Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 59, No. 23, 2012
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2012.02.021

The AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes) Trial

To Believe or Not to Believe?

Stephen J. Nicholls, MBBS, PHD

Cleveland, Ohio

The beneficial effect of lowering low-density lipoprotein cholesterol (LDL-C) in clinical trials (1) has transformed our ability to reduce cardiovascular risk. However, increasing recognition that many patients experience a clinical event, despite the use of LDL-C lowering therapies, has stimulated the ongoing search to develop additional therapeutic strategies. Although elevated levels of triglycerides and lipoprotein(a) independently predict cardiovascular events (2,3), to the author's knowledge, no clinical trial to date has demonstrated that any therapy that specifically targets either of these factors is associated with cardiovascular benefit.

High-density lipoprotein cholesterol (HDL-C) has received considerable interest with respect to potential cardiovascular protection. Population studies consistently demonstrate an inverse relationship between HDL-C levels and prospective cardiovascular risk (4), which has prompted the concept that substantially increasing HDL-C would be beneficial. Preclinical studies demonstrating favorable effects of HDL-C–based interventions in cellular and animal models provide further support for the interest in developing therapies that increase HDL-C (5). However, current lipid-modifying approaches typically have modest effects on HDL-C.

Niacin as a Viable Therapeutic Option

For >50 years, niacin has been used in clinical practice for the management of dyslipidemia. Niacin remains the most effective HDL-C increasing agent available in clinical practice and is often used in patients with very low HDL-C levels. It is also widely used by virtue of its ability to lower levels of atherogenic lipid parameters in patients with mixed dyslipidemia, suboptimal LDL-C control, or statin intolerance. The beneficial effects of niacin on levels of atherogenic and protective lipids are further supported by evidence that early formulations of niacin had a favorable cardiovascular impact. The Coronary Drug Project, conducted in the pre-statin era, demonstrated that use of immediate-release forms of niacin decreased the rates of nonfatal myocardial infarction and long-term mortality (6).

Subsequent imaging studies demonstrated that immediate-release forms of niacin produced mild, but significant, regression of coronary atherosclerosis on angiography (7), whereas more extended release formulations had a favorable impact on the progression of carotid intima–medial thickness (8,9). More recent studies using magnetic resonance imaging demonstrated similarly beneficial effects of niacin on carotid atherosclerosis in some (10), but not all (11), studies. The findings of these studies provide a strong rationale for determining the potential role of niacin in the statin era.

The AIM-HIGH Trial

The AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes) trial evaluated the impact of extended-release niacin versus placebo in patients with established atherosclerotic disease on statin therapy, with a background of low HDL-C and high triglyceride levels (12). At the time of a planned interim analysis, after an average of 3 years of treatment, the Data Safety and Monitoring Board recommended early cessation of the study due to the futility of the primary endpoint and a potential increase in the risk of stroke. Predictably, the niacin group demonstrated a greater increase in HDL-C (25.0% vs. 9.8%) and decrease in triglycerides (28.6% vs. 8.1%) and LDL-C (12.0% vs. 5.5%), the latter despite the use of an LDL-C algorithm, resulting in more placebo-treated patients requiring increases in statin dose or the addition of ezetimibe. A nearly identical number of cardiovascular events was observed in both treatment groups. Although a greater number of ischemic strokes was recorded

From the Departments of Cardiovascular Medicine and Cell Biology, Cleveland Clinic, Cleveland, Ohio. Dr. Nicholls has received research support from AstraZeneca, Roche, Novartis, Resverlogix, Anthera, Eli Lilly, and Liposcience; and consulting fees or honoraria from AstraZeneca, Merck, Takeda, Roche, Omthera, CSL Behring, and Boehringer-Ingelheim.

Manuscript received February 9, 2012; accepted February 15, 2012.

in the niacin group, many occurring >2 months after cessation of therapy, this ultimately did not meet statistical significance. The results demonstrated unequivocally no signal of potential benefit in the niacin group.

