the tendency of torcetrapib to cause blood pressure to rise and potassium levels to fall attracted much more attention after December 2006 than it had previously. In addition, medications may have interactions with other drugs, either directly or through their effect on patient adherence to treatment regimens.

As a result of these research advances, clinicians are now in a quandary. We prefer our clinical practice to be based on strong evidence. In the interest of promoting good care, we have constructed guidelines and performance measures that encourage treatment geared toward achieving ambitious goals for levels of glycated hemoglobin, lipids, and blood pressure. These treatment goals generally do not specify the strategy that should be used to reach the target. Statins are preferred in the reduction of LDL cholesterol, but guidance on their use is not strict.<sup>5</sup> If strategy matters, then guidelines should reflect this fact — and performance measures should be changed as well. After all, these measures are intended to hold clinicians accountable for practices whose benefits are widely recognized as far outweighing their risks.

How, then, should guidelines and performance measures change? First, we should no longer support

the use of targets without reference to the strategies used to achieve them. Guidelines and performance measures should reflect the evidence about interventions that are known to be beneficial. For example, guidelines for lowering lipid levels should be based on tested strategies and should make it clear that the strategies with the strongest evidence are preferred. A quality measure that incorporated the use of statins into an assessment of lipid-level control would be more scientifically sound than the simple assessment of the proportion of a physician's or practice's patients in whom a specific LDL cholesterol level was reached by any strategy. A quality measure for tight glucose control should require evidence that a proven strategy provides a strong net benefit for patients. We know that we are setting a high standard for developers of performance measures, but advances in our knowledge demand nothing less.

Second, guidelines and performance measures should incorporate more sophisticated and explicit considerations of the risks of disease and adverse consequences posed by the intervention. In patients with a low likelihood of a particular poor outcome, an in-

tervention designed to protect against that outcome is unlikely to provide substantial benefit — so if the intervention carries even a small risk, this risk can offset or even outweigh the benefit. In sicker patients and those with more complex conditions, certain interventions (such as maintenance of tight glucose control) may be more likely to produce adverse effects than they would in healthier patients, either directly or through their effect on adherence. For these patients, we need evidence that the strategy is safe and has a substantial net clinical benefit despite the greater risks of treatment.

The assessment of net clinical benefit should be based on events averted or lives improved. The promulgation of those strategies that are shown to be effective will serve as an incentive for drug and device developers to provide evidence about patient outcomes, not just about how a drug or device affects intermediate outcomes. Moving practice toward evidence-based strategies and becoming more accountable for what we do for patients represent important advances in our delivery of health care, but we must ensure that in implementing quality measures we are always acting in the patient's best interests. ACCORD, ADVANCE,

and other recent studies remind us that practice is complex and that ultimately we need to understand a strategy's effects on people, not just on surrogate end points.

No potential conflict of interest relevant to this article was reported.

This article (10.1056/NEJMp0803740) was published at [www.nejm.org](http://www.nejm.org) on June 6, 2008.

Dr. Krumholz is a professor of medicine at Yale University School of Medicine and director of the Center for Outcomes Research and Evaluation at Yale–New Haven Hospital — both in New Haven, CT. Dr. Lee is network president of Partners HealthCare System in Boston and an associate editor of the *Journal*.

1. Nissen SE, Tardif JC, Nicholls SJ, et al. Effect of torcetrapib on the progression of coronary atherosclerosis. *N Engl J Med* 2007; 356:1304-16.
  2. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative Randomized Controlled Trial. *JAMA* 2004;291:1701-12.
  3. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007;356:2457-71. [Erratum, *N Engl J Med* 2007;357:100.]
  4. The ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;358:1547-59.
  5. Smith SC Jr, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. *Circulation* 2006;113:2363-72. [Erratum, *Circulation* 2006;113(22)e847.]
- Copyright © 2008 Massachusetts Medical Society.