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Review Article

Niacin and heart disease prevention: Engraving its tombstone is a mistake

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Abstract: Niacin (nicotinic acid) has been used for primary and secondary coronary heart disease prevention for over 40 years. Until recently clinical trials incorporating niacin as part of an intervention strategy consistently demonstrated reduction in clinical events and lesion improvement, including ≥6% absolute mortality reduction. Two large clinical event trials in 2011 (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes) and 2014 (Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events) concluded that niacin added to statin therapy did not provide clinical event benefit over statin alone. This has prompted some individuals to call for an end to the use of niacin in statin-treated patients and the US Food and Drug Administration to halt marketing of statin/niacin combination tablets. There are significant differences between the earlier clinical trials that revealed cardiovascular benefit of niacin and the 2 trials that failed to demonstrate a benefit. These differences include dyslipidemia types, niacin formulation, dosing, and timing. In general, the patient population that benefits the most from incorporating niacin in their treatment regimen can be defined by elevations in low-density lipoprotein cholesterol and triglycerides, and reduced high-density lipoprotein cholesterol. The niacin formulation and dose should be capable of achieving adequate lipoprotein change. Mealtime dosing of niacin, as opposed to bedtime dosing, may avoid a counter-regulatory hormone response, including catecholamines, because of altered fuel supply potentially leading to unexpected cardiovascular outcomes.

Publication and analysis of the Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) and Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) investigations has generated some controversy and confusion among the public and medical community regarding the evidence for efficacy of niacin (nicotinic acid) as a drug for dyslipidemia and vascular disease treatment.[1,2] Most recently, the US Food and Drug Administration has announced withdrawal of previously approved indications for the use of

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extended-release (ER) niacin co-administered with a statin, commenting that existing evidence does not support that reducing triglycerides or raising of high-density lipoprotein cholesterol (HDL-C) with any drug improves cardiovascular (CV) risk in patients on statins.[3] A prominent physician stated, "There is no evidence for any meaningful benefit for addition of niacin or fibric acid derivatives to statins. There are also significant harms associated with these drugs. In the absence of benefits, there remain only harms."[4] In this review, we contend that the justification for this statement pertaining to niacin is specific only to the unique characteristics of HPS2-THRIVE and AIM-HIGH.[1,2] There is abundant evidence to support the use of niacin in combination with a statin or bile acid–binding resin when niacin is administered appropriately to the right patient populations. To appreciate evidence for niacin benefit and to avoid discarding a component of effective treatment for some patients, it is useful to understand important differences between successful studies using niacin and the lack of overall clinical event benefit in HPS2-THRIVE and AIM-HIGH. The current confusion creates the risk to patient care of avoiding beneficial treatment in specific patient groups that may benefit from niacin therapy. In regard to clinical utility, we call to attention 7 relevant points: (1) statin therapy alone is not sufficient to defeat coronary atherosclerosis in many patients; (2) niacin has provided benefit in randomized clinical trials that differed in critical ways from AIM-HIGH and HPS2-THRIVE; (3) recent discoveries about non-lipoprotein effects of niacin should guide understanding of clinical effects; (4) successful niacin clinical trials used higher doses of niacin compared with the unsuccessful studies and achieved greater blood lipid change; (5) studies powered for arteriographic change, and using niacin, reported both significant arteriographic benefit and clinical event benefit; (6) niacin has a greater effect on atherogenic dyslipidemia, a component of the metabolic syndrome, compared with statin treatment; and (7) there is a diversity of niacin preparations.

