

## Effects of Extended-Release Niacin with Laropiprant in High-Risk Patients

The HPS2-THRIVE Collaborative Group\*

### ABSTRACT

#### BACKGROUND

Patients with evidence of vascular disease are at increased risk for subsequent vascular events despite effective use of statins to lower the low-density lipoprotein (LDL) cholesterol level. Niacin lowers the LDL cholesterol level and raises the high-density lipoprotein (HDL) cholesterol level, but its clinical efficacy and safety are uncertain.

#### METHODS

After a prerandomization run-in phase to standardize the background statin-based LDL cholesterol-lowering therapy and to establish participants' ability to take extended-release niacin without clinically significant adverse effects, we randomly assigned 25,673 adults with vascular disease to receive 2 g of extended-release niacin and 40 mg of laropiprant or a matching placebo daily. The primary outcome was the first major vascular event (nonfatal myocardial infarction, death from coronary causes, stroke, or arterial revascularization).

#### RESULTS

During a median follow-up period of 3.9 years, participants who were assigned to extended-release niacin-laropiprant had an LDL cholesterol level that was an average of 10 mg per deciliter (0.25 mmol per liter as measured in the central laboratory) lower and an HDL cholesterol level that was an average of 6 mg per deciliter (0.16 mmol per liter) higher than the levels in those assigned to placebo. Assignment to niacin-laropiprant, as compared with assignment to placebo, had no significant effect on the incidence of major vascular events (13.2% and 13.7% of participants with an event, respectively; rate ratio, 0.96; 95% confidence interval [CI], 0.90 to 1.03;  $P=0.29$ ). Niacin-laropiprant was associated with an increased incidence of disturbances in diabetes control that were considered to be serious (absolute excess as compared with placebo, 3.7 percentage points;  $P<0.001$ ) and with an increased incidence of diabetes diagnoses (absolute excess, 1.3 percentage points;  $P<0.001$ ), as well as increases in serious adverse events associated with the gastrointestinal system (absolute excess, 1.0 percentage point;  $P<0.001$ ), musculoskeletal system (absolute excess, 0.7 percentage points;  $P<0.001$ ), skin (absolute excess, 0.3 percentage points;  $P=0.003$ ), and unexpectedly, infection (absolute excess, 1.4 percentage points;  $P<0.001$ ) and bleeding (absolute excess, 0.7 percentage points;  $P<0.001$ ).

#### CONCLUSIONS

Among participants with atherosclerotic vascular disease, the addition of extended-release niacin-laropiprant to statin-based LDL cholesterol-lowering therapy did not significantly reduce the risk of major vascular events but did increase the risk of serious adverse events. (Funded by Merck and others; HPS2-THRIVE ClinicalTrials.gov number, NCT00461630.)

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PATIENTS WITH CARDIOVASCULAR DISEASE remain at substantial risk for major vascular events despite current approaches to treatment of risk factors.<sup>1</sup> Observational data indicate that the low-density lipoprotein (LDL) cholesterol level is strongly positively associated with the risk of coronary heart disease and that the high-density lipoprotein (HDL) cholesterol level is strongly inversely associated.<sup>2</sup> High-dose niacin decreases the LDL cholesterol level and increases the HDL cholesterol level, as well as lowering triglyceride and lipoprotein(a) levels and blood pressure.<sup>3,4</sup> Current guidelines recommend that niacin therapy be considered for reducing cardiovascular risk,<sup>5,6</sup> and its use in the United States has been increasing steadily,<sup>7</sup> despite the lack of evidence from randomized trials of a clinical benefit when niacin is added to current treatment.

The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial, which involved 3414 high-risk patients who were receiving statin therapy, was stopped prematurely after 3 years because of an apparent lack of benefit with extended-release niacin.<sup>8</sup> However, given the small differences in blood lipid levels that were observed between randomized groups, the AIM-HIGH trial may have been too small to detect plausible reductions in vascular events.

