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Niacin in Patients with Low HDL Cholesterol Levels Receiving Intensive Statin Therapy

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ABSTRACT

BACKGROUND

In patients with established cardiovascular disease, residual cardiovascular risk persists despite the achievement of target low-density lipoprotein (LDL) cholesterol levels with statin therapy. It is unclear whether extended-release niacin added to simvastatin to raise low levels of high-density lipoprotein (HDL) cholesterol is superior to simvastatin alone in reducing such residual risk.

METHODS

We randomly assigned eligible patients to receive extended-release niacin, 1500 to 2000 mg per day, or matching placebo. All patients received simvastatin, 40 to 80 mg per day, plus ezetimibe, 10 mg per day, if needed, to maintain an LDL cholesterol level of 40 to 80 mg per deciliter (1.03 to 2.07 mmol per liter). The primary end point was the first event of the composite of death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalization for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization.

RESULTS

A total of 3414 patients were randomly assigned to receive niacin (1718) or placebo (1696). The trial was stopped after a mean follow-up period of 3 years owing to a lack of efficacy. At 2 years, niacin therapy had significantly increased the median HDL cholesterol level from 35 mg per deciliter (0.91 mmol per liter) to 42 mg per deciliter (1.08 mmol per liter), lowered the triglyceride level from 164 mg per deciliter (1.85 mmol per liter) to 122 mg per deciliter (1.38 mmol per liter), and lowered the LDL cholesterol level from 74 mg per deciliter (1.91 mmol per liter) to 62 mg per deciliter (1.60 mmol per liter). The primary end point occurred in 282 patients in the niacin group (16.4%) and in 274 patients in the placebo group (16.2%) (hazard ratio, 1.02; 95% confidence interval, 0.87 to 1.21; P=0.79 by the log-rank test).

CONCLUSIONS

Among patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of less than 70 mg per deciliter (1.81 mmol per liter), there was no incremental clinical benefit from the addition of niacin to statin therapy during a 36-month follow-up period, despite significant improvements in HDL cholesterol and triglyceride levels. (Funded by the National Heart, Lung, and Blood Institute and Abbott Laboratories; AIM-HIGH ClinicalTrials.gov number, NCT00120289.)

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More than 18 million North Americans have coronary heart disease, and despite profound advances in both pharmacologic and interventional management, both morbidity and mortality remain appreciable.[1,2] Elevated low-density lipoprotein (LDL) cholesterol levels are an established predictor of the risk of coronary heart disease. Multiple primary and secondary prevention trials have shown a significant reduction of 25 to 35% in the risk of cardiovascular events with statin therapy[3]; however, residual risk persists despite the achievement of target LDL cholesterol levels.

Epidemiologic studies have shown that, in addition to elevated LDL cholesterol levels, low levels of high-density lipoprotein (HDL) cholesterol are an independent predictor of the risk of coronary heart disease,[4,5] with a strong inverse association between HDL cholesterol levels and the rates of incident coronary heart disease events. Previously, studies from the Coronary Drug Project showed that the rate of cardiovascular events was decreased among patients with established coronary heart disease who had been randomly assigned to receive immediate-release niacin as compared with those assigned to receive placebo,[6,7] and the Veterans Affairs HDL Intervention Trial (VA-HIT; ClinicalTrials.gov number, NCT00283335)[8] suggested that raising low levels of HDL cholesterol with gemfibrozil in men with coronary heart disease and normal LDL cholesterol levels was associated with reductions in the rate of cardiovascular events. Subsequently, the HDL-Atherosclerosis Treatment Study (HATS, NCT00000553)[9] showed that treatment with simvastatin plus niacin resulted in significant regression of angiographic coronary atherosclerosis and reductions in the rate of clinical events.

At least two studies[10,11] focusing on aggressive lowering of lipid levels with high doses of statins to achieve a target LDL cholesterol level of less than 70 mg per deciliter (1.81 mmol per liter) in very-high-risk patients have shown major reductions in clinical end points. A post hoc analysis of the Treating to New Targets trial (TNT, NCT00327691)[11] showed that, among patients who had achieved LDL cholesterol values of less than 70 mg per deciliter, the 5-year rate of cardiovascular events was 25% lower among those in the highest quintile of HDL cholesterol levels than among those in the lowest quintile. This suggests that HDL cholesterol levels have a prognostic value for patients receiving statin therapy that is independent of LDL cholesterol levels.

The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial tested whether extended-release niacin added to intensive statin therapy, as compared with statin therapy alone, would reduce the risk of cardiovascular events in patients with established atherosclerotic cardiovascular disease and atherogenic dyslipidemia (low levels of HDL cholesterol, elevated triglyceride levels, and small, dense particles of LDL cholesterol). Patients with this profile represent an expanding reservoir of patients at increased risk for cardiovascular events,[12,13] for whom more effective treatment is needed.