Statin therapy alone is not sufficient to defeat coronary atherosclerosis

Although abundant evidence exists that statin therapy can statistically significantly reduce clinical events, statin therapy alone leaves substantial residual risk and will not defeat coronary atherosclerosis in many patients. Statistical significance does not necessarily mean clinical relevance for all patients. The 25% relative risk reduction (RRR) attributed to statin therapy is actually only a 3% absolute risk reduction (ARR) and reflects the need to go beyond therapy designed to primarily reduce low-density lipoprotein cholesterol (LDL-C).[5,6] For example, in a meta-analysis of 5 statin clinical trials, in 30,817 men and women, a 31% RRR in coronary heart disease (CHD) events was reported.[7] However, this represents the difference between 2042 events (13.3%) in the placebo group and 1490 events (9.7%) continuing to occur in the statin treatment group. This reflects an ARR of only 3.6% over a 5- to 6-year period. To achieve this degree of event reduction, approximately 30 subjects had to be treated to prevent 1 event. This can be compared with clinical trials that used niacin combined with an LDL-C lowering medication and reported that approximately 10 subjects had to be treated to prevent 1 event.[6] The most recent large statin study, JUPITER, treated 17,802 normolipemic primary prevention subjects with elevated high-sensitivity C-reactive protein blood levels with rosuvastatin or placebo and achieved a 50% reduction in LDL-C and a statistically significant reduction in the primary CV endpoint.[8] However, of the 8901 subjects in the placebo group, 251 (2.8%) had an event and of the 8901 rosuvastatin subjects, 142 (1.6%) still had an event. Unfortunately, many patients on statin therapy experience a CV event and thus have "failed" on statin therapy for its primary intent of preventing CV events. Recent evidence from JUPITER has revealed that residual small LDL independently predicts CV events.[9] Niacin is effective at reducing small LDL.[10]

Niacin has provided benefit in randomized clinical trials that differed in critical ways from AIM-HIGH and HPS2-THRIVE

Niacin has a long history of clinical use for treatment of dyslipidemia by clinicians and researchers dating back to the Coronary Drug Project report of 1975.[11] Reviews abound that discuss the reputedly beneficial pharmacotherapeutic effects of niacin and lipoprotein disorders that it can modify.[12–15]

The most striking benefit in any large atherosclerosis risk reduction trial was 6.2% absolute mortality benefit ($P = .0004$) for the niacin group in a 15-year follow-up of the Coronary Drug Project.[11] The small Stockholm Ischemic Heart Disease study echoed this result, showing 7.8% absolute mortality benefit ($P = .035$) over 5 years for combination niacin-clofibrate therapy vs no lipid medication.[16] In comparison, the best absolute mortality benefit from any statin trial was 3.5% ($P = .0003$) in the Scandinavian Simvastatin Survival Study.[17]

Two randomized trials with arteriographic primary endpoints, comparing placebo treatment vs combination drug regimens including niacin, found unexpectedly large reductions of combined CV events. In the HDL Atherosclerosis Treatment Study (HATS) RRR was 70% and ARR 20% over 3 years.[18] The Armed Forces Regression Study (AFREGS) found RRR of 48% and ARR of 14% over 2.5 years.[19]

In the trials cited previously mentioned, control patients did not receive statins. The presence of statin background therapy is generally suggested as the reason for lack of benefit for niacin in AIM-HIGH and HPS2-THRIVE. However, there are other major differences between these 2 trials and earlier ones. We will give attention to differing patient populations and to bedtime vs mealtime dosing of niacin.

Historically, niacin has been prescribed, either alone or in combination with other lipid medications, for patients

with specific lipoprotein disorders such as hypertriglyceridemia, hyperapobetalipoproteinemia, familial combined hyperlipidemia, and hypoalphalipoproteinemia.[20] It is generally not used in normolipidemic individuals, nor as a population-wide general heart disease prevention treatment as was tested in HPS2-THRIVE.

Successful studies recruited a patient population most likely to benefit from niacin and avoided those in whom niacin would not normally be used. For example, CHD patients with elevated apolipoprotein B in Familial Atherosclerosis Treatment Study (FATS) or low HDL-C in HATS.[18,21] The HPS2-THRIVE population did not express the lipoprotein disorders that would clinically prompt the use of niacin and had a mean baseline LDL-C of 1.63 mmol/L (63 mg/dL), triglycerides of 1.43 mmol/L (127 mg/dL), and HDL-C of 1.28 mmol/L (49.6 mg/dL), which excluded patients most likely to benefit from niacin.[1] The AIM-HIGH study did address a population thought to benefit from niacin because of low HDL-C.[2] AIM-HIGH addressed the hypothesis that treatment with ER niacin, in patients with optimally controlled LDL-C levels of 1.03 to 2.07 mmol/L (40–80 mg/dL), but low HDL-C would decrease the rate of CV events in patients with a documented history of atherosclerotic CV disease and an atherogenic lipid profile consisting of low HDL-C (<1.03 mmol/L (<40 mg/dL for men), <1.29 mmol/L (<50 mg/dL for women)) and elevated triglycerides >1.69 mmol/L (>150 mg/dL). For patients on a statin at entry, the mean LDL-C was 1.83 mmol/L (71 mg/dL), HDL-C was 0.90 mmol/L (34.9 mg/dL), and triglycerides were 1.82 mmol/L (161 mg/dL). Thus, AIM-HIGH patients had only moderate expression of the atherogenic lipoprotein phenotype (ALP), which is the phenotype most likely to benefit from niacin therapy.