The Heart Protection Study 2—Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) was designed to assess the effects of adding extended-release niacin in combination with laropiprant to effective statin-based LDL cholesterol-lowering treatment in 25,673 high-risk patients with prior vascular disease. Laropiprant is an antagonist of the prostaglandin D<sub>2</sub> receptor DP<sub>1</sub> that has been shown to improve adherence to niacin therapy by reducing flushing in up to two thirds of patients.<sup>9,10</sup>

## METHODS

### STUDY ORGANIZATION

HPS2-THRIVE was a randomized, double-blind, multicenter trial that enrolled patients at 245 sites in the United Kingdom (89 sites), Scandinavia (84), and China (72). The trial was designed, conducted, and analyzed by the Clinical Trial Service Unit at Oxford University, which was the independent regulatory sponsor of the trial. Merck

(manufacturer of the study drugs) funded the trial, had nonvoting membership on the steering committee, and provided trial coordination within Scandinavia through its subsidiaries (under the direction of Oxford University). Although Merck had the opportunity to comment on preliminary drafts of the manuscript, it otherwise had no role in the design or conduct of the trial, the analysis of the data, the approval of the manuscript, or the decision to submit it for publication. The study protocol (available with the full text of this article at NEJM.org) was approved by the relevant institutional review board for each participating center. The last member of the writing committee vouches for the data and analyses and for the fidelity of this report to the study protocol.

As prespecified, the trial design, characteristics of the study participants, and effects of niacin-laropiprant on certain safety outcomes were reported before the scheduled end of the study.<sup>11</sup> The methods are summarized below, with further details provided in Supplementary Appendix 1, available at NEJM.org.

### STUDY PARTICIPANTS

Men and women 50 to 80 years of age were eligible if they had a history of myocardial infarction, cerebrovascular disease, peripheral arterial disease, or diabetes mellitus with evidence of symptomatic coronary disease. There were no entry criteria regarding lipid levels. Patients were excluded if they had clinically significant hepatic, renal, muscle-related, or other disease, were receiving concurrent treatment with potentially interacting drugs, or were receiving LDL cholesterol-lowering treatment that was more effective than simvastatin at a dose of 40 mg plus ezetimibe at a dose of 10 mg daily.<sup>11</sup> Details of the trial inclusion and exclusion criteria are provided in Supplementary Appendix 1.

### STUDY PROCEDURES

Potentially eligible patients were identified from hospital or clinic records, or by means of advertisement, and were invited to attend a study clinic. Patients who appeared to be eligible for inclusion in the study were asked to provide written informed consent and to discontinue any statin therapy. In a prerandomization run-in phase, each participant received simvastatin at a dose of 40 mg daily; if this dose was not as effective as their prior treatment or if their total cholesterol

level was 135 mg per deciliter (3.50 mmol per liter) or higher after 4 weeks, ezetimibe at a dose of 10 mg daily was added. After LDL cholesterol-lowering therapy had been standardized, participants received a combination tablet containing 1 g of extended-release niacin and 20 mg of laropiprant daily for 4 weeks, followed by two tablets daily providing a total of 2 g of niacin and 40 mg of laropiprant for 3 to 6 weeks. Participants who did not report clinically significant adverse effects with this treatment and who remained eligible<sup>11</sup> were randomly assigned to receive two niacin-laropiprant combination tablets (a total of 2 g of niacin and 40 mg of laropiprant) daily or matching placebo.

After randomization, follow-up assessments of participants were to take place at 3 months and 6 months and then every 6 months for a median duration of 4 years. All serious adverse events, including potential study outcomes, were recorded. In addition, nonserious adverse events that were considered by the participants to be related to the study drug or that resulted in discontinuation of the study drug were recorded, as were symptoms of muscle pain or weakness and hepatitis (e.g., nausea, vomiting, or jaundice). Adherence, which was defined as self-reported consumption of at least 80% of the study drug, was recorded, and blood tests were performed for liver and muscle safety monitoring.

## STUDY OUTCOMES

The primary outcome was the first major vascular event, defined as a major coronary event (nonfatal myocardial infarction or death from coronary causes), stroke of any type, or coronary or noncoronary revascularization. Secondary outcomes included the components of the primary outcome, different types of stroke, and mortality (overall and in specific categories). Additional prespecified secondary outcomes included the primary outcome after the exclusion of hemorrhagic stroke, the primary outcome after the exclusion of both hemorrhagic stroke and any arterial revascularization procedure, and the primary outcome separately in the first year and in later years. Detailed definitions of the outcomes for the prespecified analyses are provided in Supplementary Appendix 1.

All the reports of possible major vascular events or safety outcomes were centrally adjudicated according to prespecified criteria by clini-

cians who were unaware of the study-treatment assignments. Analyses were based on confirmed plus unrefuted reports of events; 95 to 99% of the myocardial infarctions, strokes, and revascularizations that were included were confirmed.

