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Search and rescue for hypotheses surviving AIM-HIGH, the niacin therapy earthquake: Still problematic after the primary publication

About 58 years ago, niacin became one of the first medications reported to lower cholesterol levels when Rudolf Altschul and coworkers first published results in rabbits.[1] During the next 10 years, they and other scientists extended those observations to humans and extended them beyond total cholesterol-lowering,[2–4] to LDL-lowering,[3,4] HDL-raising,[3,4] reduction of cutaneous atheromata,[4] and even regression of lower-extremity atherosclerosis.[5] Niacin research has continued forward from this promising early beginning to show many additional benefits, including a reduction in the plasma levels of apolipoprotein (apo)B,[6,7] triglycerides,[6,7] and lipoprotein (a)[7,8]; increased plasma apoA-I[7]; as well as regression and/or reduced progression of atherosclerosis in the coronary,[9–13] femoral,[5,14] and carotid[15–19] arteries. Most importantly, niacin has been shown consistently to reduce cardiovascular disease (CVD), including coronary[20–22] and cerebrovascular events,[20,22] although several of these were in combination with other agents and was the first lipid agent shown to reduce total mortality, in the Coronary Drug Project (CDP) and in combination with clofibrate.[21,23]

This impressive record of evident benefits from niacin, however, came primarily from studies of monotherapy, or of combination therapy in which niacin was not studied separately,[10,12,21] and so it became important to test the CVD effects of niacin added to statins, the current "gold-standard" of lipid therapy.[24] Two large clinical end-point studies were designed to explore this question. The clinical trial Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH, NCT00120289) was designed to test the HDL hypothesis that CVD events would decrease when HDL-C levels were increased by adding extended-release niacin to aggressive LDL-lowering therapy with statins, and other agents, in patients with low levels of HDL-C.[25] Because of the high CVD risk of the subjects, it was calculated that 3300 would provide adequate power to detect the expected 25% reduction in CVD events.[25] In the other clinical trial of this question, Heart Protection Study-2, Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE, NCT00461630), researchers are using a slightly different extended-release niacin formulation, to which is added laropiprant, an agent to reduce the common problem of flushing with niacin.[26]

Unexpectedly, on May 26, 2011, the National Institutes of Health announced that the AIM-HIGH study was being terminated, at an average of 32 months follow-up, about 18 months early, for futility, a lack of likely ability to show any benefit.[27] More surprising still was the secondary reason for early termination, a ~2-fold increase in stroke.[27] Another unwelcome surprise was that among the 511 CVD events in the primary end point, there was a trend towards an increase in overall CVD events. The publication of the analysis of the full data set in November 2011[28] differed only modestly from the preliminary report. The apparent increase in stroke was not statistically significant and the adverse trend in total CVD events was slightly lower (hazard ratio 1.02), but the lack of overall CVD benefit remained, and no subject subgroup was reported to have reduced CVD.[29]

Given nearly six decades of scientific evidence consistently showing the benefits of niacin on all major lipid fractions, atherosclerosis, and CVD events, the results from AIM-HIGH have come as an unsettling shock, even an earthquake, to many general clinicians and to most lipidologists. Surrounded by the rubble of the implosion of this study, lipid scientists are now digging for long-standing hypotheses that might somehow have survived the impact of the unanticipated neutral-to-adverse findings in AIM-HIGH.

Limitations of the AIM-HIGH study design and execution

Peculiarities of the study design and the premature termination of AIM-HIGH limit its interpretation and clinical impact. First and foremost AIM-HIGH was not a placebo-controlled study and so was not designed to test the effects of niacin on CVD events. Instead it was intended to

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test the CVD effects of HDL-raising by means of niacin, rather than the effects of niacin per se, as noted in the concluding paragraph of the design paper, "In summary, AIM-HIGH was designed to provide a rigorous test of the HDL hypothesis…"[25] and in the announcement of the premature termination of the study, "AIM-HIGH [was]… designed specifically to evaluate the impact of raising HDL on the risk of cardiovascular events while maintaining excellent LDL control."[27] Given the study goal to test the HDL-C−raising hypothesis, the protocol tried to keep on-study LDL-C levels equally low in both study arms, within a range of 40 to 80 mg/dL by allowing adjustment of simvastatin dose, up to 80 mg/d or down to 5 mg/d and/or the addition of ezetimibe 10 mg/d.[25] Because niacin lowers LDL-C by approximately 10% to 20%,[6,7,30] the matching of on-study LDL-C levels required significantly greater doses of simvastatin and greater frequency of ezetimibe use in the control arm.[28] Nearly twice as many subjects in the niacin versus the control arm (18.6% vs 10.9%) were down-titrated to less than 40 mg/d, whereas fewer (17.8% vs 25.3%) were uptitrated greater than that dose ($P = .02$).[28] Even more strikingly, ezetimibe was given to far fewer niacin compared with control subjects (9.5% vs 21.5%, $P < .001$).[28] Ironically, LDL-C remained significantly lower in the niacin arm, and the reporting of LDL-C to study sites to allow these adjustments of nonrandomized treatment surely tended to unblind the study. Likely trends to unblinding were compounded by greater flushing in the high-dose niacin arm, in which resulting study drug dose downtitration and discontinuation were also significantly more common.[28]