Selecting a study population most likely to benefit from a specific treatment makes rational sense. This is particularly evident in patients expressing the metabolic syndrome. In these patients, a combined analysis of the FATS, the HATS, and the AFGEGS revealed that patients with the metabolic syndrome had 50% more rapid coronary stenosis progression and a 64% increased CV event frequency compared with those without the metabolic syndrome.[22] More rapid coronary stenosis progression was significantly and independently associated with a 3.5-fold increased event risk in the metabolic syndrome group ($P < .001$). The combination niacin therapy used in these trials reduced the event rate by 54% ($P = .03$) in the metabolic syndrome patients and 82% ($P = .002$) in those without the metabolic syndrome. A further analysis in AIM-HIGH showed that a subgroup of patients with high triglycerides ≥2.24 mmol/L (≥198 mg/dL) and low HDL-C < 0.85 mmol/L (<33 mg/dL) potentially could benefit from the combination of statin and niacin therapy with a hazard ratio of 0.74 ($P = .07$).[23]

In addition, beneficial effects of combination niacin therapy in both coronary stenosis and clinical events in FATS and HATS appear to be closely associated with reduction in triglyceride-rich lipoprotein particles including dense LDL, intermediate-density lipoprotein, and dense VLDL.[24] Subjects enrolled in AIM-HIGH had median baseline triglycerides of 1.82 mmol/L (161 mg/dL) while triglyceride levels were in the range of 2.26 mmol/L (200 mg/dL) in FATS and HATS. We would hypothesize that patients on niacin with high triglycerides would have a greater CV benefit that those with normal-low plasma triglycerides by maximizing the benefits associated with a significant decrease of triglyceride-rich VLDL, their remnants, and dense LDL particles. Normotriglyceridemic individuals do not have the lipid phenotype with increased lipoprotein remnants and dense LDL, thereby limiting the potential benefits on coronary stenosis and CV events associated with changes in these lipoproteins.[10]

Niacin given to fasting or nearly fasting subjects, as occurs with bedtime dosing, has been shown to reduce nonesterified fatty acid levels in plasma by more than 60%.[12,13] Myocardial fuel metabolism shifts substantially from fatty acids to glucose and a counter-regulatory hormone response to increase glucose production by the liver is postulated.[12,25] Consistent with this view, plasma epinephrine has been shown to increase 2.7-fold ($P < .05$) in fasting subjects 1 hour after oral niacin administration.[26] Sympathetic activation (and consequent CV events) may differ depending on whether niacin is dosed at mealtime or not. Prior trials generally dosed niacin at mealtime to reduce flushing, but AIM-HIGH and HPS2-THRIVE dosed niacin at bedtime.

Recent discoveries about non-lipoprotein effects of niacin should guide understanding of clinical effects

Lipoprotein and non-lipoprotein effects of niacin may help to explain beneficial effects of niacin on atherosclerosis. The discovery that the G-protein coupled receptor, now called hydroxycarboxylic acid receptor-2 (HCAR2; synonyms GPR109A, HM74A), mediates niacin-induced skin flushing and anti-lipolysis in adipocytes opened a new era for understanding niacin pharmacology.[27] In response to niacin, HCAR2 on monocytoid cells and macrophages leads to suppression of inflammatory responses and increased cholesterol efflux. Importantly, Lukasova et al. showed, in a mouse bone marrow replacement experiment that atherosclerosis prevention by niacin in LDL receptor-deficient mice depended on the presence of HCAR2 in the transplanted bone marrow cells.[28] Thus, niacin may act to improve atherosclerotic lesions by mechanisms independent of changes in plasma lipoproteins and even independent of cholesterol efflux potential.