## STATISTICAL ANALYSIS

On the basis of data from trials involving similar populations<sup>12-14</sup> and expected secular trends, we calculated that 20,000 participants would need to undergo randomization for the study to have more than 95% power to detect a proportional reduction in risk of 15% in the primary outcome with niacin-laropiprant, at a significance level of less than 0.05 (see Supplementary Appendix 1). However, on the basis of the observed changes in the lipid levels during the prerandomization run-in phase and adherence to the regimen during the scheduled randomized study-treatment period, it was estimated that differences in the lipid levels during the randomized phase would be smaller than originally anticipated. Consequently, the steering committee increased the sample to 25,000 participants; we estimated that with more than 3400 major vascular events, the study would have more than 80% power to detect a proportional reduction in risk of 10%, at a significance level of less than 0.05.

Data-analysis plans were prespecified in the original protocol and published on the study website ([www.ctsuo.ox.ac.uk/thrive](http://www.ctsuo.ox.ac.uk/thrive)) before unblinded analyses were available to the steering committee. Prespecified comparisons involved log-rank analyses of the first occurrence of particular events during the scheduled treatment period after randomization among all the participants assigned to niacin-laropiprant versus all those assigned to placebo (i.e., intention-to-treat analyses).<sup>15,16</sup> The log-rank analysis yielded the average rate ratio for an event or death, with the proportional reduction in this ratio expressed as a percentage, and a two-sided significance test.

## RESULTS

### STUDY PARTICIPANTS

Of 51,698 people who were screened, 42,424 entered the prerandomization run-in phase (Fig. S1 in Supplementary Appendix 1). In summary, 11.2% of the patients who started the LDL cholesterol-standardization phase withdrew during this phase, and 33.1% of those who started the

active niacin-laropiprant phase withdrew during that phase (chiefly because of skin-related, gastrointestinal, diabetes-related, and musculoskeletal adverse effects).<sup>11</sup> From April 2007 through July 2010, a total of 25,673 participants underwent randomization (Table 1, and Fig. S1 in Supplementary Appendix 1). The mean age of the participants was 64.9 years, and 82.7% of the participants were men.

Coronary disease was reported by 78.4% of the participants, cerebrovascular disease by 31.8%, peripheral arterial disease by 12.5%, and diabetes mellitus by 32.3%, and 36.3% of the participants met the criteria for the metabolic syndrome.<sup>11,17</sup> Baseline cholesterol levels were well controlled with the LDL cholesterol-lowering regimen established during the run-in phase, with an average LDL cholesterol level of 63 mg per deciliter (1.64 mmol per liter, as measured in the central laboratory) and an average HDL cholesterol level of 44 mg per deciliter (1.14 mmol per liter). The median duration of follow-up was 3.9 years (mean, 3.6 years), yielding 46,239 person-years in the niacin-laropiprant group and 46,359 person-years in the placebo group.

#### ADHERENCE AND LIPID LEVELS

Reported adherence to niacin-laropiprant fell to 89.1% during the first year and to 69.9% by the scheduled end of the study period, yielding a study average of 77.7% (Table S1 in Supplementary Appendix 1). Overall, significantly more participants in the niacin-laropiprant group than in the placebo group discontinued the study drug (25.4% vs. 16.6%,  $P<0.001$ ), with discontinuations attributable primarily to recognized side effects of niacin (e.g., skin-related, gastrointestinal, musculoskeletal, and diabetes-related adverse events).<sup>11</sup> Participants who discontinued the randomized study drug were also more likely to discontinue their background-study LDL cholesterol-lowering treatment and were encouraged to take a nonstudy statin. There was negligible use of nonstudy niacin (three participants in the niacin-laropiprant group and nine in the placebo group).

During the study, assignment to treatment with niacin-laropiprant was associated with an average reduction in the LDL cholesterol level of 10 mg per deciliter (0.25 mmol per liter, as measured in the central laboratory), an average increase in the HDL cholesterol level of 6 mg per deciliter (0.16 mmol per liter), and an average reduction in the triglyceride level of 33 mg per deciliter

(0.37 mmol per liter), as compared with assignment to placebo (Tables S2 and S3 in Supplementary Appendix 1). Niacin-laropiprant was also associated with a number of other effects, including reductions in weight, blood pressure, and lipoprotein(a) level and an increase in the glycated hemoglobin level (Table S4 in Supplementary Appendix 1).

