Statin Strikeout

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The results of two randomized, controlled trials, supported by the U.S. National Institutes of Health, in which inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase, commonly known as statins, were tested for efficacy in sepsis-associated acute respiratory distress syndrome (ARDS) and in chronic obstructive pulmonary disease (COPD) are now reported in the Journal. The rationale of the trials was based largely on observational data showing that patients with these conditions who were taking statins had better outcomes than patients who were not. Both trials were stopped by the data and safety monitoring boards before the projected enrollment was completed because no therapeutic benefit was apparent. The cynic would say that the public’s money had been wasted — we had struck out swinging.

Is the cynic right, or did we benefit from the resources spent on these trials? To answer this question, we need to consider two major sources of ideas for clinical trials. One approach starts with a hypothesis, founded on some basic scientific understanding, that an intervention to interrupt or augment a pathway will ameliorate the clinical, physiological, and biochemical manifestations of disease. The clinical trial uses the intervention to test the hypothesis. If the trial succeeds, the biologic principle is established, and depending on the toxicity and availability of the intervention, the test agent could become clinically useful for diagnosis or treatment. The recent successes in the treatment of hepatitis C fit this paradigm, but there are many others, including the use of statins for preventing cardiovascular disease and the treatment of chronic myelogenous leukemia with tyrosine kinase inhibitors. This paradigm demonstrates the power of “bench-to-bedside” translational investigation. Unfortunately, despite increased reliance on this model of drug discovery, the failure rate of new agents remains high: only 10% of new drugs that enter phase 1 clinical trials make it into widespread use.

This sobering statistic has put the spotlight on the second approach. Here, the test agent is already in use for a defined indication. If that indication is reasonably common, then over time, observations tend to emerge about unexpected benefits or side effects of the drug. When an association is observed, usually from a number of distinct sources, and if a reasonable biologic rationale can be proffered, trialists take the next logical step and devise a randomized, controlled trial to determine whether a causal relationship between administration of the agent and desired clinical outcomes can be shown. If the trial “works,” the relationship is established, and the therapeutic scope of the test agent may be expanded.

There are important examples of this “discovery-in-practice” approach. Aspirin, arguably the most widely used drug in the world, was introduced as an analgesic and antipyretic and later discovered in observational studies and confirmed in randomized, controlled trials, to have cardiovascular benefits in preventing myocardial infarction. Bupropion, introduced as an antidepressant, was incidentally found to be an effective smoking-cessation aid. Similarly, anticonvulsants, which originally targeted epilepsy, were found to be effective mood stabilizers in patients with bipolar disorders.

In the past, new uses were often found for old drugs owing to insights from individual observations, and the process was slow: it took more than half a century for the cardiovascular benefits of aspirin to be recognized. In this era of electronic health records, interest has grown in accelerating the discovery and introduction of new indications for existing therapeutics by using new computational tools to analyze much broader experience through databases that include information on the effects of compounds on cellular physiology, drug use, pharmacogenomics, and adverse events — databases capturing many “off-target” outcomes. Data scientists seek signals of possible associations between these outcomes and treatment with the agent. Such findings represent one promise of “big data.”

As noted above, both trials now reported in the Journal tested statins, drugs with known
pleomorphic antiinflammatory properties, in conditions in which inflammatory events are thought to drive disease pathobiology. In both diseases, our therapeutic armamentarium is meager, the public health need is great, and the intervention was reasonable and had face validity. Although both trials had negative results, they had to be done — not because statins were widely used for COPD or sepsis-associated ARDS, but because we needed to bridge the gap between information gleaned by deduction from observation (something we thought was working) and information gleaned from interventional experimentation (something we know works — or in this case, does not work). It would have been a big mistake to accept the findings without a test.

Our response to the cynic is simple: we struck out this time, but there will be more chances to hit in the future. Had we accepted the observational data at face value, we might have spent the cost of the trials many times over in useless treatments before recognizing our errors. That raises a hard question: With the advent of big data, which observational associations should we test in rigorous trials? The answer will not come easily, but in the end, a batting average of .400 would be terrific.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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