Table 1 Clinical trials and the subject type, dose of niacin (immediate release [IR] or delayed release [DR]) and other medications, and general outcomes used in the investigations

Study	Patient type	Medications	Outcome
CLAS[34]	CABG	4.3 g/d IR niacin	Arteriographic regression $P = .002$
FATS[21]	CHD, ApoB > 1.25 g/L (>125 mg/dL)	4 g/d IR niacin + 30 g/d colestipol	Reduced arteriographic progression $P < .005$, and events $P = .01$
HATS[18]	Low HDL-C, CHD, Trig ~2.26 mmol/L (~200 mg/dL), dose individualized	2.4 g/d niacin (combo Slo-Niacin or IR niacin) + 12 mg/d simvastatin	Regression $P = .001$, reduced events $P = .03$
AFREGS[19] CHD	CHD, low HDL-C	3 g/d IR niacin, 16 g/d cholestyramine, 1200 mg/d gemfibrozil	Arteriographic regression $P = .04$, reduced events $P = .04$
HPS2-THRIVE[1] CVD	CVD, no lipid criteria	2 g/d ER niacin, 40 mg/d simvastatin, 10 mg/d laropiprant	No benefit of niacin + laropiprant added to simvastatin
AIM-HIGH[2] CVD	CVD, HDL-C <1.03 mmol/L (<40 mg/dL) males, <1.29 mmol/L (<50 mg/dL) females, Trig 1.69–4.52 mmol/L (150–400 mg/dL)	1.5–2.0 g/d ER niacin, simvastatin + ezetimibe	No benefit of niacin added to simvastatin + ezetimibe

AFREGS, Armed Forces Regression Study; AIM-HIGH, Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes; ApoB, apolipoprotein B; CHD, coronary heart disease; CLAS, Cholesterol Lowering and Atherosclerosis Study; CVD, cardiovascular disease; ER, extended release; FATS, Familial Atherosclerosis Treatment Study; HATS, HDL Atherosclerosis Treatment Study; HDL-C, high-density lipoprotein cholesterol; HPS2-THRIVE, Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events.

Successful niacin clinical trials used higher doses of niacin compared with the unsuccessful studies and achieved greater blood lipid changes

Successful studies used higher doses of immediate release niacin (average = 3.4 g/d) and achieved greater blood lipid change than in HPS2-THRIVE and AIM-HIGH (Table 1). In HPS2-THRIVE, a dose of 2 g/d ER niacin + laropiprant was used with a 78% compliance rate and in AIM-HIGH 1.5-2.0 g/d of an ER niacin was used with 75% compliance.[1,2] It has been suggested that the improved tolerability of ER lower dose niacin regimen may have come at the cost of diminished efficacy.[29] HPS2-THRIVE and AIM-HIGH used an average ER niacin dose of 1.9 g/d and achieved an average change of LDL-C −16.0%, triglycerides −24.0%, and HDL-C +22.0% compared with the 4 successful studies noted in Table 1 that averaged a daily dose of immediate release niacin of 3.4 g that produced a change in LDL-C of −35.8%, triglycerides −35.0%, and HDL-C +35.5%. Immediate release niacin, compared with slow-release niacin has been shown to have greater effects on blood lipids and HDL2-C.[30]

Investigation of the relationship of lipoproteins to CV events in AIM-HIGH showed that in-trial lipoprotein levels were associated with CV events in the statin group: LDL-C (hazard ratio [HR] = 1.39, 95% confidence interval [CI]: 1.16–1.67, $P < .001$), non-HDL-C (HR = 1.31, 95% CI: 1.13–1.52, $P < .001$), and total cholesterol over HDL-C ratio (HR = 1.20, 95% CI: 1.06–1.53, $P = .003$). However, combination therapy with statin and niacin in AIM-HIGH basically eliminated the CV event risk associations with these lipoprotein parameters.[23] This raised the possibility that ER niacin might have off-target effects such as catecholamine release that possibly diminished the anticipated clinical benefit associated with the favorable lipid effects.[31] Similarly, there may be off-target or non-lipoprotein beneficial effects of immediate release niacin.[27,28]