#### EFFECTS ON MAJOR VASCULAR EVENTS

Assignment to niacin-laropiprant, as compared with assignment to placebo, was not associated with a significant reduction in the incidence of major vascular events (1696 participants with events [13.2%] and 1758 participants with events [13.7%], respectively; rate ratio, 0.96; 95% confidence interval [CI], 0.90 to 1.03;  $P=0.29$ ) (Fig. 1 and 2). There was no apparent effect in the first year after randomization (rate ratio, 1.01; 95% CI, 0.90 to 1.14) or in subsequent years (rate ratio, 0.94; 95% CI, 0.87 to 1.02;  $P=0.17$ ). Similarly, there were no significant effects of assignment to niacin-laropiprant, as compared with assignment to placebo, on the secondary outcomes of the incidence of major vascular events excluding hemorrhagic stroke (12.4% and 13.1%, respectively; rate ratio, 0.95; 95% CI, 0.88 to 1.01;  $P=0.12$ ) or excluding both hemorrhagic stroke and revascularization procedures (7.9% and 8.4%, respectively; rate ratio, 0.95; 95% CI, 0.87 to 1.03;  $P=0.20$ ).

With respect to the separate components of major vascular events, there was no significant effect of niacin-laropiprant, as compared with placebo, on the incidence of major coronary events (rate ratio, 0.96; 95% CI, 0.87 to 1.07;  $P=0.51$ ) or any stroke (rate ratio, 1.00; 95% CI, 0.88 to 1.13;  $P=0.56$ ), but there was a nominally significant 10% proportional reduction in arterial revascularization procedures (rate ratio, 0.90; 95% CI, 0.82 to 0.99;  $P=0.03$ ). With respect to subtypes of stroke, there was no significant effect of niacin-laropiprant as compared with placebo on the incidence of presumed ischemic stroke (3.0% and 3.2%, respectively; rate ratio, 0.94; 95% CI, 0.82 to 1.08) or hemorrhagic stroke (0.9% vs. 0.7%, respectively; rate ratio, 1.28; 95% CI, 0.97 to 1.69).

#### SUBGROUP ANALYSES

Prespecified secondary analyses examined the effect of niacin-laropiprant on the incidence of major vascular events in subgroups defined according to history of various types of vascular disease or

**Table 1. Characteristics of the Participants at Baseline.\***

Characteristic	Niacin–Laropiprant (N=12,838)	Placebo (N=12,835)	All Participants (N=25,673)
<b>Age</b>			
Distribution — no. (%)			
<65 yr	6,470 (50.4)	6,462 (50.3)	12,932 (50.4)
≥65 to <70 yr	2,814 (21.9)	2,810 (21.9)	5,624 (21.9)
≥70 yr	3,554 (27.7)	3,563 (27.8)	7,117 (27.7)
Mean — yr	64.9±7.5	64.9±7.5	64.9±7.5
<b>Sex — no. (%)</b>			
Male	10,614 (82.7)	10,615 (82.7)	21,229 (82.7)
Female	2,224 (17.3)	2,220 (17.3)	4,444 (17.3)
<b>Region — no. (%)</b>			
Europe	7,374 (57.4)	7,367 (57.4)	14,741 (57.4)
China	5,464 (42.6)	5,468 (42.6)	10,932 (42.6)
<b>Prior disease — no. (%)</b>			
Myocardial infarction	8,685 (67.7)	8,660 (67.5)	17,345 (67.6)
Other coronary heart disease	8,424 (65.6)	8,346 (65.0)	16,770 (65.3)
Cerebrovascular disease	4,058 (31.6)	4,112 (32.0)	8,170 (31.8)
Peripheral arterial disease	1,622 (12.6)	1,592 (12.4)	3,214 (12.5)
Diabetes	4,134 (32.2)	4,165 (32.5)	8,299 (32.3)
<b>LDL cholesterol</b>			
Distribution — no. (%)			
<58 mg/dl	4,933 (38.4)	4,927 (38.4)	9,860 (38.4)
≥58 to <77 mg/dl	5,505 (42.9)	5,549 (43.2)	11,054 (43.1)
≥77 mg/dl	2,400 (18.7)	2,359 (18.4)	4,759 (18.5)
Mean — mg/dl	64±17	63±17	63±17
<b>HDL cholesterol</b>			
Distribution — no. (%)			
<35 mg/dl	2,459 (19.2)	2,441 (19.0)	4,900 (19.1)
≥35 to <43 mg/dl	4,098 (31.9)	4,037 (31.5)	8,135 (31.7)
≥43 mg/dl	6,281 (48.9)	6,357 (49.5)	12,638 (49.2)
Mean — mg/dl	43.9±11.2	44.0±11.2	43.9±11.2
<b>Total cholesterol</b>			
Distribution — no. (%)			
<116 mg/dl	3,547 (27.6)	3,582 (27.9)	7,129 (27.8)
≥116 to <135 mg/dl	4,800 (37.4)	4,691 (36.5)	9,491 (37.0)
≥135 mg/dl	4,491 (35.0)	4,562 (35.5)	9,053 (35.3)
Mean — mg/dl	128±22	128±22	128±22

