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Is niacin ineffective? Or did AIM-HIGH miss its target?

■ ABSTRACT

The AIM-HIGH trial (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes) found, in an interim analysis, no cardiovascular benefit from taking extended-release niacin (Niaspan). In fact, there was a trend toward a greater risk of ischemic stroke, which did not reach statistical significance. But questions remain about this complex trial, which included intensive statin therapy in the active-treatment group and the control group.

■ KEY POINTS

The study was stopped early because of the concerns raised by the interim analysis.

The AIM-HIGH results can be interpreted in several ways: perhaps niacin is no good as a preventive agent; perhaps raising levels of high-density lipoprotein cholesterol (HDL-C) is flawed as a preventive strategy; perhaps AIM-HIGH had methodologic flaws; or perhaps statins are so good that, once you prescribe one, anything else you do will not make much of a difference.

It seems reasonable to continue niacin treatment in patients who need its multiple lipid-modifying effects. It is uncertain if clinicians will be less likely to prescribe niacin therapy until we have clear evidence of clinical benefit. As for HDL-C, it remains to be determined whether any therapy targeting quantitative or qualitative changes will be beneficial.

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THE RECENT PUBLICATION of the AIM-HIGH trial (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes)¹ has thrown the use of niacin as a lipid-modifying therapy into question. The trial was stopped early because an interim analysis found that the patients who took extended-release niacin had no clinical benefit. In addition, it found a trend toward more ischemic strokes, though this finding was later found not to be statistically significant.

Complicating the interpretation, while both the treatment group and the control group in the study received statin therapy, the researchers attempted to keep low-density lipoprotein cholesterol (LDL-C) levels equal, meaning that patients in the control group received more intensive statin therapy than those in the treatment group. And the placebo that the control patients received was actually a low dose of niacin, to induce flushing and thus to blind study participants and their physicians to which drug they were taking.

In the article that follows, I will explore the background, design, findings, and implications of this key trial and try to untangle the many questions about how to interpret it.

■ LOWERING LDL-C REDUCES RISK, BUT DOES NOT ELIMINATE IT

Large randomized controlled trials have consistently shown that lowering the level of LDL-C reduces cardiovascular event rates by 25% to 45% both in people who are known to have coronary artery disease and in those who are not.²⁻⁴ As a result, guidelines for preventing cardiovascular disease have increasingly

emphasized maintaining low LDL-C levels. This has led to a proliferation in the use of inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (statins) in patients at high cardiovascular risk.

However, these agents only reduce the risk—they do not eliminate it. Needed are additional therapies to complement existing LDL-C-lowering approaches to lower the cardiovascular risk even further.

Raising HDL-C: The next frontier

One such strategy for further lowering cardiovascular risk that has received considerable interest is to promote the biological activity of the “good” cholesterol.

Studies have consistently shown that the higher the plasma level of high-density lipoprotein cholesterol (HDL-C), the lower the risk of cardiovascular events, suggesting that raising HDL-C may be beneficial.⁵ Studies in animals with atherosclerosis show that raising HDL-C via genetic modification of the animal or direct infusion of the molecule has a favorable impact on both the size and the structure of experimental plaque.^{6,7}

Accordingly, much activity has focused on developing new therapies that raise HDL-C more effectively than current ones.

Why niacin should protect the heart

For more than 50 years, niacin has been used to manage dyslipidemia.

In addition to raising HDL-C levels more effectively than any other agent available today, niacin also lowers the levels of LDL-C, triglycerides, and lipoprotein (a).⁸ Before statins were available, the Coronary Drug Project found that niacin reduced the rate of nonfatal myocardial infarction and the 15-year mortality rate.⁹ In addition, niacin has been shown to slow the progression of carotid intimal-medial thickness and coronary atherosclerosis, and even to reverse these processes in some trials.¹⁰⁻¹²

However, a number of issues remain about using niacin to prevent cardiovascular events. Nearly all patients who take it experience flushing, which limits its tolerability and, thus, our ability to titrate doses to levels needed for adequate lipid changes. While a number of modifications of niacin administration have been developed (eg, extended-release

formulations and products that inhibit flushing), no large study has tested the clinical efficacy of these strategies. Furthermore, until AIM-HIGH, no large-scale trial had directly evaluated the impact of niacin therapy on a background of statin therapy.

AIM-HIGH STUDY DESIGN

The intent of the AIM-HIGH trial was to determine whether extended-release niacin (Niaspan) would reduce the risk of cardiovascular events when added to therapy with a statin—in this case, simvastatin (Zocor) supplemented with ezetimibe (Zetia).¹

The trial was funded by the National Heart, Lung, and Blood Institute (NHLBI) and by Abbott Laboratories, which also supplied the extended-release niacin and the ezetimibe. Merck donated the simvastatin.