Clinical trials powered for arteriographic change reported both significant arteriographic benefit and clinical event benefit

The beneficial effect of niacin appears to be easier to detect in patients with established coronary artery disease (CAD) and dyslipidemia. Arteriographic regression studies using niacin and a statin have demonstrated beneficial effects on arteriographic outcome. Of clinical relevance is the finding that improvement in arteriographic obstruction is associated with reduced clinical events.[32,33] Change in arteriographic outcomes are valid clinical endpoints and do not require the very large sample size and funding support as needed in clinical event trials such as HPS2-THRIVE and AIM-HIGH.

Four well-conducted clinical investigations have demonstrated a significant beneficial effect of niacin on arteriographic disease progression and clinical events (Fig. 1). They used higher doses of niacin and in patient populations most likely to benefit from niacin and who had not

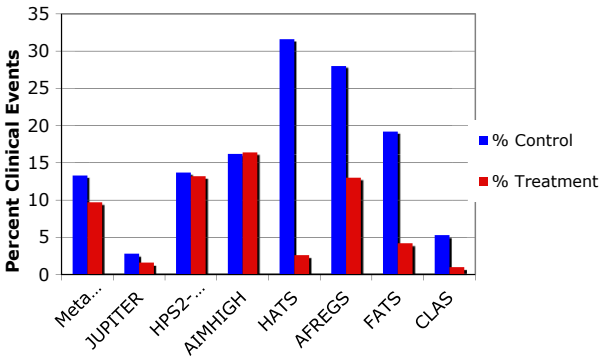

Figure 1 Percent of patients with clinical cardiovascular events in the control and treatment group of statin studies (meta-analysis and JUPITER) compared with the extended-release niacin plus statin studies (HPS2-THRIVE [(1)] and AIM-HIGH [(2)]) and compared with the arteriographic studies using higher doses of niacin and statin or bile acid–binding resin (HATS,[18] AFREGS,[19] FATS,[21] CLAS[34]).

previously received intensive lipid treatment before entering these studies.[18,19,21,34] The Cholesterol Lowering and Atherosclerosis Study was the first investigation to demonstrate in 162 subjects that arteriographically defined CAD regression was possible with a combination of colestipol and immediate-release niacin.[34] LDL-C was reduced 43% and HDL-C increased 37% and new lesion formation significantly reduced ($P < .03$). The average on-trial colestipol dose was 29.5 g/d and immediate release niacin was 4.3 g/d.

The FATS investigated the effect of 3 treatments on arteriographic disease progression.[21] Treatment groups were lovastatin 40 mg/d + colestipol 30 g/d, immediate-release niacin (4 g/d) and colestipol 30 g/d, and "conventional therapy" plus placebo in 120 men with established CAD and apolipoprotein B ≥ 1.25 g/L (≥125 mg/dL). Compliance to niacin + colestipol was reported to be 86% and showed greater benefit than statin + colestipol. The niacin + colestipol combination reduced LDL-C 32% and increased HDL-C 43% compared with −7% and +5% in the conventional therapy group. Arteriographic progression was less frequent among patients who received lovastatin + colestipol (21%) and those who received niacin and colestipol (25%), and regression more frequent in the lovastatin + colestipol group (32%) and the niacin + colestipol group (39%) compared with the control group. Important for this discussion was the finding that clinical CV disease events occurred in 19.2% of the conventional therapy group compared with 8.3% in the lovastatin + colestipol group and 4.2% in the niacin + colestipol group.

