Niacin: Time to Believe Outcomes Over Surrogate Outcomes
If Not Now, When?

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Long-acting niacin, a blockbuster drug for many years, emerged during an era in which the simple assumption was that favorably modifying patients’ lipid profiles was tantamount to lowering their risks for cardiovascular disease. The implicit assumption in the medical community and among regulators was that improving lipid profiles would improve outcomes even as the mechanism of the drug action was not clear. This approach holds sway today as evidenced by the recent approval of the PCSK9 inhibitor drugs before the completion of the definitive phase 3 outcome trials.1,2 The evidence suggests that the way in which a risk factor is modified matters for whether it produces a benefit.3

Long-acting niacin is a particularly interesting case because it was included in one of the earliest outcome trials, the Coronary Drug Project, initiated in 1966, although the results were equivocal.4 With 5 to 8 years of follow-up, niacin failed to improve mortality, the primary end point. The 5-year rates of death were 21.2% for niacin and 20.9% for placebo. Death rates because of coronary heart disease were also close and not significantly different: 15.9% for niacin and 16.2% for placebo. The niacin group did have a lower risk of nonfatal myocardial infarction, one of the secondary end points. It should also be noted that because of the side effects of the drug, the investigators conceded that the niacin group was essentially unblinded which could have introduced bias. A 15-year follow-up study of the Coronary Drug Project, >9 years after its termination, found that the niacin group had an 11% lower mortality, but that study is properly considered exploratory.5

From its introduction, long-acting niacin was strongly promoted and quickly became a blockbuster drug. Between 2002 and 2009, use of niacin in the United States increased by 191.2%, reaching 696,000 prescriptions per month in December 2009.6 In 2009, prescription niacin expenditures in the United States totaled almost $900 million. In 2013, the year that long-acting niacin went generic, worldwide sales for the branded version surpassed $1 billion.7

More recently, 2 major clinical trials finally evaluated the effect of long-acting niacin on patient outcomes; both showed the drug in a negative light. The AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes) trial, sponsored by the National Institutes of Health, enrolled 3414 patients with established atherosclerotic cardiovascular disease, low high-density lipoprotein cholesterol, and elevated triglycerides.8 The investigators found no clinical benefit with 36 months of follow-up, with the primary outcome occurring in 16.4% of the niacin group and 16.2% of the placebo group.

The HPS2-THRIVE (Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events) trial, sponsored by Merck, assessed long-acting niacin in combination with laropiprant in 25,673 high-risk patients.9 Laropiprant was intended to blunt the side effects of niacin and improve adherence. Again, niacin failed to produce clinical benefit and was associated with an excess of diabetes mellitus, infections, gastrointestinal effects, and bleeding. It is possible that the combination or laropiprant alone was responsible for the harm, but the evidence suggests niacin as the cause; it would seem irresponsible to assume otherwise without more proof given that the benefit of niacin in the current era is not established.

A meta-analysis of niacin clinical trials, which included these recent trials, studied 11 trials and 35,301 patients.10 The conclusion was that niacin did not reduce all-cause mortality, coronary heart disease mortality, myocardial infarction, or stroke in patients treated with statins. In patients not treated with statins, there was a benefit for nonfatal myocardial infarction and stroke, but these studies are largely older. The lack of benefit for the other end points persisted in the group not treated with statin.

In this issue, the HPS2-THRIVE Investigators have evaluated healthcare costs associated with long-acting niacin/laropiprant combination and as expected, the news is not good. They report that the combination reduced quality of life–adjusted survival and increased hospital costs. Assignment to the niacin group resulted in 300 fewer years of life in good health and almost $2 million more in hospital costs.11

The challenge now is to change practice. The impulse of many practitioners is to treat laboratory values, and although niacin sales have dropped (particularly as the long-acting agent became generic), there remain many prescriptions written and dollars spent. The outcomes trials have failed to show benefit in the current era, and until other evidence emerges, this drug should be relegated to medical history. Moreover, we need to be accountable for responding to such evidence. This situation may be a prime opportunity for quality measures that assess...
use of discredited clinical strategies, with an opportunity for rare exceptions if those strategies could truly be justified.

The evidence has implications for patients. At a minimum, those for whom niacin is contemplated should be part of a shared decision-making and informed consent process. No one should take the drug without information about the trials, with particular attention to the lack of clinical benefit and the evidence of harm. People may speculate about yet-to-be studied subgroups that could benefit, but it needs to be clear that it is speculation. The risks of such a decision should be delineated.

The real challenge is to gather this evidence before billions are spent on the next drug and before people are exposed to a potentially harmful agent. It is becoming abundantly clear that even the best risk factors cannot take the place of outcomes. That failure is often not because the risk factor is flawed, but that drug interventions have many off-target effects that can counter or even reverse any benefit that might be expected from the risk factor modification. We are doing a disservice to our patients if drugs like niacin and ezetimibe are only truly tested when the patent protection ends. There need to be strong incentives to generate this type of information earlier.

Medicine needs to accept the challenge to generate knowledge with greater alacrity and urgency. The costs of delay, in many cases, are much greater than the costs of the studies. When we connect the dots, we will recognize that the costs of harm are real—and preventable only with earlier knowledge—and build a system that acts quickly on that knowledge.

**Disclosures**

Dr Krumholz is a 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 UnitedHealth.

**References**


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