METHODS

TRIAL OVERSIGHT

The AIM-HIGH Study was an investigator-initiated trial that was approved and sponsored by the National Heart, Lung, and Blood Institute (NHLBI). The design and organization of the trial and the baseline data have been described previously.[14,15] Abbott Laboratories provided additional support from an unrestricted research grant. The extended-release niacin (Niaspan), the matching placebo, and the ezetimibe were provided by Abbott Laboratories; Merck donated the simvastatin. The companies that provided financial support or products had no role in the oversight or design of the study or in the analysis or interpretation of the data. The study protocol, available with the full text of this article at NEJM.org, was reviewed and approved by an independent protocol review committee and by the institutional review board at each participating clinical site. An independent data and safety monitoring board oversaw the conduct of the trial and reviewed the safety and efficacy data. Data management and statistical analyses were performed at the data coordinating center (Axio Research, Seattle) with oversight by the executive committee for the trial (see the Supplementary Appendix, available at NEJM.org). After termination of the blinded study treatment on May 25, 2011, the members of the executive committee had full access to trial information and vouch for the accuracy and completeness of the data and analyses.

STUDY DESIGN

Patients were recruited at 92 clinical centers in the United States and Canada. After providing written informed consent, eligible patients entered a 4-to-8-week open-label phase during which they received simvastatin at a dose of 40 mg per day, plus niacin at doses that were increased weekly from 500 mg per day to 2000 mg per day. Patients in whom a dose of at least 1500 mg of niacin per day was associated with an acceptable side-effect profile were randomly assigned, in a 1:1 ratio, to niacin or matching placebo. Randomization was performed with the use of a secure Internet application. Patients attended clinic visits at 6-month intervals and were contacted by telephone in alternate quarterly intervals.

STUDY POPULATION

Eligible patients were 45 years of age or older and had established cardiovascular disease, which was defined as documented stable coronary heart disease, cerebrovascular or carotid disease, or peripheral arterial disease (Table 1 in the Supplementary Appendix). All eligible patients had low baseline levels of HDL cholesterol (<40 mg per deciliter [1.03 mmol per liter] for men; <50 mg per deciliter [1.29 mmol per liter] for women), elevated triglyceride levels (150 to 400 mg per deciliter [1.69 to 4.52 mmol per liter]), and LDL cholesterol levels lower than 180 mg per deciliter (4.65 mmol per liter) if they were not taking a statin at entry. Patients who were screened were required to discontinue lipid-modifying drugs, except for statins or ezetimibe, at least 4 weeks before enrollment. A fasting lipid profile was obtained in eligible patients to establish baseline levels; analyses were performed by the core laboratory. Potential participants were excluded if, within 4 weeks before enrollment, they had been hospitalized for an acute coronary syndrome or had undergone a planned revascularization procedure or if they had had a stroke within the preceding 8 weeks. Details of the inclusion and exclusion criteria are provided in the Supplementary Appendix.

STUDY INTERVENTION AND ADHERENCE

Patients in the niacin group received niacin at a dose of 1500 to 2000 mg per day plus simvastatin. Patients in the placebo group received simvastatin plus a matching placebo that contained a small dose (50 mg) of immediate-release niacin in each 500-mg or 1000-mg tablet to mask the identity of the blinded treatment to patients and study personnel. In both groups, the dose of simvastatin was adjusted according to an algorithm specified in the protocol to achieve and maintain the LDL cholesterol level during treatment in the range of 40 to 80 mg per deciliter (1.03 to 2.07 mmol per liter). Subjects in both groups could receive ezetimibe, at a dose of 10 mg per day, to achieve the target LDL cholesterol level. To maintain the masking of the therapy, only LDL cholesterol levels were reported to the clinical sites. Adherence to niacin or placebo was measured by means of manual pill counts at clinic visits.

END POINTS

The primary end point was the composite of the first event of death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalization (for >23 hours) for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization. Secondary composite end points included death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, or hospitalization for a "high-risk" acute coronary syndrome (with high risk characterized by accelerating ischemic symptoms or prolonged chest pain with electrocardiographic evidence of ischemia or increases in biomarker values to greater than the upper limit of the normal range but less than 2 times that upper limit); death from coronary heart disease, nonfatal myocardial infarction, or ischemic stroke; and death from cardiovascular causes. Tertiary end points included death from any cause, individual components of the primary end point, and prespecified subgroups defined according to sex, history or no history of diabetes, and presence or absence of the metabolic syndrome.

ASCERTAINMENT OF END POINTS

A clinical events committee reviewed suspected primary end points (including silent myocardial infarction) with supporting documentation that did not reveal the treatment assignments. Electrocardiograms were read at a central reading facility at Saint Louis University; all lipid and serum chemical analyses were performed at the Northwest Lipid Metabolism and Diabetes Research Laboratory.

After the database was locked, the clinical events committee was asked to review all nonstroke events of the central nervous system again, with treatment assignments masked, to classify potential transient ischemic attacks, since these were not categorized at the initial review; stroke events were not re-reviewed. The results of this post hoc review are noted separately but are not included in the analyses.