The HATS investigated the effect of simvastatin + niacin, simvastatin + niacin + antioxidants, antioxidant vitamins, and placebo in 160 subjects with established CAD and low HDL-C ~0.78 mmol/L (~30 mg/dL) and relatively normal LDL-C ~3.31 mmol/L (~128 mg/dL) on arteriographic change.[18] Niacin therapy was either slow-release niacin (Slo-Niacin) or immediate release niacin (Niacor) based on individual subject dosing needs to achieve an HDL-C goal. In the simvastatin + niacin group, LDL-C was reduced 42% and HDL-C increased 26%. The average stenosis progressed by 3.9% with placebo, 1.8% with antioxidants ($P = .16$ for the comparison with the placebo group), and 0.7% with simvastatin + niacin + antioxidants ($P = .004$) and regressed by 0.4% with simvastatin + niacin alone group ($P < .001$). The frequency of the clinical endpoint was 24% with placebo, 21% in the antioxidant therapy group, 14% in the group given simvastatin + niacin plus antioxidants, and 3% in the group treated with simvastatin + niacin alone. The risk of the composite primary endpoint was 90% lower in the simvastatin + niacin group than in the placebo group ($P = .03$).

The AFREGS investigated the effect of combination therapy with gemfibrozil (1200 mg/d), immediate-release niacin (3 g/d), and cholestyramine (16 g/d) compared with "conventional therapy" on arteriographic change in 143 subjects with established CAD and low HDL-C of 0.88 mmol/L (34 mg/dL).[19] Mean LDL-C at baseline was 3.31 mmol/L (128 mg/dL). Treatment reduced LDL-C 26% and increased HDL-C 36%. Focal coronary stenosis increased by 1.4% in the placebo group but decreased by 0.8% in the drug group (difference, −2.2 percentage points [CI, −4.2 to −0.1 percentage points]). A composite CV event endpoint was reached in 26% of patients in the placebo group and 13% of those in the drug group. Drug therapy significantly reduced CV events ($P = .04$).

Two additional clinical trials gave similar results, but are not reviewed in detail here. The University of California San Francisco – SCOR trial, which used immediate-release niacin and bile acid–binding resins, and/or lovastatin, in patients with familial hypercholesterolemia, showed mean regression of coronary lesions vs progression in control patients ($P = .039$).[35] The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 3 trial found mean regression of carotid intima-media thickness ($P < .001$ vs baseline) in patients treated for 2 years with ER niacin added to simvastatin.[36]

The results and implications of these well-conducted clinical trials should not be ignored based on the results of HPS2-THRIVE, which used lower doses of ER niacin in a patient population not normally treated with niacin. An initial mean LDL-C of 1.63 mmol/L (63 mg/dL) and HDL-C of 1.14 mmol/L (44.1 mg/dL) and triglycerides of 1.43 mmol/L (127 mg/dL) in HPS2-THRIVE does not represent a patient population that most clinicians would elect to treat with niacin.[1] The "exploratory analysis" in a subset defined by HDL-C <40 mg/dL in men and <51 mg/dL in women and triglyceride values above 151 mg/dL is inadequate to conclude niacin ineffectiveness. Fasting triglyceride in this range is a poor predictor of the atherogenic lipoprotein profile.[37] The lower dose of niacin used in HPS2-THRIVE, compared with the successful clinical trials, may have also failed to achieve an adequate therapeutic threshold particularly in patients with low HDL-C and elevated triglycerides. It is important to recall that HPS2-THRIVE was not a test of the 2 drugs ER niacin and a statin, but rather of 3 drugs, ER niacin, statin, and

laropiprant. Most of the side effects reported in HPS2-THRIVE have also been previously associated with niacin treatment but new to this debate is the additional complexity of the new drug laropiprant and potential interaction with niacin in regard to established side effects and particularly in regard to the statistically significant 1.4% point difference in infection. Although most basic science research suggests laropiprant has no adverse effect on lipid metabolism, it has been suggested that it may restrain the atheroprotective effects of niacin by enhancing the effect of thromboxane A2.[38,39] Suspicion has also been raised that the addition of laropiprant to niacin may be responsible for an impairment of endothelial function that might explain, at least in part, the lack of a clinical net benefit of niacin/laropiprant in the HPS2-THRIVE study.[40] Thus, it is inappropriate to conclude that niacin alone failed to achieve statistical significance, but rather it was the combination of niacin and laropiprant that failed.

