Published in final edited form as:
Am Heart J. 2011 March ; 161(3): 538–543. doi:10.1016/j.ahj.2010.12.007.

The role of niacin in raising high-density lipoprotein cholesterol to reduce cardiovascular events in patients with atherosclerotic cardiovascular disease and optimally treated low-density lipoprotein cholesterol: Baseline characteristics of study participants. The Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides: Impact on Global Health outcomes (AIM-HIGH) trial

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Abstract

Objectives—The study aims to report the baseline characteristics of the fully randomized AIM-HIGH study population.

Background—Residual risk persists despite aggressive low-density lipoprotein cholesterol (LDL-C) reduction in patients with atherosclerotic cardiovascular (CV) disease, many of whom have atherogenic dyslipidemia (low levels of high-density lipoprotein cholesterol (HDL-C), elevated triglycerides, and small dense LDL particles).

Methods—All study participants had established CV disease and atherogenic dyslipidemia. Participants received simvastatin (or simvastatin plus ezetimibe) at a dose sufficient to maintain LDL-C at 40 - 80 mg/dL (1.03-2.07 mmol/L) and were randomized to receive extended-release niacin or matching placebo. The primary end point is time to the first occurrence of coronary heart disease death, nonfatal myocardial infarction, ischemic stroke, hospitalization for acute coronary syndrome or symptom-driven coronary or cerebral revascularization with average follow-up of 4.1 years.

Results—Between 2006 and 2010, 8,162 individuals signed consent to be screened, 4,275 began study drug run-in, and 3,414 were randomized to treatment. Mean age at entry was 64 ± 9 years, 85% were men, and 92% were white. As expected, risk factors were prevalent with 34% having diabetes; 71%, hypertension; and 81%, metabolic syndrome. Most participants had coronary artery disease (92%), whereas 11% had peripheral arterial disease; and 12%, cerebrovascular disease. Previous coronary revascularization occurred in 82%, and 54% reported a prior myocardial infarction. Among participants on a statin at entry (94%), mean baseline LDL-C was 71 mg/dL (1.84 mmol/L); mean HDL-C, 34.9 mg/dL (0.90 mmol/L); and median triglycerides, 161 mg/dL (1.82 mmol/L).

Summary—AIM-HIGH enrolled a high-risk group of patients with established atherosclerotic CV disease and atherogenic dyslipidemia. This study should determine whether there is incremental clinical benefit of niacin in reducing cardiovascular events in patients who have attained optimal on-treatment levels of LDL-C with a statin.

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Background

Atherogenic dyslipidemia is an important and increasing cause of cardiovascular risk. It is characterized by a high-risk phenotype with associated low levels of high-density lipoprotein cholesterol (HDL-C), high triglycerides, and small dense low-density lipoprotein (LDL) particles often in the setting of insulin resistance and metabolic syndrome.[1] Extensive clinical trial evidence has established 3-hydroxy-3methylglutaryl coenzyme A reductase inhibitors (statins) as the backbone of preventive therapy in patients with atherosclerotic cardiovascular disease[2,3]; however, aggressive LDL cholesterol (LDL-C) lowering alone only results in a relative risk reduction of 30% to 35%.[2,3] The remaining residual cardiovascular risk with statin therapy has been the focus of intensive research efforts.

Different therapeutic approaches have been evaluated. Some have been directed at the lipoprotein abnormalities themselves, whereas others have been a more general approach to the atherosclerotic milieu. To date, disappointing results have been obtained with anti-inflammatory therapies,[4] thiazoladenediones,[5] modulators of the endocannabanoid system,[6] and cholesterol-ester transport protein inhibitors.[7] More favorable results have been obtained with fibrates in some[8,9] but not all studies.[10] Even in the neutral studies, there was an encouraging signal in those subjects with low HDL-C and high triglycerides,[8,9] suggesting that atherogenic dysplipidemia was an important and relevant target.