STATISTICAL ANALYSIS

The original composite primary end point consisted of death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, or high-risk acute coronary syndrome.[14] Because the rate of the primary end point was lower than projected, the protocol was amended to change the end point of "high-risk acute coronary syndrome" to include hospitalization for an acute coronary syndrome and symptom-driven coronary or cerebral revascularization, on the basis of a blinded examination of data by the executive committee; an independent review committee appointed by the NHLBI, whose members did not have access to data on treatment-specific results, reviewed and recommended approval of this amendment in March 2010. In this event-driven trial, we expected to observe 800 adjudicated primary events during a mean follow-up period of 4.6 years. With this number of events, we estimated that the study would have 85% power to detect a 25% reduction in the revised five-component primary end point, at a one-sided alpha level of 0.025. A formal interim analysis plan specified asymmetric boundaries for stopping the trial early on the basis of a demonstration of efficacy or lack of efficacy. The boundary for lack of efficacy required an observed hazard ratio of 1.02 or greater with a P value for futility of less than 0.001 when 50% of events were reported. The follow-up period was scheduled to end in December 2012. At a meeting on April 25, 2011, the data and safety monitoring board recommended that the blinded intervention be stopped because the boundary for lack of efficacy had been crossed and an unexpected higher rate of ischemic stroke had been observed among patients who were being treated with niacin; the NHLBI accepted that recommendation.

The baseline characteristics of the patients, the data on adherence to the study drug, and the difference in the percentage change in lipid levels were compared between the study groups with the use of the chi-square test or two-sample t-test, as appropriate. The significance of the changes in lipid values among the participants in the niacin group was tested with the use of a Wilcoxon signed-rank test. Ranked data such as the dose of statins were compared with the use of Spearman rank correlation. All end-point analyses were performed according to the intention-to-treat principle. The analyses of efficacy end points were performed with the use of time-to-event methods. We used an unadjusted log-rank statistic to compare the two treatment groups and a Cox proportional-hazards model to estimate hazard ratios, confidence intervals, and the adjusted Wald statistic for various end points. The models were adjusted for history or no history of diabetes and for sex. The analyses of prespecified subgroups are reported with no adjustment for multiplicity. We used a Cox model to test for the significance of the interaction between treatment and subgroup variable with respect to the primary outcome.

RESULTS

STUDY POPULATION

Among 8162 patients who gave written informed consent, 4273 (52.4%) began the open-label niacin run-in phase, and 3414 of those patients (79.9%) were randomly assigned to a study group — 1718 to the niacin group and 1696 to the placebo group (Fig. 1 in the Supplementary Appendix). The mean (±SD) age of the patients was 64±9 years; 85.2% were men, 92.2% were white, 33.9% had diabetes (type 1 or type 2), 71.4% had hypertension, and 81.0% had the metabolic syndrome. The population was well-balanced with respect to all recorded characteristics (Table 1).

LIPID LEVELS

Among the 3196 patients (93.6%) who were taking a statin at entry, the baseline median LDL cholesterol level was 71 mg per deciliter (1.84 mmol per liter), the median HDL cholesterol level was 35 mg per deciliter (0.91 mmol per liter), and the median triglyceride level was 161 mg per deciliter (1.82 mmol per liter). Before entry, 76.2% of patients had been taking statins for at least 1 year, and 39.5% had been taking them for 5 years or longer. Among the 218 patients who were not taking a statin at entry, the baseline LDL cholesterol level was 124 mg per deciliter (3.21 mmol per liter), the HDL choles-

terol level was 33 mg per deciliter (0.85 mmol per liter), and the triglyceride level was 215 mg per deciliter (2.43 mmol per liter).

At 2 years, the HDL cholesterol level had increased by 25.0% to 42 mg per deciliter (1.09 mmol per liter) in the niacin group, whereas it had increased by 9.8% to 38 mg per deciliter (0.98 mmol per liter) in the placebo group (P<0.001). Triglyceride levels had decreased by 28.6% in the niacin group and by 8.1% in the placebo group. The LDL cholesterol level had further decreased by 12.0% in the niacin group and by 5.5% in the placebo group. These lipid findings persisted through 3 years of follow-up (Table 2, and Fig. 2 in the Supplementary Appendix).

ADHERENCE

The end points could be ascertained for all but 52 patients. During the follow-up period, the dose of the study drug was reduced in 6.3% of the patients in the niacin group and 3.4% of the patients in the placebo group (P<0.001). The study drug was discontinued in 25.4% of the patients in the niacin group and in 20.1% of the patients in the placebo group (P<0.001). The annualized rate of discontinuation of niacin was 8.4% per patient-year, but the overall rate of adherence among the patients who continued treatment was at least 75% (Table 3). More than 86% of the patients continued to receive simvastatin, and approximately 50% were taking 40 mg per day. More patients in the placebo group than in the niacin group were taking 80 mg per day (24.7% vs. 17.5%, P=0.02), which was the maximum dose of simvastatin. More patients in the placebo group than in the niacin group were taking ezetimibe (21.5% vs. 9.5%, P<0.001). The proportions of patients receiving cardiac preventive therapies (e.g., aspirin and other antiplatelet therapies, beta-blockers, and inhibitors of the renin–angiotensin system) were high and were similar in the two groups during the follow-up period.