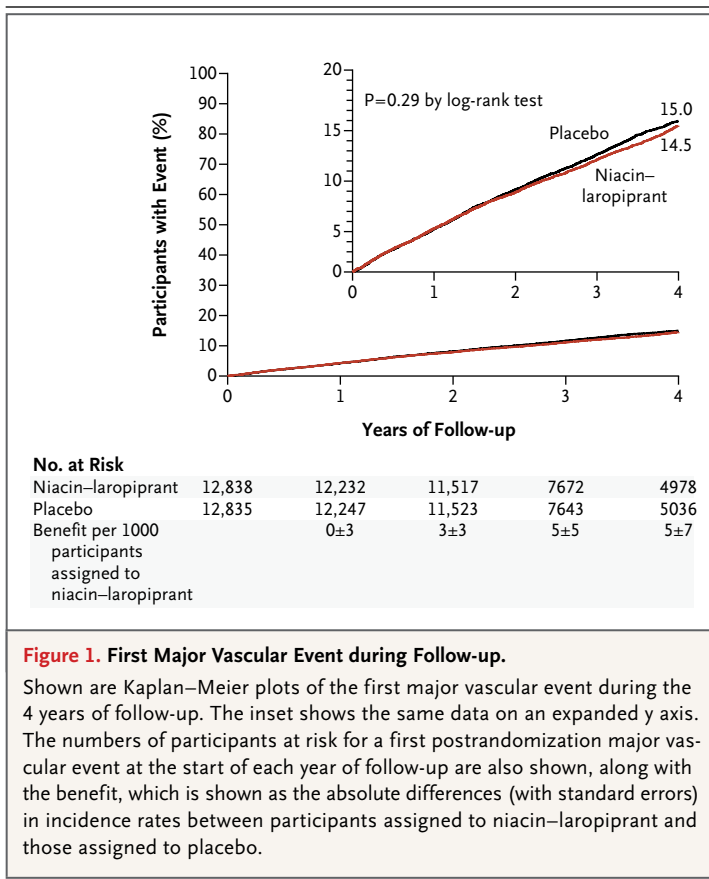
\* Plus–minus values are means ±SD. There were no significant differences in the baseline characteristics between the study groups. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. Additional details are provided in Figure S2 in Supplementary Appendix 1.

diabetes. Between the subgroups, there were no significant differences in the absolute changes in lipid levels or the proportional reductions in risk (Table S3 and Fig. S2 in Supplementary Appendix 1).

Tertiary assessments included the effects on

major vascular events in more than 30 additional prespecified subgroup categories. Even without adjustment for multiple comparisons, there were no significant differences among most of these subgroups in the proportional reductions in ma-





major vascular events (Fig. S2 in Supplementary Appendix 1). An unadjusted P value of less than 0.05 for heterogeneity or trend was observed in the following categories: smoking status, alcohol intake, beta-blocker use, and LDL cholesterol and apolipoprotein B levels. The nominally significant trend ( $P=0.02$ ) toward a greater reduction in risk in the subgroup with a higher baseline LDL cholesterol level may be related, at least in part, to the greater reduction in the LDL cholesterol level in that subgroup. Similarly, apparent differences between other subgroups in the observed effects on major vascular events may be related to differences between them in observed changes in the lipid levels, or they may be due to chance (Table S3 in Supplementary Appendix 1).