The AIM-HIGH study was designed to evaluate the effect of extended-release niacin in subjects with established atherosclerotic cardiovascular disease and atherogenic dyslipidemia, whose LDL-C is optimally treated. The rationale for niacin in this setting is robust. Epidemiological studies have shown a strong, independent relationship between low levels of HDL-C and increased cardiovascular risk, even in subjects on statin therapy.[7,10] Niacin is the most effective modulator of HDL-C currently available and may also have favorable effects on the functionality of HDL-C.[11] Secondly, niacin has a beneficial effect on atherogenic apolipoprotein B (apoB)–containing particles and free fatty acids found in excess in subjects with metabolic syndrome. This includes a further 15% to 20% relative risk reduction in LDL-C levels on top of that seen with statin treatment. Thirdly, niacin may have positive effects on other aspects of vascular biology including endothelial dysfunction and the proinflammatory state of atherosclerosis.[12] Finally, niacin has been used for more than 50 years, so its safety profile is well known and supporting evidence of its efficacy has accumulated.[13-16]

The design and methodology of the AIM-HIGH study also appears in this issue.[17] The study completed recruitment of 3,414 participants in April 2010. The purpose of the current report is to present the baseline characteristics of the study population.

Methods

AIM-HIGH is a double-blind, randomized, controlled clinical trial designed to examine the hypothesis that treatment with extended-release niacin in patients with optimally controlled LDL-C levels (40-80 mg/dL) would decrease the rate of cardiovascular events (coronary heart disease death, nonfatal myocardial infarction, ischemic stroke, hospitalization for acute coronary syndrome or symptom-driven coronary or cerebral revascularization) in patients with a documented history of atherosclerotic cardiovascular disease and an atherogenic lipid profile consisting of low HDL-C (if off statin ≤40 mg/dL for men [1.0 mmol/L] or ≤50 mg/dL for women [1.3 mmol/L]), high triglycerides (if off statin 150-400 mg/dL [1.7-4.5 mmol/L]), and untreated LDL-C ≤180 mg/dL (4.7 mmol/L). For those screened on a statin, lipid criteria were modified based on published effects of various doses of the particular statin on LDL-C, HDL-C, and triglycerides. After signing informed written consent, eligible potential

participants were given extended-release niacin beginning with 500 mg/d, increasing to 2,000 mg/d during 4 - 8 weeks or as tolerated in an open-label run-in period. Those tolerating at least 1,500 mg/d were randomized to the maximally tolerated doses of extended-release niacin (1,500-2,000 mg/d) or a placebo "spiked" with 50 mg of immediate-release niacin sufficient to induce a flush and maintain masking to both the study participants and investigators. All participants had their dose of simvastatin adjusted during the first 6 months post randomization to a target of 40 - 80 mg/dL (1.0-2.1 mmol/L). Ezetimibe could be added at the discretion of the investigator if the participant could not achieve LDL-C goal of 80 mg on simvastatin. Participants were followed up in clinic and by telephone to a common termination date, expected late 2012. Details regarding the design, rationale, and methods are discussed in the companion article.[17]

Data were collected on standardized electronic case report forms. On-site clinical monitoring documented proper enrollment and adherence and a sampling of baseline data. Analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Results of screening are described in the companion design manuscript. Briefly, 8,162 participants signed informed consent to be screened, 4,275 were eligible and began open-label run-in on extended-release niacin, and 3,414 were randomized.

Among the 3,569 men and 706 women enrolled into the open-label run-in, 2,910 men (82% of those enrolled) and 504 women (71% of those enrolled) were ultimately randomized to extended-release niacin or placebo. The difference between the proportions of men and women in the reasons for "failing to be randomized" is largely accounted for by more cutaneous adverse events (eg, flushing, itching, etc) among women. One participant discontinued open-label run-in because of myopathy and was not randomized. Approximately 3 weeks after starting extended-release niacin, the participant developed severe muscle aches with elevated creatine kinase (1,755 mg/dL). After stopping the extended-release niacin, the symptoms resolved, and laboratory values returned to normal.

Among randomized participants, mean age at entry was 64 years and 85% were men (Table I). The vast majority (92%) were white. Thirty-four percent of participants had a history of type 1 (26 patients) or type 2 diabetes mellitus; and 71%, hypertension. By National Cholesterol Education Panel (NCEP) criteria,[18] 81% had metabolic syndrome and 74% were current or former smokers. Potential participants could qualify for entry with one or more cardiovascular diagnoses; 92% qualified based on coronary artery disease, 12% with carotid disease, and 11% with peripheral arterial disease. Fifty-six percent had previous myocardial infarction and 84% had coronary revascularization before entry, either coronary artery bypass graft surgery or percutaneous coronary revascularization. Most patients (80%) were receiving β-blockers, and almost all (92%) were taking aspirin regularly.