PRIMARY AND SECONDARY END POINTS

The primary end point occurred in 282 patients in the niacin group (16.4%) and 274 in the placebo group (16.2%) (hazard ratio with niacin, 1.02; 95% confidence interval [CI], 0.87 to 1.21; P=0.80 for the superiority of niacin therapy with the use of a Cox proportional-hazards model and P=0.79 by the log-rank test) (Table 4 and Fig. 1). Among components of the primary end point, there was an unexpected imbalance with respect to the rate of ischemic stroke as the first event between patients assigned to niacin and those assigned to placebo (27 patients [1.6%] vs. 15 patients [0.9%]). A total of 8 patients, all of whom had been in the niacin group, had an ischemic stroke sometime between 2 months and 4 years after discontinuation of the study drug. When all the patients with ischemic strokes were considered, rather than just those in whom the stroke was the first study event, a nonsignificant trend persisted among patients assigned to niacin as compared with those assigned to placebo (29 patients vs. 18 patients; hazard ratio, 1.61; 95% CI, 0.89 to 2.90; P=0.11). In a blinded, exploratory re-review of all possible neurologic events by the clinical events committee, three cases of transient ischemic attacks in the niacin group were reclassified as ischemic strokes, but these post hoc reclassifications are not included in the analyses.

Niacin therapy had a similar lack of effect on the composite secondary end point of death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, or hospitalization for a high-risk acute coronary syndrome (hazard ratio, 1.08; 95% CI, 0.87 to 1.34; P=0.49) and on the composite secondary end point of death from coronary heart disease, nonfatal myocardial infarction, or ischemic stroke (hazard ratio, 1.13; 95% CI, 0.90 to 1.42; P=0.30) (Table 4, and Fig. 3A in the Supplementary Appendix). The number of patients who died from cardiovascular causes was low in both the niacin group and the placebo group (45 patients [2.6%] and 38 patients [2.2%], respectively; P=0.47).

There were no significant interactions with respect to the primary end point between the treatment assignment and prespecified subgroups defined according to age (<65 years vs. ≥65 years), sex, presence or absence of diabetes, presence or absence of the metabolic syndrome, prior or no prior myocardial infarction, and use or no use of statins at entry (Fig. 3B in the Supplementary Appendix).

ADVERSE EFFECTS

Symptoms leading to discontinuation of the study drug are noted in Table 3. Adverse effects were rare and included liver-function abnormalities (0.5% in the placebo group and 0.8% in the niacin group), muscle symptoms or myopathy (0.3% of the patients overall), and rhabdomyolysis (1 pa-

tient in the placebo group and 4 in the niacin group).

DISCUSSION

In this trial involving patients with established, nonacute cardiovascular disease and low levels of baseline HDL cholesterol who achieved and maintained low levels of LDL cholesterol (<70 mg per deciliter) while receiving intensive statin treatment, extended-release niacin plus simvastatin as compared with simvastatin alone was associated with significant increases in HDL cholesterol levels and decreases in triglyceride levels, but there was no significant reduction in the primary composite end point of cardiovascular events over a mean follow-up period of 36 months. A very high percentage of patients (94%) were already taking a statin at trial entry, and many had taken one for long periods; 20% had taken niacin previously. At 2 years of follow-up, among patients assigned to niacin, LDL cholesterol levels had decreased by an additional 12.0% to a median of 62 mg per deciliter and HDL cholesterol levels had increased by 25.0% to 42 mg per deciliter, whereas in the placebo group, LDL cholesterol levels had decreased minimally to a median of 68 mg per deciliter and HDL cholesterol levels had increased by 9.8% to 38 mg per deciliter.

Although previous studies of niacin[6,16-18] have

Table 1. Baseline Demographic and Clinical Characteristics of the Study Patients.*

Characteristic	Placebo plus Statin (N=1696)	Extended-Release Niacin plus Statin (N=1718)
Age		
Mean — yr	63.7 (8.7)	63.7 (8.8)
Distribution — no. (%)		
<65 yr	915 (54.0)	917 (53.4)
≥65 yr	781 (46.0)	801 (46.6)
Sex — no. (%)		
Female	251 (14.8)	253 (14.7)
Male	1445 (85.2)	1465 (85.3)
Race or ethnic group — no. (%)†		
White	1576 (92.9)	1572 (91.5)
Black	49 (2.9)	68 (4.0)
Asian	21 (1.2)	20 (1.2)
American Indian, Alaskan Native, or Aboriginal Canadian	11 (0.6)	11 (0.6)
Native Hawaiian or other Pacific Islander	5 (0.3)	7 (0.4)
Multiracial or other	33 (1.9)	40 (2.3)
Hispanic or non-Hispanic ethnic group — no. (%)†		
Non-Hispanic	1619 (95.5)	1654 (96.3)
Hispanic	77 (4.5)	63 (3.7)
Presenting history or diagnosis — no. (%)		
History of myocardial infarction	955 (56.3)	968 (56.3)
CABG	627 (37.0)	600 (34.9)
PCI	1044 (61.6)	1057 (61.5)
Stroke or cerebrovascular disease	362 (21.3)	358 (20.8)
Peripheral vascular disease	231 (13.6)	234 (13.6)
Metabolic syndrome	1353 (79.8)	1414 (82.3)
History of hypertension	1189 (70.1)	1250 (72.8)
History of diabetes	570 (33.6)	588 (34.2)

Table 1. (Continued.)