Importantly, in addition to the aforementioned significant differences in ancillary and primary study treatment, the control arm was not treated with inert placebo, despite statements to the contrary in the primary study publication.[28] Instead, to help maintain the double-blind every placebo tablet, whether replacing a 500-mg or 1000-mg active tablet, contained 50 mg immediate-release niacin.[28] In the niacin arm, subjects were maintained on the maximum tolerated dose of extended-release niacin, roughly half each taking three 500 mg tablets, and two 1000 mg tablets daily. Control subjects similarly were given two or three tablets daily and so received niacin at 100 to 150 mg/d, which increased 11.8% from baseline throughout the study in the "placebo" arm of AIM-HIGH.[28] Importantly, an even lower dose of niacin was previously reported to increase by 6%.[31] Thus, AIM-HIGH was actually a comparison between standard-dose (1500−2000 mg/d) and low-dose (100−150 mg/d) niacin, and the key 25.0% HDL-C increase in the niacin arm was partially negated by the unexpected rise in the "placebo" subjects.[28] Thus, it is hazardous, at best, to draw conclusions either regarding the prespecified question of the CVD efficacy of HDL-C−raising, or the post-hoc question of the CVD effects of niacin per-se.

The early study termination of AIM-HIGH (shortened from the planned 4.1 to approximately 3 years) limits study interpretation because it may well have obscured an eventual study benefit. The May 26 press-release reported that "the study's DSMB (data and safety monitoring board) concluded that high-dose, extended-release niacin offered no benefits beyond statin therapy alone in reducing cardiovascular-related complications in this trial. The rate of clinical events was the same in both treatment groups, and there was no evidence that this would change by continuing the trial. For this reason, the DSMB recommended that the NHLBI end the study." Unfortunately, despite this lack of evidence, the slopes of the event curves might have eventually diverged. In the only other large prospective lipid treatment study of subjects with low HDL-C and normal LDL-C, aside from AIM-HIGH, the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT), the CVD event curves of gemfibrozil vs placebo also failed to separate by three years, but later became significantly different.[32,33] Although continued subject follow-up of AIM-HIGH subjects off-drug is planned for an additional 12 months,[27] 3 years of treatment and 4 years of total follow-up are very short periods compared with the 5 years of treatment and 15 years of total follow-up which was required to show reduction of the primary endpoint with niacin in the CDP. Thus, AIM-HIGH addresses only the effects of relatively short-term HDL-raising with high vs low-dose niacin.

Another important study limitation is that AIM-HIGH subjects are somewhat unusual. There are very few females (14.8%), or nonwhite subjects (7.8%).[28] The 3414 subjects are relatively modest in number and rather constrained in the range of their baseline lipid levels, which limits generalizability of study results. Baseline LDL-C averaged an extremely low 71 mg/dL in the 94% of subjects already on statins. Further, by selection mean baseline HDL-C was very low at 35 mg/dL, in contrast, median TG was only slightly elevated at 161 mg/dL, and only one quarter of subjects had a baseline TG greater than 218 mg/dL.[28] In addition, (1) subjects were selected for tolerance to niacin, (2) trial sites were selected for extensive prior experience with niacin, and (3) previous niacin treatment was not a study exclusion, although baseline lipid values were obtained after a one-month washout of non-statin lipid treatment.[25,28]

Nearly 20% of subjects had taken niacin before study randomization, and the average duration of that treatment and, more importantly, any effect of prestudy niacin on trial results remain to be reported. This question is of interest because niacin appears to have a substantial "legacy" or carry-over effect on CVD events. The primary end point of the CDP, total mortality, was not significantly reduced until 5 years of treatment and 10 years of further follow-up after discontinuation of study treatment.[23] Thus, prolonged CVD effects of prestudy niacin use might have partially obscured on-study niacin effects, especially given the relatively short study period. The criticism that AIM-HIGH was underpowered because of low on-study CVD risk is clearly not true because the CVD event rate was greater than 5% per year.[28] Thus, aggressive statin therapy before and during