Among the 3,194 participants (94%) who were taking a statin at trial entry, baseline LDL-C was 71.0 mg/dL (1.84 mmol/L); mean HDL-C, 34.9 mg/dL (0.90 mmol/L); and median triglycerides,161.0 mg/dL (1.82 mmol/L) (Table II). Among the remaining 6% of participants not taking a statin at entry, baseline LDL-C was 119.2 mg/dL (3.08 mmol/L), mean HDL-C was 32.8 mg/dL (0.85 mmol/L), and median triglycerides was 215.0 mg/dL (2.43 mmol/L). Relatively few study participants (n = 405, 12%) had an estimated glomerular filtration rate <60 mL/min; the overall median high sensitivity C-reactive protein (hsCRP) was 2.83 mg/L (Table III).

Discussion

AIM-HIGH is the first large randomized trial to evaluate the effect of niacin on cardiovascular events among statin-treated patients with established atherosclerotic cardiovascular disease who are at goal for LDL-C but who have residual abnormalities in HDL-C and triglycerides (ie, so-called atherogenic dyslipidemia). Previous studies with niacin as secondary prevention have several limitations. The Coronary Drug Project,[19] the only large placebo-controlled trial of niacin monotherapy, enrolled 1,119 patients on niacin (niacin was one of 5 active treatments) and 2,789 on placebo. Participants were followed for approximately 5 years. Although the results show a decrease in fatal and nonfatal cardiovascular events, including stroke,[19] and a late benefit on total mortality 10 years after the trial ended,[15] the study was conducted over 40 years ago, long before the advent of statins. Clinical studies with primarily coronary angiographic end points using niacin, such as the Familial Atherosclerosis Treatment study[13] and the HDL Atherosclerosis Treatment study,[20] or noninvasive imaging studies using B-mode carotid ultrasound (eg, ARBITER 2, 3, and 6[16,21,22]) have all been limited in size (generally in the range of 150-300 randomized subjects who were likewise followed for limited periods [1-2.5 years]) and were not primarily powered statistically to detect the effects of treatment on clinical outcome.

Thus, AIM-HIGH will provide much needed clinical and scientific information on the potential impact of HDL-C raising among patients who have achieved their target LDL-C primarily on a statin to more fully test the so-called HDL hypothesis that there is incremental risk reduction with combination dyslipidemic therapy. It should be noted that although the mean LDL-C at baseline in the study among participants on a statin was 71 mg/dL, there were participants with an LDL-C as low as 19 mg/dL, while 25% of the patients had LDL-C <59 mg/dL.

The baseline demographic characteristics of AIM-HIGH further show a study population with atherogenic dyslipidemia, a high prevalence of hypertension (71%) and metabolic syndrome (81%), enriched in diabetes (34%), and with a large number of current or former smokers (20% and 55%, respectively). This pattern of risk factors is typical of patients with coronary heart disease, among whom 80% to 90% have one or more of the conventional risk factors of smoking, hypertension, hyperlipidemia, or diabetes.[23] Furthermore, residual low HDL-C, with or without high triglycerides, is quite commonly seen in clinical practice, in up to 50% of such individuals currently receiving statin therapy in a general medical environment.[24] Thus, the results of AIM-HIGH should be broadly applicable to the typical coronary patient population commonly seen in clinical practice today.

It is noteworthy that the study participants had well-controlled levels of apoB-containing lipoproteins, as indicated by the low baseline LDL-C, apoB, very low density lipoprotein cholesterol (VLDL-C), and lipoprotein (a), with only moderately elevated triglycerides (Table II). Also of interest is that ApoCIII, a VLDL apolipoprotein that inhibits lipolysis and hepatic VLDL uptake,[25] was at the upper limit of normal; however, total HDL-C was low, and most HDL is in the HDL3 subclass, with depressed HDL2 levels.

Thus, in addition to having multiple major coronary risk factors such as hypertension and diabetes, participants in this study have a pro–atherogenic lipoprotein profile. Although LDL-C was well controlled, there is likely to be a preponderance of small dense LDL particles, as suggested by the low total HDL-C, depressed HDL2, and reduced LDL-C/apoB ratio of 0.88, a ratio <1.3 being a good indicator of the atherogenic LDL phenotype B.[26] Actual LDL and HDL particle size and distribution are being assessed in a prospective substudy. Nonetheless, this is a study population whose principal lipid abnormality is in the

HDL number and fractions. These patients are precisely the ones who are likely to respond to niacin therapy, which principally impacts the number of HDL particles and fractions.