Niacin has been recommended particularly for patients who have the combination of low HDL cholesterol and high triglyceride levels.<sup>5,6</sup> Consequently, an exploratory analysis was conducted that included participants with both an HDL cholesterol level of less than 40 mg per deciliter (1.03 mmol per liter) in men or 51 mg

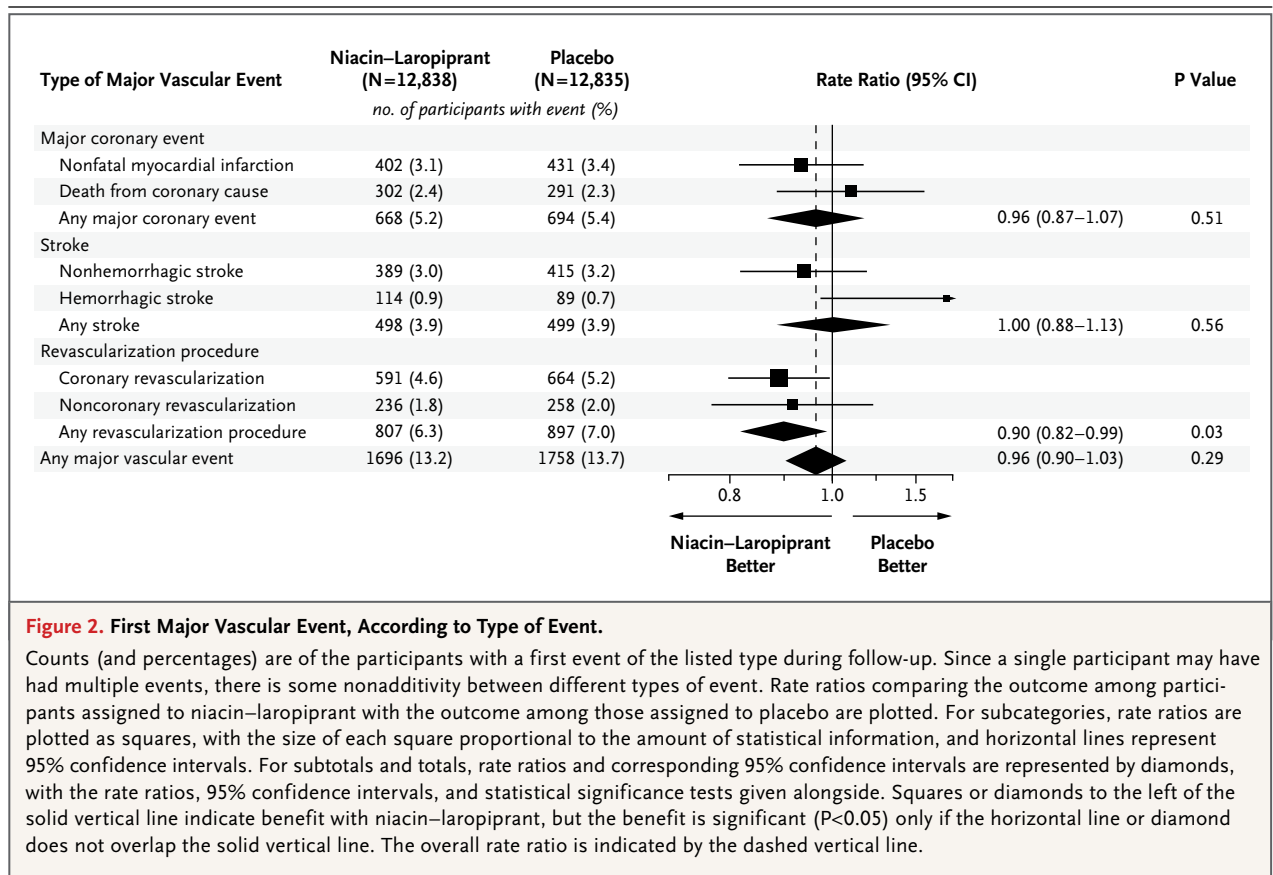
per deciliter (1.32 mmol per liter) in women and a triglyceride level of more than 151 mg per deciliter (1.70 mmol per liter) in either sex. In this analysis, there was no significant difference between the niacin-laropiprant group and the placebo group in the incidence of major vascular events (333 of 2203 participants [15.1%] and 334 of 2159 participants [15.5%], respectively, with an event).