Characteristic	Placebo plus Statin (N=1696)	Extended-Release Niacin plus Statin (N=1718)
Laboratory values in patients with history of diabetes		
Glucose — mg/dl	126.4±27.1	126.9±26.9
Glycated hemoglobin — %	6.68±0.85	6.70±0.88
Insulin — μU/ml	25.63±31.09	25.32±29.23
Concomitant medications — no. (%)		
Statin		
Use at baseline	1601 (94.4)	1595 (92.8)
Duration of prior statin therapy‡		
<1 yr	190 (11.2)	202 (11.8)
1–5 yr	629 (37.1)	627 (36.5)
>5 yr	684 (40.3)	669 (38.9)
Previous use of niacin or Niaspan§	338 (19.9)	324 (18.9)
Beta-blocker	1342 (79.1)	1377 (80.2)
ACE inhibitor or ARB	1271 (74.9)	1258 (73.2)
Aspirin or other antiplatelet or anticoagulant agent	1654 (97.5)	1680 (97.8)

* Plus–minus values are means ±SD. There were no significant differences between the treatment groups at baseline in any of the baseline characteristics. To convert the values for glucose to millimoles per liter, multiply by 0.05551. ACE denotes angiotensin-converting enzyme, ARB angiotensin II–receptor blocker, CABG coronary-artery bypass grafting, and PCI percutaneous coronary intervention.
† Race or ethnic group was self-reported.
‡ The duration of prior statin therapy was not ascertained in 204 patients (6.0%).
§ Niacin and other lipid-modifying drugs except statins and ezetimibe were discontinued 30 days before enrollment.

shown apparent benefits both in surrogate outcome measures (improvements in carotid intima–media thickness[19] and regression of angiographic coronary-artery stenoses[18]) and in clinical outcomes, we observed no clinical benefit with extended-release niacin in patients with established coronary heart disease and low levels of baseline HDL cholesterol. In the original placebo-controlled Coronary Drug Project trial,[6] treatment with immediate-release niacin in high doses (3000 mg per day) was associated with a significant reduction (by 14%) in the rate of death from coronary heart disease or myocardial infarction and a reduction by 26% in the rate of strokes or transient ischemic attacks — event-rate reductions that are similar to those in placebo-controlled trials of statins. In the 5-year placebo-controlled Veterans Affairs HDL Intervention Trial[8] involving 2531 men with low HDL cholesterol levels at baseline, treatment with gemfibrozil was associated with a reduction by 22% in the rate of the primary end point (death from coronary heart disease or nonfatal myocardial infarction) and a reduction by 27% in the rate of stroke, despite the fact that HDL cholesterol levels were increased by only 6% (from 32 mg per deciliter [0.83 mmol per liter] to 34 mg per deciliter [0.88 mmol per liter]). However, the baseline LDL cholesterol level in that trial, which predated the widespread use of statins, was 111 mg per deciliter (2.87 mmol per liter), as compared with 71 mg per deciliter in the present study among patients who were taking a statin at trial entry. This between-trial difference of 40 mg per deciliter in the baseline LDL cholesterol level is consistent with the considerable effect statins have had on reducing both elevated LDL cholesterol levels and the rate of cardiovascular events.

Beyond the important role of statins in secondary prevention of cardiovascular events, our findings further underscore the profound, continuing evolutions in medical therapy over the past several decades, with the development of other disease-modifying interventions such as antiplatelet therapy, beta-blockers for patients who