Patient characteristics

The patients were all at least 45 years of age with established, stable coronary heart disease, cerebrovascular or carotid arterial disease, or peripheral arterial disease. They also had to have low levels of HDL-C (< 40 mg/dL in men, < 50 mg/dL in women), elevated triglycerides (150–400 mg/dL), and LDL-C levels lower than 180 mg/dL if they were not taking a statin at entry.

The mean age of the patients was 64 years, 85% were men, and 92% were white. They had a high prevalence of cardiovascular risk factors: 34% had diabetes, 71% had hypertension, and 81% had metabolic syndrome. Nearly all (94%) of the patients were taking a statin at entry; 76% had been taking one for more than 1 year, and 40% had been taking one for more than 5 years.¹

Simvastatin, ezetimibe, and either niacin or placebo

All lipid-modifying agents except statins and ezetimibe were stopped for least 4 weeks after enrollment.

All patients then entered a 4- to 8-week open-label period, during which they took simvastatin 40 mg daily and extended-release niacin starting at 500 mg and increased weekly up to 2,000 mg daily. Patients who could tolerate at least 1,500 mg daily were randomly

Studies have consistently shown that the higher the HDL-C, the lower the risk

assigned to treatment with either niacin 1,500 to 2,000 mg or matching placebo. Both groups continued to receive simvastatin. The placebo contained a small dose of immediate-release niacin (50 mg) in each tablet to induce flushing and to maintain blinding of treatment.

Given that niacin also lowers LDL-C, an algorithm was used to try to keep LDL-C levels roughly the same in both treatment groups. This involved adjusting the simvastatin dose and permitting the use of ezetimibe 10 mg to keep the LDL-C level between 40 and 80 mg/dL. Accordingly, participating physicians were told their patients' LDL-C levels but were blinded to their HDL-C and triglyceride levels throughout the study.

Every 6 months, patients had a follow-up visit in the clinic, and midway through each 6-month interval they received a phone call from the investigators.¹

AIM-HIGH end points

The **primary end point** was the composite of the first event of death due to coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalization for acute coronary syndrome, or symptom-driven revascularization of the coronary or cerebral arteries.

Secondary end points were:

- Death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, or hospitalization for acute coronary syndrome
- Death from coronary heart disease, nonfatal myocardial infarction, or ischemic stroke
- Death from cardiovascular causes.

Tertiary end points included:

- Death from any cause
- Individual components of the primary end point
- Prespecified subgroups according to sex, history or no history of diabetes, and presence or absence of the metabolic syndrome.¹

All clinical events were adjudicated by a central committee.

STUDY HALTED EARLY

The study was planned to run for a mean of 4.6 years, during which 800 primary end point events were expected. With these numbers, the

investigators calculated that the study had 85% power to detect a 25% reduction in the primary end point, at a one-sided alpha level of 0.025.

The plan called for an interim analysis when 50% of the anticipated events had occurred, with prespecified stopping boundaries based on either efficacy or futility. The boundary for lack of efficacy required an observed hazard ratio of at least 1.02 with a probability of less than .001.

In the interim analysis, after a median follow-up of only 3 years, the data and safety monitoring board recommended stopping the study early because the boundary for futility had been crossed and, unexpectedly, the rate of ischemic stroke was higher in the niacin-treated patients than in those receiving placebo.

MAJOR FINDINGS OF AIM-HIGH

Of 4,273 patients who began open-label treatment with niacin, 3,414 were randomized to treatment with niacin or placebo.¹

HDL-C levels went up in both groups

At 2 years:

- HDL-C levels had increased by 25.0% (to 42 mg/dL) in the niacin group and by 9.8% (to 38 mg/dL) in the placebo group
- Triglycerides had decreased by 28.6% with niacin and by 8.1% with placebo
- LDL-C had decreased by 12.0% with niacin and by 5.5% with placebo.

Patients in the placebo group were more likely to have subsequently received the maximum dose of simvastatin, ie, 80 mg/day (24.7% vs 17.5%), and to have received ezetimibe (21.5% vs 9.5%). More patients in the niacin group required either dose reduction of the study drug (6.3% vs 3.4%) or drug discontinuation (25.4% vs 20.1%).¹

No difference in the primary end point

There was no difference between the two treatment groups in the rate of the primary end point, which occurred in 282 (16.4%) of the 1,718 patients in the niacin group and 272 (16.2%) of the 1,696 patients in the placebo group ($P = .79$; hazard ratio 1.02, 95% confidence interval 0.87–1.21).¹

However, more patients in the niacin group than in the placebo group who reached the primary end point did so by having a first

Niacin not only raises HDL-C, it lowers LDL-C, triglycerides, and lipoprotein (a)

ischemic stroke: 27 patients (1.6%) vs 15 patients (0.9%). Eight of these patients, all in the niacin group, had their stroke between 2 months and 4 years after they had stopped taking the study drug.