#### EFFECTS ON MORTALITY AND RATES OF CANCER

Niacin-laropiprant, as compared with placebo, was associated with a nonsignificant 9% proportional increase in the incidence of death from any cause (798 participants [6.2%] and 732 participants [5.7%], respectively; rate ratio, 1.09; 95% CI, 0.99 to 1.21;  $P=0.08$ ), with similar nonsignificant increases in both vascular and nonvascular mortality (Fig. S3 in Supplementary Appendix 1). No significant increases were seen in any prespecified subgroups with regard to specific causes of death, including cancer. There were no significant increases in the incidence of cancer overall (4.8% with niacin-laropiprant and 4.7% with placebo,  $P=0.67$ ) or at any prespecified site (Fig. S4 in Supplementary Appendix 1).

#### EFFECTS ON OTHER ADVERSE EVENTS

Assignment to niacin-laropiprant, as compared with assignment to placebo, was associated with a highly significant excess of participants with fatal or nonfatal serious adverse events (7137 [55.6%] vs. 6762 [52.7%],  $P<0.001$ ), with many participants having more than one serious adverse event (Table S5 in Supplementary Appendix 1). The largest excesses in serious adverse events (nonfatal and fatal combined) were related to effects on glucose metabolism (Table 2, and Table S6 in Supplementary Appendix 1). In an analysis of the 8299 participants who had diabetes at the time of randomization, assignment to niacin-laropiprant, as compared with assignment to placebo, was associated with a 55% proportional increase in disturbances in diabetes control that were considered to be serious, most of which led to hospitalization (11.1% vs. 7.5%,  $P<0.001$ ). In an analysis of the 17,374 participants who did not have diabetes at the time of randomization, assignment to niacin-laropiprant, as compared with assignment to placebo, was associated with a 32% proportional increase in the diagnosis of diabetes (5.7% vs. 4.3%,  $P<0.001$ ).



**Figure 2. First Major Vascular Event, According to Type of Event.**

Counts (and percentages) are of the participants with a first event of the listed type during follow-up. Since a single participant may have had multiple events, there is some nonadditivity between different types of event. Rate ratios comparing the outcome among participants assigned to niacin-laropiprant with the outcome among those assigned to placebo are plotted. For subcategories, rate ratios are plotted as squares, with the size of each square proportional to the amount of statistical information, and horizontal lines represent 95% confidence intervals. For subtotals and totals, rate ratios and corresponding 95% confidence intervals are represented by diamonds, with the rate ratios, 95% confidence intervals, and statistical significance tests given alongside. Squares or diamonds to the left of the solid vertical line indicate benefit with niacin-laropiprant, but the benefit is significant ( $P < 0.05$ ) only if the horizontal line or diamond does not overlap the solid vertical line. The overall rate ratio is indicated by the dashed vertical line.

There were also highly significant excesses of other recognized adverse effects of niacin, including gastrointestinal, musculoskeletal, and skin-related serious adverse events. The excess of gastrointestinal serious adverse events in the niacin-laropiprant group as compared with the placebo group (4.8% vs. 3.8%,  $P < 0.001$ ) included bleeding and peptic ulceration, as well as other problems in the upper and lower gastrointestinal tracts (mostly dyspepsia and diarrhea, respectively). The excess of musculoskeletal serious adverse events with niacin-laropiprant (3.7% vs. 3.0%,  $P < 0.001$ ) reflected primarily a risk of myopathy with niacin-laropiprant that was four times as high as that with placebo,<sup>11</sup> plus a smaller excess of gout. In contrast to the large excess in skin-related nonserious adverse events that led to some participants discontinuing niacin-laropiprant,<sup>11</sup> there was only a small excess of skin-related serious adverse events (0.7% vs. 0.4%,  $P = 0.003$ ) — mostly rashes and skin ulcerations.

In addition to these known side effects of niacin, niacin-laropiprant was associated with highly significant excesses of infection and bleeding that were considered to be serious (Table 2). The excess of infections with niacin-laropiprant versus placebo (8.0% vs. 6.6%,  $P < 0.001$ ) was distributed across a range of sites and types of infection (Table S6 in Supplementary Appendix 1). Similarly, the excess of bleeding events with niacin-laropiprant versus placebo (2.5% vs. 1.9%,  $P < 0.001$ ) was distributed across a number of sites (and included gastrointestinal bleeding and intracranial hemorrhage).