Table 2. Lipid Values at Baseline and during Follow-up.*

Variable	Placebo plus Statin (N=1696)				Extended-Release Niacin plus Statin (N=1718)			
	Baseline (N=1696)	Year 1 (N=1554)	Year 2 (N=1326)	Year 3 (N=873)	Baseline (N=1718)	Year 1 (N=1561)	Year 2 (N=1329)	Year 3 (N=865)
LDL cholesterol								
Mean (mg/dl)	75.8±24.3	70.4±18.9	69.5±19.9	68.3±19.3	76.2±25.7	66.4±19.9	65.0±20.5	65.2±21.8
Median (mg/dl)	74	69	68	67	74	64	62	62
Interquartile range (mg/dl)	60–87	59–79	57–78	56–78	59–87	54–75	52–74	51–74
Median change from baseline (%)		–4.3	–5.5	–7.6		–10.0	–12.0	–13.6
Triglycerides								
Median (mg/dl)	162	155	153	152	164	121	122	120
Interquartile range (mg/dl)	128–218	118–208	117–210	114–204	127–218	86–170	85–170	84–172
Median change from baseline (%)		–5.0	–8.1	–9.9		–28.2	–28.6	–30.8
HDL cholesterol								
Mean (mg/dl)	35.3±5.9†	38.4±7.6	38.7±7.4	39.1±7.7	34.8±5.9	43.6±10.9	43.9±10.6	44.1±11.3
Median (mg/dl)	35	38	38	38	35	42	42	42
Interquartile range (mg/dl)	31–39	34–43	34–43	34–44	31–39	36–49	37–50	36–50
Median change from baseline (%)		9.1	9.8	11.8		23.3	25.0	25.0
Non-HDL cholesterol (mg/dl)								
Mean	111.9±28.3	105.0±24.9	Not analyzed	102.3±23.7	112.6±30.5	94.3±27.2	Not analyzed	92.8±28.6
Median	108	102		99	108	90		90
Interquartile range	93–126	89–117		87–114	93–127	78–107		74–105
HDL2 cholesterol (mg/dl)								
Mean	6.3±2.5	7.4±3.8	Not analyzed	7.6±3.9	6.1±2.3	10.2±6.2	Not analyzed	10.8±7.0
Median	6	7		7	6	9		9
Interquartile range	4–8	5–9		5–9	4–7	6–13		6–13
HDL3 cholesterol (mg/dl)								
Mean	29.0±4.3	31.0±5.2	Not analyzed	31.4±5.1	28.7±4.3	33.4±6.1	Not analyzed	33.3±5.9
Median	29	31		31	29	33		33
Interquartile range	26–32	28–34		28–34	26–32	29–37		29–37

Apolipoprotein A-I (mg/dl)							
Mean	123.7±16.2‡	127.4±17.5	Not analyzed	127.5±17.0	122.5±16.3	132.2±20.1	Not analyzed	132.5±20.4
Median	123	127		127	122	131		131
Interquartile range	113–134	115–138		116–138	112–132	119–144		120–144
Apolipoprotein B (mg/dl)								
Mean	82.8±20.7	79.3±17.8	Not analyzed	77.6±16.9	83.2±20.2	71.4±18.2	Not analyzed	70.4±19.7
Median	81	78		76	81	70		69
Interquartile range	69–94	68–89		66–88	70–94	59–81		57–80
Lipoprotein(a) (nmol/liter)								
Median	32.7	30.6	Not analyzed	Not analyzed	36.1	27.1	Not analyzed	Not analyzed
Interquartile range	13.1–122.6	10.9–121.1			13.5–126.6	8.3–106.5		

* Plus–minus values are means ±SD. The percentage change from baseline was calculated at the patient level for each follow-up time, according to the following equation: [(value at follow-up − baseline value) ÷ baseline value] × 100. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. HDL denoted high-density lipoprotein, and LDL low-density lipoprotein.
† HDL cholesterol levels differed nominally between the treatment groups at baseline (P=0.04).
‡ Apolipoprotein A-I levels differed nominally between the treatment groups at baseline (P=0.03).

have had a myocardial infarction, and inhibitors of the renin–angiotensin system, all of which improve outcomes and were widely used in our study. The aggregate effects of contemporary medical therapy, particularly if such therapy incorporates the intensive use of statins and reduces LDL cholesterol levels to approximately 60 mg per deciliter (1.55 mmol per liter) in both groups, may have further reduced the rates of incident cardiovascular events during the follow-up period. This may make it difficult to show incremental clinical benefit with the administration of additional therapeutic lipid-modifying interventions such as niacin, fibrates, and inhibitors of the cholesterol ester transfer protein. Nevertheless, trials of niacin (Heart Protection Study 2: Treatment of HDL to Reduce the Incidence of Vascular Events [HPS2-THRIVE], NCT00461630) and inhibitors of the cholesterol ester transfer protein (A Study of the Effect of Dalcetrapib on Atherosclerotic Disease in Patients with Coronary Artery Disease [dal-OUTCOMES], NCT01059682; and the Randomized Evaluation of the Effects of Anacetrapib through Lipid Modification trial [REVEAL], NCT01252953) are ongoing in patients with stable cardiovascular disease. A large, international trial of simvastatin plus niacin and laropiprant as compared with simvastatin alone in patients with coronary heart disease (the HPS2-THRIVE) is in the follow-up phase; enrollment has been completed. Unlike in the present study, enrolled patients were not preselected on the basis of a particular lipid profile such as low baseline HDL cholesterol levels.