Further analysis that included all ischemic strokes revealed the same trend: 29 vs 18 patients ($P = .11$).¹

No benefit was observed for niacin-treated patients in terms of any of the secondary or tertiary end points.

Subgroup analysis revealed no evidence of statistical heterogeneity: ie, niacin seemed to lack efficacy in all the prespecified subgroups studied (age 65 and older vs younger, men vs women, and those with or without diabetes, metabolic syndrome, prior myocardial infarction, or statin use at entry).

In general, niacin was well tolerated in the active-treatment group, with a low incidence of liver and muscle abnormalities.

■ PUTTING AIM-HIGH IN CONTEXT

How should practicing clinicians interpret these outcomes?

Ever since the NHLBI reported (in an urgent press release) that it was stopping the study early due to futility and a potential excess of strokes,¹³ there has been considerable debate as to which factors contributed to these outcomes. In the wake of the publication of more detailed information about the trial,¹ this debate is likely to continue.

The AIM-HIGH results can be interpreted in several ways:

- Perhaps niacin is no good as a preventive agent
- Perhaps raising HDL-C is flawed as a preventive strategy
- Perhaps AIM-HIGH had methodologic flaws, such as looking at the wrong patient cohort or using a treatment protocol that set itself up for failure
- Perhaps statins are so good that, once you prescribe one, anything else you give provides no additional benefit.

Which of these is correct?

Is niacin no good?

In its most simple form, AIM-HIGH has always been seen as a clinical trial of niacin. While the

early trials of immediate-release niacin were encouraging in terms of its effects on lipids, atherosclerotic plaque, and cardiovascular outcomes, using it in clinical practice has always been challenging, largely because many patients cannot tolerate it in doses high enough to be effective. A number of developments have improved niacin's tolerability, but its clinical impact in the statin era has not been evaluated.

Niacin's lack of efficacy in this trial will ultimately be viewed as a failure of the drug itself, but is this the case?

AIM-HIGH was not simply a direct comparison of niacin vs placebo on top of standard medical practice. The investigators recognized that niacin has additional effects—in particular, lowering levels of atherogenic lipids—and they attempted to control for these effects by titrating the other LDL-C-lowering therapies during the study. As a result, the trial was actually a comparison between niacin plus low-dose simvastatin on the one hand, and placebo plus high-dose simvastatin (and, more often, also ezetimibe) on the other.

Furthermore, the placebo-treated patients received small doses of immediate-release niacin to induce flushing and maintain blinding. It is therefore hard to conclude that this clinical trial was a direct evaluation of the impact of niacin.

In contrast, the Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) study is currently evaluating extended-release niacin in combination with laropiprant, a prostaglandin receptor antagonist, vs placebo in more than 24,000 statin-treated patients.¹⁴ Without any in-trial titration of lipids, this study provides a more direct comparison of the effects of niacin in the statin era.

Niacin continues to attract interest, largely because it can raise HDL-C by 20% to 30% when given at doses of 1,500 mg or more. Also, consistent observations from population studies of an inverse relationship between HDL-C levels and cardiovascular risk⁵ have stimulated interest in developing novel agents that substantially raise HDL-C.

Is raising HDL-C a flawed strategy?

The failure of HDL-C-raising therapies in clinical trials^{15,16} has fueled concern that HDL may not be the magic elixir that many have

The placebo contained niacin 50 mg to induce flushing and maintain blinding

sought. Given that niacin is the most effective HDL-C-raising agent currently available, its lack of efficacy in AIM-HIGH could be perceived as another nail in the coffin of the hypothesis that raising the HDL-C level with pharmacologic agents is beneficial.

AIM-HIGH was designed to examine the effects of raising HDL-C. To this end, it was performed exclusively in patients with low HDL-C levels, and the investigators tried to isolate the potential effects of raising HDL-C by equalizing the LDL-C levels in the treatment groups.

However, the HDL-C changes observed in AIM-HIGH are likely to have undermined the study objective. While niacin predictably increased HDL-C levels by 25%, an unexpected increase in HDL-C of 9.8% in the placebo-treated patients resulted in a difference in achieved HDL-C levels of only 4 mg/dL between the groups. This was far less than anticipated, and it likely had a major impact on an already underpowered study.