Challenges for Interpreting AIM-HIGH

Although AIM-HIGH was stopped in May 2011, the formal results were not revealed until November. This permitted considerable time for widespread speculation of the reasons underlying the failure of efficacy and potential mechanisms leading to an increase in stroke risk. This included media coverage and uncertainty in clinical practice whether to continue use of niacin for cardiovascular risk prevention. Now that the definitive findings of the study have been revealed, how should they be interpreted for the management of patients with dyslipidemia? To do this, one must determine what the real objective was of AIM-HIGH.

Given that the fundamental comparison was between extended-release niacin and placebo, the easiest conclusion would be that AIM-HIGH was a test of the niacin hypothesis. The overwhelming majority of data in niacin trials, using either the immediate- or extended-release formulation, demonstrated potential cardiovascular benefit. However, the clinical event benefit was observed in the pre-statin era and involved formulations that are poorly tolerated by many patients. There is substantial interest in determining whether a well-tolerated form of niacin is beneficial in the setting where statin therapy has become almost ubiquitous. However, AIM-HIGH was not a simple comparison of niacin and placebo. In fact, the authors, appreciating that niacin lowers atherogenic lipid parameters, used a lipid-lowering algorithm to equilibrate LDL-C levels. What eventuated was a comparison of niacin- and placebo-treated patients who were more likely to be treated with ezetimibe and higher doses of simvastatin. Furthermore, placebo-treated patients actually received as much as 200 mg daily of immediate-release niacin to induce flushing and maintain the blind. The rationale for this action lay in the experience that, although flushing occurs at low doses, beneficial effects of niacin on lipids are typically not observed until doses of at least 1,500 mg/day are administered. However, the possibility that niacin had some favorable effects, reported by some investigators (13), cannot be excluded. Therefore, it is not possible to simply conclude that AIM-HIGH was a straightforward arbiter of the potential cardiovascular benefits of niacin. That remains the opportunity for a more simply designed study.

The other factor implicated in the futility of AIM-HIGH is increasing HDL-C. Niacin continues to be the most effective HDL-C–increasing agent in clinical practice. Considerable interest has focused on the potential benefit of HDL-C–increasing therapies, based on findings from population and animal studies (4,5). This is of most importance in the statin-treated patient whose HDL-C remains low, with evidence that these patients have a substantial ongoing risk of cardiovascular events (14). In many ways, such observations underscored the selection of low HDL-C patients in the AIM-HIGH trial. However, although a number of reports suggest that a modest increase in HDL-C may contribute to the benefits of statins and fibrates, more recent high-profile failures in clinical trials of fenofibrate (15), torcetrapib (16), and now niacin in the AIM-HIGH trial provide further ammunition for those skeptical of increasing HDL-C as a viable cardioprotective strategy.

Was AIM-HIGH a true test of the HDL-C hypothesis? The use of LDL-C equilibration strategies further aimed to focus the spotlight on increasing HDL-C. However, the final publication revealed an underwhelming result, with a much smaller difference in HDL-C than expected in the 2 treatment groups. Although a greater increase in HDL-C was observed with niacin, the absolute difference in achieved HDL-C levels was only 4 mg/dl (42 vs. 38 mg/dl). This was largely due to an unexpected increase in HDL-C by 9.8% in the placebo group. Although the reason for this is uncertain, it may reflect the use of higher statin doses, small doses of immediate-release niacin, and potential regression to the mean in these patients. Moreover, niacin has additional effects, beyond its effects on HDL-C and LDL-C. Niacin lowers triglycerides and is the most effective agent for decreasing levels of lipoprotein(a). Whether these effects, in addition to the reported favorable effects on endothelial function, have further effects in these patients is uncertain, but must be considered when seeking the rationale for futility. Accordingly, it seems premature to attribute these disappointing findings to a failure of the HDL hypothesis. Although one should not throw the baby out with the bathwater, the attempts to demonstrate the potential benefit of increasing HDL-C will be limited. The clock continues to tick.