The unexpected rate of ischemic stroke among patients in the niacin group warrants comment. Although the number of ischemic strokes was higher in the niacin group, the overall rate was low, and we cannot be certain whether this observation reflects a causal association or possibly the statistical "play of chance." No previous studies or meta-analyses[20] have shown an increased incidence of stroke with niacin in any therapeutic formulation, dose, or dosing regimen. Although careful review of the stroke outcomes and potential predisposing factors in the present study have failed to provide evidence that there is a causal link between extended-release niacin and ischemic stroke, this finding will be examined further in additional analyses and in other studies of niacin involving patients with cardiovascular disease.

Table 3. Reductions and Discontinuation of Study Drugs and Levels of Statins.

Variable	Placebo plus Statin (N=1696)	Extended-Release Niacin plus Statin (N=1718)	P Value
Reduction of study-drug dose after randomization			
Patients requiring dose reduction — no. (%)	58 (3.4)	109 (6.3)	<0.001
Primary reason for dose reduction — no. (%)			
Flushing or itching	23 (1.4)	57 (3.3)	
Abnormality on liver-function test	0	1 (0.1)	
Request by patient	11 (0.6)	13 (0.8)	
Request by nonstudy physician	3 (0.2)	1 (0.1)	
Other clinical reason	10 (0.6)	21 (1.2)	
Increased glucose level	5 (0.3)	10 (0.6)	
Gastrointestinal symptoms	4 (0.2)	4 (0.2)	
Reason not specified	2 (0.1)	0	
Discontinuation of study drug after randomization			
Patients discontinuing study drug — no. (%)	341 (20.1)	436 (25.4)	<0.001
Time to discontinuation — days	579.6±463.5	568.1±480.2	
Primary reason for discontinuation — no. (%)			
Flushing or itching	43 (2.5)	104 (6.1)	
Abnormality on liver-function test	5 (0.3)	5 (0.3)	
Request by patient	137 (8.1)	126 (7.3)	
Request by nonstudy physician	35 (2.1)	49 (2.9)	
Other clinical reason	95 (5.6)	96 (5.6)	
Increased glucose level	14 (0.8)	29 (1.7)	
Gastrointestinal symptoms	12 (0.7)	26 (1.5)	
Reason not specified	0	1 (0.1)	
Overall adherence to study drug — no./total no. (%)*			
≥75%	1324/1419 (93.3)	1275/1417 (90.0)	
50 to <75%	77/1419 (5.4)	115/1417 (8.1)	
<50%	18/1419 (1.3)	27/1417 (1.9)	
Statin dose after adjustment — no. (%)†			
5 mg/day	2 (0.1)	4 (0.2)	0.02‡
10 mg/day	48 (2.8)	87 (5.1)	
20 mg/day	136 (8.0)	228 (13.3)	
40 mg/day	852 (50.2)	851 (49.5)	
60 mg/day	8 (0.5)	4 (0.2)	
80 mg/day	419 (24.7)	300 (17.5)	
Data missing	1 (0.1)	1 (0.1)	
Not taking simvastatin	230 (13.6)	243 (14.1)	
Use of ezetimibe — no. (%)	365 (21.5)	163 (9.5)	<0.001

* Rates of adherence were calculated over all follow-up clinic visits.
† Doses listed here are those that patients were taking after the 12-month follow-up visit or after two consecutive follow-up visits with the same dose before the 12-month follow-up visit.
‡ The P value was for the Spearman rank correlation for the overall comparison of the dose level between the treatment groups.

Table 4. Primary, Secondary, and Tertiary End Points.

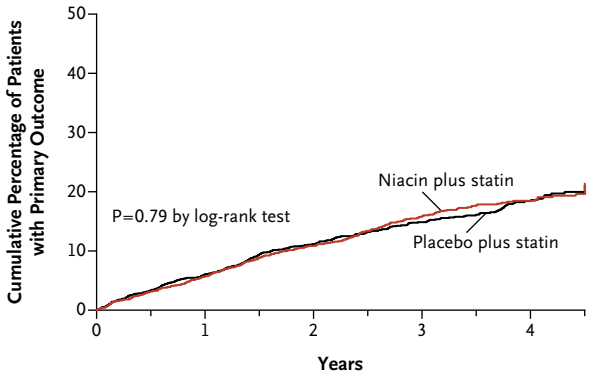
End Point	Placebo plus Statin (N=1696)	Extended-Release Niacin plus Statin (N=1718)	Hazard Ratio with Niacin (95% CI)	P Value*
	number of patients (percent)			
Primary end point: death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalization for acute coronary syndrome, or symptom-driven coronary or cerebral revascularization	274 (16.2)	282 (16.4)	1.02 (0.87–1.21)	0.80
Individual primary-end-point events				
Death from coronary heart disease	26 (1.5)	20 (1.2)		
Nonfatal myocardial infarction	80 (4.7)	92 (5.4)		
Ischemic stroke	15 (0.9)	27 (1.6)		
Hospitalization for acute coronary syndrome	67 (4.0)	63 (3.7)		
Symptom-driven coronary or cerebral revascularization	86 (5.1)	80 (4.7)		
Secondary end points				
Death from coronary heart disease, nonfatal myocardial infarction, high-risk acute coronary syndrome, or ischemic stroke	158 (9.3)	171 (10.0)	1.08 (0.87–1.34)	0.49
Death from coronary heart disease, nonfatal myocardial infarction, or ischemic stroke	138 (8.1)	156 (9.1)	1.13 (0.90–1.42)	0.30
All deaths from cardiovascular causes	38 (2.2)	45 (2.6)	1.17 (0.76–1.80)	0.47
Tertiary end points†				
Death from coronary heart disease	34 (2.0)	38 (2.2)	1.10 (0.69–1.75)	0.68
Death from any cause	82 (4.8)	96 (5.6)	1.16 (0.87–1.56)	0.32
Nonfatal myocardial infarction	93 (5.5)	104 (6.1)	1.11 (0.84–1.47)	0.46
Hospitalizations for acute coronary syndrome	82 (4.8)	72 (4.2)	0.87 (0.63–1.19)	0.38
Symptom-driven coronary or cerebral revascularizations	168 (9.9)	167 (9.7)	0.99 (0.80–1.22)	0.90
Ischemic stroke‡	18 (1.1)	29 (1.7)	1.61 (0.89–2.90)	0.11
Ischemic stroke or stroke of uncertain origin	18 (1.1)	30 (1.7)	1.67 (0.93–2.99)	0.09