AIM-HIGH was designed to have 85% power to demonstrate a 25% reduction in clinical events, which was an optimistic estimate. On the basis of population studies, a difference of 4 mg/dL in HDL-C would be anticipated to result in no more than a 10% lower rate of clinical events, far beyond AIM-HIGH's limit of detection.

The reasons for the increase in HDL-C in the placebo group are unknown, but they likely reflect the use of higher doses of simvastatin, some regression to the mean, and, possibly, the small doses of immediate-release niacin that the placebo contained. (Contrary to the belief of the investigators, there have been some reports of lipid changes with such doses,¹⁷ which may have contributed to the observed HDL-C-raising.)

Given that the HDL-C difference between the groups was relatively small and that niacin has additional effects beyond raising HDL-C and lowering LDL-C, it is unlikely that the futility of AIM-HIGH reflects a major indictment of HDL-C-raising. For the time being, the jury is still out on this question.

Was AIM-HIGH methodologically flawed?

A number of methodologic issues may have affected AIM-HIGH's ability to adequately address its objectives.

The wrong cohort? In planning a study such as AIM-HIGH, the need for a relatively small sample size and the need to detect the greatest relative risk reduction with niacin would require enrollment of patients at the highest risk of cardiovascular events despite the use of statins. These needs were satisfied by only including patients who had atherosclerotic cardiovascular disease and low HDL-C levels. The inclusion of patients with low levels of HDL-C was also expected to promote greater increases in this lipid, and potentially event reduction, with niacin.

But no benefit was observed. It remains to be determined whether the inclusion of a high proportion of patients with the metabolic syndrome adversely affected the ability to detect a benefit with niacin. While post hoc analyses of studies of carotid intimal-medial thickness demonstrated no relationship between raising HDL-C with niacin and slowing of disease progression in patients with the metabolic syndrome,¹⁸ it remains to be determined whether this would translate to any effect on cardiovascular event rates.

Inadequate statistical power? An underpowered study would leave very little room for error, a pertinent point given the variability in therapeutic response in both actively treated and placebo-treated patients typically encountered in clinical trials. Giving low doses of immediate-release niacin and titrating the simvastatin dose to control LDL-C, resulting in imbalances in lipid-modifying therapies, represent additional flaws in the study design.

Stopped too soon? The early cessation of the study was somewhat questionable. The study crossed the prespecified boundary for lack of efficacy at the time of the interim analysis, and initial review by the data and safety monitoring board suggested an excess rate of ischemic stroke with niacin. The inclusion of this latter finding in the press release prompted considerable speculation regarding potential mechanisms and also concern among patients currently taking niacin. The subsequent finding that this signal was not statistically significant serves as an important warning for those conducting clinical trials not to prematurely overstate preliminary observations.

The implications for agents used in clinical practice are considerable: negative find-

AIM-HIGH was really a trial of niacin plus low-dose statin vs placebo plus high-dose statin

ings should not be overemphasized without robust evidence.

Do statins make everything else irrelevant?

The final factor to consider is the relative modifiability of residual clinical risk in statin-treated patients.

While residual risk is often cited as the reason to develop new antiatherosclerotic therapies, it is unknown how many of these ongoing events can be prevented. Several nonmodifiable factors such as age and concomitant disease are likely to contribute to these clinical events, which may limit our ability to further reduce event rates in patients who have already achieved low LDL-C levels with statin therapy. This may underscore the observation that no major clinical trial has demonstrated clinical benefit of an antiatherosclerotic agent on top of background medical care that included statins.

The finding that atherosclerosis continues to progress in many patients even though they take statins in high doses or achieve low LDL-C levels suggests that there is still room for improvement.

■ WHAT FUTURE FOR NIACIN?

So what does the future hold for niacin? The ongoing HPS2-THRIVE study provides an-

other opportunity to evaluate the potential clinical efficacy of niacin in statin-treated patients. For now, we must wait for the results of this study.

In the meantime, it would seem reasonable to continue treatment with niacin in patients who need it for its multiple lipid-modifying effects. Whether clinicians will be less likely to initiate niacin therapy until there is clear evidence of clinical benefit remains uncertain. As for HDL-C, it remains to be determined whether any therapy targeting either quantitative or qualitative changes will be beneficial.

Over the last 3 decades, clinical trials have provided important insights into the prevention of cardiovascular events and have had a profound impact on clinical practice. Such studies simply evaluate whether one strategy is better or worse than the existing standard of care. They do not provide mechanistic insights, and when attempts have been made to address mechanisms in the study design, the trial, as in the case of AIM-HIGH, leaves more questions than answers.

Future trials will provide more clarity as to the optimal way to treat patients, but they must be based on a robust design that permits the study question to be adequately addressed. ■

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