A drug, a concept, and a clinical trial on trial

The cornerstone of evidence-based medicine is the randomized controlled trial. To use the trial results, and for the trial to have external validity, we have to be able to extrapolate the population studied, the approach used in the trial, and the trial outcome measures to the patient on our examination table.

Many trials are funded by industry and carried out by clinical investigators in academic and private practice. Drug companies must perform these trials to win approval from the US Food and Drug Administration (FDA) for their new drugs and package inserts, which dictates what they can and can't say in their advertising. This latter requirement often leads to trials after a drug is approved in an effort to aid drug promotion and improve its position in the marketplace.

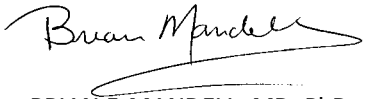
The FDA is increasingly demanding that new drug studies use "hard" measures of efficacy and less reliance on surrogate end points. This requires larger, longer, more expensive trials.

A recent trial that relied on surrogate end points was the ENHANCE trial, which evaluated the addition of a second approved cholesterol-lowering drug (ezetimibe) to a statin in a relatively small number of mostly pretreated patients. The surrogates were lipid-lowering and carotid intima-media thickness. At the time the study was designed, I'm sure it seemed obvious that lowering low-density lipoprotein cholesterol (LDL-C) or reducing the measured burden of atherosclerosis would reduce the consequences of hypercholesterolemia, including myocardial infarction and stroke. Therefore, the use of surrogate markers seemed an acceptable expediency.

However, the ENHANCE results hit the national news when the two surrogates didn't coincide as anticipated. Although ezetimibe/simvastatin (Vytorin) lowered the LDL-C level more than simvastatin alone (Zocor), it did not reduce carotid intima-media thickness.

The response was intense. Trialists, drug safety pundits, industry representatives, politicians, and clinicians all weighed in. Some patients apparently stopped taking their lipid-lowering medications. Without any striking evidence of worse outcome, doubt has been cast on the safety and efficacy of the drug and—perhaps inappropriately—on the entire LDL-C hypothesis of atherosclerosis.

In this issue, Dr. Michael Davidson (page 479) and Dr. Allen Taylor (page 497), two clinical experts in atherosclerosis, present widely divergent views on the conduct, results, and implications of the ENHANCE trial. Dr. Taylor was afforded the opportunity to read Dr. Davidson's manuscript before writing his own editorial. I'm not sure their discussion will settle this intense debate, but they outline the issues clearly.



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