AIM-HIGH was designed with an active lead-in, during which tolerability to the combination of extended-release niacin and simvastatin was assessed, randomizing only those who tolerated a dose of extended-release niacin of ≥1,500 mg/d. Results show that the combination of extended-release niacin with simvastatin was well tolerated, despite the rapid uptitration of the dose from 500 mg/d to 2,000 mg/d during a 4-week period (up to 8 weeks was permitted). Ultimately, 19% were not subsequently randomized to double-blind therapy, largely accounted for by intolerance of the ≥1,500-mg dose. The predominant reason for inability to tolerate this dose was cutaneous side effects, especially among women. Participant refusal was cited as the reason for another 17% (women) and 19% (men) not continuing to be randomized. None had elevated liver enzymes that prevented subsequent entry into the double-blind portion of the study.

In summary, AIM-HIGH is a secondary prevention trial that provides a robust test of the HDL hypothesis in patients with optimally treated LDL-C levels on a statin and residually low levels of HDL-C at baseline, using a well-tolerated combination dyslipidemic therapy regimen. The results of this trial should significantly inform clinical practice as to the incremental benefit of niacin in reducing cardiovascular events in patients with atherosclerotic cardiovascular disease and optimally controlled LDL-C levels.

Acknowledgments

Supported in part by National Institutes of Health, National Heart, Lung, and Blood Institute component grants U01 HL081616 and U01 HL081649, with additional unrestricted grant support and drug supply from Abbott Laboratories, Abbott Park, Illinois, and by drug supply from Merck, Inc, West Point, Pennsylvania.

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Table I

Baseline demographic and clinical characteristics

	Randomized participants (N = 3,414)
Demographics	
Men	2,910 (85%)
Age (mean ± SD)	64 ± 9
Race	
White	3,148 (92.2%)
African American	117 (3.4%)
Asian	41 (1.2%)
Multiracial or other	107 (3.1%)
Cardiovascular risk factors	
Diabetes mellitus	1,158 (33.9%)
Metabolic syndrome	2,762 (80.9%)
Hypertension	2,427 (71.1%)
Systolic blood pressure, mm Hg (mean ± SD)	128.3 ± 16.3
Diastolic blood pressure, mm Hg (mean ± SD)	74.4 ± 9.8
Body mass index, kg/m^2 (mean ± SD)	31.2 ± 5.4
Waist circumference, cm (mean ± SD)	107.5 ± 13.4
Smoking history	
Current smoker	673 (19.7%)
Former smoker	1,865 (54.6%)
Presenting history or diagnosis *	
Coronary artery disease	3,148 (92.2%)
Myocardial infarction	1,925 (56.4%)
Hospitalization for acute coronary syndrome	1,110 (32.5%)
Angina pectoris	1,778 (52.1%)
Coronary bypass graft surgery	1,229 (36.0%)
Percutaneous coronary intervention (with or without stent)	2,101 (61.5%)
Any prior coronary revascularization	2,851 (83.5%)
Congestive heart failure	249 (7.3%)
Carotid disease	414 (12.1%)
Stroke	216 (6.3%)
Transient ischemic attack	186 (5.4%)
Carotid endarterectomy	167 (4.9%)
Carotid stent	60 (1.8%)
Peripheral artery disease	375 (11.0%)
Peripheral vascular disease	446 (13.1%)
Peripheral stent/angioplasty	209 (6.1%)
Concomitant cardiovascular drug use	

	Randomized participants (N = 3,414)
β-Blockers	2,717 (79.6%)
Calcium-channel Blockers	771 (22.6%)
Angiotensin-converting enzyme inhibitors	1,970 (57.7%)
Angiotensin II receptor blocker	634 (18.6%)
Aspirin	3,140 (92.0%)
Other antiplatelet or anticoagulant	1,472 (43.1%)

* Percentages sum to more than 100%: participants could present with more than one diagnosis.