The success or failure of treatment in these investigations is dependent not only on the type of therapy but also the characteristics of the dose and duration as well as the population selected to be tested. The significant reduction in all-cause mortality at 15 years of follow-up in the Coronary Drug Project prompted the investigators to suggest that the benefit of niacin may require >6 years of treatment.[11] Thus AIM-HIGH and HPS2-THRIVE may have inadequate time for the beneficial effects of relatively low-dose niacin to be appreciated.

It would be a disservice to patients and the medical community to conclude from the HPS2-THRIVE results that niacin was ineffective in reducing CV disease risk, or excessively dangerous because of adverse effects. Niacin is not a drug useful in all patients but in patient populations with disorders addressed by niacin, it can result in arteriographic regression and a significant reduction in clinical events. Clinicians familiar with the clinical use of niacin have appreciated for over 50 years that it requires patient management and follow-up to maintain compliance and deal with side effects that are often temporary and manageable. When used in the correct population and at a therapeutic dose, niacin can assist in significantly reducing coronary arteriographic progression and clinical events.

AIM-HIGH did address the effect of niacin plus statin and/or ezetimibe in a population deemed to be appropriate for such intervention. At entry, the median LDL-C was 1.84 mmol/L (71 mg/dL), HDL-C 0.91 mmol/L (35 mg/dL), and TG 1.82 mmol/L (161 mg/dL). Of relevance to our discussion, 81% of the subjects had the metabolic syndrome. The elevated triglycerides and reduced HDL-C identified a patient population that would be expected to benefit from niacin treatment. The lack of a significant reduction in clinical events in response to the addition of 1.5 to 2.0 g/d ER niacin to 40 to 80 mg/d simvastatin could be because of an insufficient dose of niacin. The 12% reduction in LDL-C, 28% reduction in triglycerides, and 28% increase in HDL-C were less than the average in the "successful" niacin studies (Table 2). The AIM-HIGH investigators conducted an important investigation. However, it was plagued by several issues that could impact the results interpretation. Ninety-four percent of the subjects were already taking a statin at entry to the study and the baseline LDL-C level was more than 50% lower than the average "successful" niacin studies, which may have created a more stable atherosclerosis status from which to assess clinical events. Furthermore, the anticipated between group difference in HDL-C values was not achieved because of an unexpected rise in HDL-C in the placebo group. Sub-group analysis has suggested a clinical benefit in patients with higher triglyceride values. A subgroup analysis from the AIM-HIGH trial showed that in 552 patients with triglycerides ≥198 mg/dL and HDL-C <33 mg/dL, there was a close to significant ($P = .07$) reduction in events.[41]

Niacin has a greater effect on atherogenic dyslipidemia compared with statin treatment

The recent Food and Drug Administration announcement raises the issue of whether there is a need for niacin or whether statins alone are adequate to provide optimal

Table 2 Baseline blood lipid values in mmol/L (mg/dL) and change (Δ) in response to treatment during the studies

Study	LDL-C	Triglyceride	HDL-C	Baseline LDL/HDL	%Δ LDL-C	%Δ Triglyceride	%Δ HDL-C
CLAS[33]	4.42 (171)	1.71 (151)	1.15 (44.6)	3.84	−43	−21	37
FATS[20]	4.91 (190)	2.19 (194)	1.01 (39.1)	4.86	−32	−33	43
HATS[17]	3.26 (126)	2.45 (217)	0.80 (31)	4.08	−42	−38	26
AFREGS[18]	3.31 (128)	1.90 (168)	0.88 (34)	3.76	−26	−50	36
Weighted mean	3.96 (153)	2.04 (181)	0.97 (37.5)	4.08	−36.6	−34.6	35.1
HPS2-Thrive[1]	1.63 (63)	1.43 (127)	1.14 (44.1)	1.43	−20	−20	17
AIM-HIGH[2]	1.84 (71)	1.82 (161)	0.90 (34.9)	2.04	−12	−28	28
Weighted mean	1.66 (64)	1.48 (131)	1.11 (43)	1.50	−19.1	−20.9	18.3