* The P value is for the superiority of niacin therapy over placebo, adjusted for sex and history or no history of diabetes, with the use of a Cox proportional-hazards model to estimate the Wald statistic.

† The tertiary end point included all events, rather than just those that occurred as the first study event (which are listed in the category of individual primary-end-point events).

‡ Three strokes in the niacin group were detected during a blinded re-review, after the database was locked, of cases of transient ischemic attack; these three events are not included in these analyses.

There are several limitations to our study. First, our findings may not be generalizable to all patients with coronary disease or all patients with low HDL cholesterol levels. Although the results of the study may cast doubt on the clinical importance of therapeutic interventions directed toward modulating low levels of HDL cholesterol and elevated triglyceride levels — at least with respect to niacin therapy in patients with cardiovascular disease and dyslipidemia whose condition is stable — it remains unclear whether other populations may benefit from such treatment. Our trial excluded patients who had had a recent hospitalization for an acute coronary syndrome or acute myocardial infarction; such patients are at much higher risk than were the patients in our study. Only 6% of the patients in our study were not taking statins at entry, and these patients had much higher LDL cholesterol levels and lower HDL cholesterol levels at baseline than did the patients who were taking statins. Thus, it is unclear whether the 94% of patients who were taking statins at entry and had very low levels of LDL cholesterol at baseline had a lower risk of subsequent cardiovascular events than we originally projected or whether, as a recent study suggests,[21] the intensive use of statins for 1 year or more may have caused "delipidation" of the lipid-



No. at Risk

Placebo plus statin	1696	1581	1381	910	436
Niacin plus statin	1718	1606	1366	903	428

Figure 1. Kaplan–Meier Curve for the Primary End Point.

rich necrotic core and potentially converted coronary plaques vulnerable to rupture into stable, quiescent ones. In addition, the generalizability of the findings of our trial is further limited by the low percentage of women enrolled (15%) and the very low rate of ethnic minorities recruited (8%).

Second, the patients in the placebo group received a small dose (50 mg) of immediate-release niacin in each placebo tablet to mask the identity of the blinded treatment to patients and study personnel. It seems highly unlikely that the moderate increase in HDL cholesterol levels observed in the patients receiving placebo could have resulted from the very small dose of immediate-release niacin contained in each 500-mg or 1000-mg placebo tablet (a cumulative dose of 100 to 200 mg per day); data from studies involving persons who were given 100, 200, or even 500 mg per day as a single dose for 5 weeks showed no change in any monitored lipid value beyond 4 hours after each daily dose.[22] Multiple doses of short-acting niacin must be given daily to observe an effect on lipid or lipoprotein variables.

Finally, it is possible that the follow-up period of the trial (mean, 36 months) was not long enough to show a clinical treatment effect of niacin. However, the Kaplan–Meier curves for the primary end point were nearly identical at the time of termination of the study.

In summary, the AIM-HIGH trial was designed to determine the superiority of treatment with niacin plus a statin as compared with statin therapy, with or without ezetimibe, in further decreasing the incidence of major cardiac events among patients with coronary heart disease who had residual dyslipidemia and low levels of HDL cholesterol at baseline but who met a treatment goal of an LDL cholesterol level of 40 to 80 mg per deciliter. In such patients who had established, nonacute, atherosclerotic cardiovascular disease and guideline-driven, intensively controlled levels of LDL cholesterol while receiving simvastatin, we found no incremental benefit of niacin in reducing cardiovascular events over a follow-up period of 36 months, despite significant increases in HDL cholesterol levels and decreases in triglyceride levels. Whether such benefits might be observed in higher-risk cardiac patients or in those whose LDL cholesterol levels are not intensively controlled by statins will require further prospective study.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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