Table II

Lipoproteins at entry

		Participants ON statin at entry	Participants OFF statin at entry
		n = 3194	n = 220
Women		472	32
HDL-C (mg/dL)	Mean (SD)	40.1 (6.7)	36.5 (5.1)
Triglycerides (mg/dL)	Median (Q1, Q3[*,†])	166 (133, 209.5)	217.5 (189.5, 256.5)
Men		2722	188
HDL-C (mg/dL)	Mean (SD)	34.0 (4.9)	32.1 (4.8)
Triglycerides (mg/dL)	Median (Q1, Q3)	159 (128, 214)	212.5 (176, 270)
All patients		3194	220
LDL-C (mg/dL)	Mean (SD)	71.0 (18.0)	119.2 (36.7)
	Median (Q1, Q3)	71.0 (59.0, 83.0)	124.0 (92.0, 146.5)
Triglycerides (mg/dL)	Median (Q1, Q3)	161 (129, 213)	215 (178, 263.5)
VLDL-C (mg/dL)	Mean (SD)	35.8 (13.0)	46.1 (13.2)
	Median (Q1, Q3)	32 (26, 43)	43 (35.5, 52.5)
Non-HDL cholesterol (mg/dL)	Mean (SD)	106.8 (21.1)	165.4 (38.0)
	Median (Q1, Q3)	106 (92, 121)	166 (138, 193.5)
HDL-C (mg/dL)	Mean (SD)	34.9 (5.6)	32.8 (5.1)
HDL2-C (mg/dL)	Mean (SD)	6.1 (2.4)	5.6 (2.1)
	Mean (Q1, Q3)	6 (4, 7)	5 (4, 7)
HDL3-C (mg/dL)	Mean (SD)	28.7 (4.1)	27.1 (4.0)
	Median (Q1, Q3)	29 (26, 32)	27 (24, 30)
ApoAI (mg/dL)	Mean (SD)	123.3 (16.2)	120.6 (16.5)
	Median (Q1, Q3)	123 (113, 133)	120.5 (110, 131)
ApoB (mg/dL)	Mean (SD)	81.1 (18.3)	110.7 (28.1)
	Median (Q1, Q3)	80 (69, 92)	108 (93, 131)
ApoB/ApoA1 (mg/dL)	Mean (SD)	1.59 (0.39)	1.16 (0.37)
	Median (Q1, Q3)	1.54 (1.32, 1.79)	1.05 (0.91, 1.34)
ApoCIII (mg/dL)		70	163
	Mean (SD)	12.26 (4.60)	15.06 (5.24)

		Participants ON statin at entry	Participants OFF statin at entry
		n = 3194	n = 220
ApoCIIIhp (mg/dL)	Median (Q1, Q3)	11.95 (9.10, 15.10)	13.70 (11.90, 17.80)
		50	132
	Mean (SD)	5.49 (2.39)	6.18 (2.40)
	Median (Q1, Q3)	4.85 (3.80, 6.50)	6.10 (4.30, 7.70)
Lipoprotein(a) (nmol/L)	Median (Q1, Q3)	33.8 (13.2, 126.6)	33.7 (15.5, 104.8)

Abbreviations: *ApoA*, apolipoprotein-A; *ApoB*; apolipoprotein-B; *ApoC111hp*, apolipoprotein CIII, heparin percipitate.

*Conversion factor for LDL-C, HDL-C, VLDL-C to Standard International units (SI, mmol/L) is 0.02586. Conversion factor to convert triglycerides to SI is 0.01129.

†Q1 and Q3, 25th and 75th percentiles.

Table III

Baseline serum chemistries

		Participants randomized (N = 3,414)
Patients without history of diabetes		2256
HbA_{1c} (%)	Mean (SD)	5.63 (0.46)
Fasting glucose (mg/dL)	Mean (SD)	102.3 (14.0)
Insulin (μU/mL)	Mean (SD)	17.33 (22.17)
Patients with history of diabetes		1158
HbA_{1c} (%)	Mean (SD)	6.69 (0.88)
Fasting glucose (mg/dL)	Mean (SD)	126.6 (27.0)
Insulin (μU/mL)	Mean (SD)	25.44 (30.04)
All patients		
Creatinine (mg/dL)	Mean (SD)	0.991 (0.234)
Estimated glomerular filtration rate*	Mean (SD)	82.8 (19.8)
	Number (%) <60	405 (11.9%)
Creatine kinase (U/L)	Mean (SD)	122.2 (86.3)
Uric acid (mg/dL)	Mean (SD)	6.74 (1.51)
AST† (U/L)	Mean (SD)	26.9 (9.2)

Abbreviations: *HbA1c*, glycated hemoglobin.

*Estimated using Modification of Diet in Renal Disease Study Group (MDRD) formula.[27]

†AST, Aspartate aminotransferase.