AFREGS, Armed Forces Regression Study; AIM-HIGH, Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes; CLAS, Cholesterol Lowering and Atherosclerosis Study; FATS, Familial Atherosclerosis Treatment Study; HATS, HDL Atherosclerosis Treatment Study; HDL-C, high-density lipoprotein cholesterol; HPS2-THRIVE, Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events; LDL-C, low-density lipoprotein cholesterol.

beneficial effects on blood lipids and associated clinical events. The atherogenic dyslipidemia associated with the metabolic syndrome and obesity is characterized by an abundance of small, dense LDL particles.[42] Statin medications have little effect on altering LDL particle size.[43] Niacin has a greater effect on reducing atherogenic lipoproteins in the small, dense LDL region than other pharmacologic treatments including statins.[44,45] A reduction in small LDL attributed to niacin has recently been shown to correlate significantly with arteriographic and clinical event benefit independent of standard lipid measurements in patient populations with lipid disorders appropriate to the use of niacin.[46,47] In addition, like the "pleotropic effects" attributed to statin drugs, niacin has other metabolic effects including cellular effects on cholesterol efflux and inflammation that may benefit patients with atherosclerosis.[12,13,25,26,30,32,33,39,40]

Diversity of niacin preparations

Niacin is available in a variety of forms and composition. For clinical purposes, niacin preparations can be divided into 2 basic groups, immediate-release niacin and niacin formulated in a manner to delay the release of the niacin, including a wax matrix version, slow release, and polygel ER. It is recommended that doses not exceed 2000 mg/d for any of the non-immediate release versions. The studies using higher doses of niacin used immediate release versions. A dose and niacin preparation "type" investigation revealed that 3000 mg/d immediate-release niacin had significantly greater effects on lipids and LDL subclass distribution compared with 1500 mg/d ER niacin.[44] This difference was particularly powerful when subjects were classified as the small LDL pattern B compared with the large LDL pattern A phenotype. While ER niacin has been shown to have similar lipid effects as immediate-release niacin and better tolerance after 8 weeks of treatment, after 16 weeks of treatment, the ER effect remained stable while the immediate-release niacin doubled the change in lipid measurements suggesting a delayed efficacy effect of immediate-release niacin.[48]

Conclusion

Treatment with niacin, in combination with a statin or bile acid–binding resin, has been shown to significantly reduce the rate of arteriographic CAD progression and significantly reduce clinical CV events in several studies. HPS2-THRIVE and AIM-HIGH have not replicated these earlier clinical trial results, which has prompted some individuals to proclaim that there is no benefit to the combination of niacin and a statin and call for putting an end to the combined use of statins with niacin. This is a dangerous conclusion not consistent with previous well-designed and conducted clinical trials. Both HPS2-THRIVE and AIM-HIGH have critical design issues that call into question the overreaching conclusion that niacin has no benefit in statin-treated patients, including failure to build on the design of the previously "successful" niacin studies. Some of these issues include patient population selection (greatly differing lipoprotein patterns at baseline), type of niacin, dose and timing of administration of niacin, blood lipid change achieved, duration of treatment, and the use of a third medication, laropiprant, that may have blunted the beneficial effect of niacin. Indeed, engraving the tombstone for niacin plus statin is premature and a mistake that removes a proven effective therapy in appropriate patient populations, treated with the appropriate dose to achieve adequate blood lipid change and a reduction in atherosclerosis progression and clinical events. We strongly encourage the AIM-HIGH and HPS2-THRIVE investigators to make their data available for further analysis by outside scholars to help clarify the clinical utility of niacin + statin therapy.

Future research with niacin should examine in detail the postulated counter-regulatory hormone response to niacin administered at bedtime, as well as the effect of mealtime dosing.[23] Clinical trial designs should address specific patient subgroups. Of particular interest would be the effect on patients with the ALP compared with subjects with similar LDL-C values but lacking the atherogenic aspects of ALP.[49] Subjects with ALP have been shown to have a 3-fold increased risk for CAD independent of other risk factors and have a greater response to niacin compared with those without ALP.[44] Genetic markers can now identify polygenic attributes associated with this phenotype and triglyceride blood levels.[50] Future research may help to determine if genetic analysis is an efficient way to identify patients most likely to have a beneficial CV response to niacin.

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