The ultimate question when interpreting AIM-HIGH is to ask whether the trial delivered the comparison that it sought to carry out. The study endeavored to determine whether niacin, which would increase HDL-C, would decrease events in patients with atherosclerotic disease and low HDL-C and high triglyceride levels, when LDL-C levels were kept at comparable levels in the 2 groups. The study needed to enroll 3,414 patients to have 85% power to demonstrate a 25% reduction in clinical events with niacin. In the statin era with decreasing event rates, these sample-size assumptions seemed overly optimistic. Many contemporary studies require well in excess of 10,000 patients to demonstrate adequate power and target much more realistic relative-risk reductions, on the order of 15%. Considering that the achieved lipid levels demonstrated a small difference between treatment groups in terms of both HDL-C (4 mg/dl) and LDL-C (5 mg/dl), the most optimistic relative-risk reduction that one could predict would be closer to 10%. There is no doubt that AIM-HIGH demonstrated unequivocal futility and should have been stopped, the question being if the investigators knew at the outset what

they know now, would they have started at all? Ultimately, with the assistance of the faithful "retrospectoscope," it would appear that even an optimist would have to concede that this was the wrong trial to answer the important question that the investigators sought to answer.

Where to From Here?

AIM-HIGH is an important study with considerable implications for physicians and clinical trialists. In this issue of the *Journal*, Michos et al. (17) place the AIM-HIGH trial in the context of previous studies of niacin and recent high-profile failures of lipid-modifying therapies in statin-treated patients. Before one embarks on trying to find some clinical context for the findings, we need to ask whether the study truly ended up meeting its initial objectives. For this, the answer unfortunately has to be no. Herein lies the difficulty of knowing when to accept and adopt the findings of clinical trials. The randomized, clinical trial has guided much of our practice over the course of the past 3 decades. Unfortunately, trials do not always provide the clear answer that we are looking for.

Do the findings change the way in which niacin is used in clinical practice? For those who perceive the results as a failure of niacin, they are likely to use this agent less for risk reduction. For those who do not think that AIM-HIGH proved a lack of efficacy of niacin, they will continue to use it for its range of lipid-modifying effects, particularly in those treated with maximally tolerated statin doses but are still not at their LDL-C goal, and wait for the findings of future clinical trials to make their ultimate decision. The HPS2-THRIVE (Treatment of HDL to Reduce the Incidence of Vascular Events) study is designed to directly compare the effects of the combination of extended-release niacin and the prostaglandin receptor antagonist laropiprant with those of placebo, and no in-study titration of LDL-C, in >24,000 statin-treated patients (18). It would seem that this trial represents a more adequately powered and simple study to determine whether the use of niacin is efficacious in the setting of statin therapy.

However, the findings of AIM-HIGH do add to a mounting challenge for those developing new antiatherosclerotic therapies. LDL-C lowering, particularly with statins, has had a profound impact on cardiovascular event rates. We highlight the ongoing occurrence of events as the rationale to develop new therapies, yet, to date, we have failed to demonstrate that any new strategy has a favorable outcome on a background of statin therapy. Does this imply that we have come to the end of the road in terms of reducing cardiovascular risk, when patients achieve effective LDL-C lowering, perhaps? Is it possible that much of the residual risk that we highlight is not modifiable? Or perhaps do we need to identify alternative targets for modification? That remains the focus for future clinical trials, and for that reason, we continue to believe that we can further reduce the burden of cardiovascular disease.

Reprint requests and correspondence: Dr. Stephen J. Nicholls, Department of Cardiovascular Medicine, Mail Code JJ-65, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, Ohio 44195. E-mail: nichols1@ccf.org.

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Key Words: AIM-HIGH ■ HDL ■ lipids ■ niacin ■ review.