Searchable tabulations of all the serious adverse events (fatal and nonfatal combined), as well as all the adverse reactions that were not considered to be serious, are provided in Supplementary Appendix 2, available at NEJM.org. They are grouped on the basis of the *Medical Dictionary for Regulatory Activities*, version 14.0, classification system, according to system organ class, higher-level general term, and higher-level term.

**Table 2.** Effects of Niacin–Laropiprant on Selected Serious Adverse Events and Diabetes.\*

Event Type	Niacin– Laropiprant (N = 12,838)	Placebo (N = 12,835)	Rate Ratio (95% CI)	Absolute Excess with Niacin– Laropiprant  percentage points	P Value
Serious adverse event — no. (%)					
Gastrointestinal event	620 (4.8)	491 (3.8)	1.28 (1.13–1.44)	1.0±0.3	<0.001
Musculoskeletal event	481 (3.7)	385 (3.0)	1.26 (1.10–1.44)	0.7±0.2	<0.001
Skin-related event	86 (0.7)	51 (0.4)	1.67 (1.20–2.34)	0.3±0.1	0.003
Infection event	1031 (8.0)	853 (6.6)	1.22 (1.12–1.34)	1.4±0.3	<0.001
Bleeding event	326 (2.5)	238 (1.9)	1.38 (1.17–1.62)	0.7±0.2	<0.001
Diabetes mellitus — no./total no. (%)					
New-onset diabetes in participants without diabetes at baseline	494/8704 (5.7)	376/8670 (4.3)	1.32 (1.16–1.51)	1.3±0.3	<0.001
Disturbed diabetes control in participants with diabetes at baseline	460/4134 (11.1)	311/4165 (7.5)	1.55 (1.34–1.78)	3.7±0.6	<0.001

\* Plus-minus values are means ±SE. Results are shown for the serious adverse events (fatal and nonfatal combined) for which there was a significant difference between the randomized study groups. All the categories are mutually exclusive, except for bleeding, which includes serious adverse events from various categories. Only participants with diabetes at randomization were at risk for disturbed diabetes control, and only those without diabetes at randomization were at risk for new-onset diabetes (defined here as either self-reported new-onset diabetes or new use of medication for glycemic control). In an analysis that included patients with an elevated glycated hemoglobin level (defined as >48 mmol of glycated hexapeptide per mole of total hexapeptide, according to the method recommended by the International Federation of Clinical Chemistry and Laboratory Medicine) in the definition of new-onset diabetes, we found 792 cases (9.1%) with niacin–laropiprant versus 632 (7.3%) with placebo (rate ratio, 1.27 [95% CI, 1.14 to 1.41]; absolute excess, 1.8±0.4 percentage points; P<0.001). Additional details are provided in Table S6 in Supplementary Appendix 1.

## DISCUSSION

HPS2-THRIVE showed that adding niacin–laropiprant to effective statin-based LDL cholesterol-lowering therapy in patients known to have vascular disease did not significantly reduce the risk of major vascular events, either overall or in any particular subgroup of patients. However, the study also identified significant hazards, some of which had not been reported previously with niacin.

On the basis of meta-analyses of statin trials, the reduction of 10 mg per deciliter in the LDL cholesterol level in HPS2-THRIVE would have been expected to produce a 5 to 6% proportional reduction in the risk of major vascular events.<sup>1</sup> There is no similar evidence from randomized trials regarding the effects of raising the HDL cholesterol level, but if the inverse association with vascular disease risk in observational studies is causal (which has been questioned)<sup>18</sup> and half of it is reversible within a few years (as with LDL cholesterol-lowering therapy<sup>1</sup>) then the increase of 6 mg per deciliter in the HDL cholesterol level observed in HPS2-THRIVE might have been associated with a reduction in the risk of major vascular events of 4 to 5%.<sup>2</sup> Consequently,

the combined changes in the lipid levels would have been expected to reduce the risk of major vascular events by approximately 10%, which is slightly larger than the observed result (although still statistically compatible with it).

The findings regarding major vascular events in HPS2-THRIVE are consistent with those of previous randomized trials of high-dose niacin alone. In the Coronary Drug Project (CDP), which was conducted before effective LDL cholesterol-lowering agents were available, niacin reduced the total cholesterol level by 26 mg per deciliter (0.67 mmol per liter) from a high baseline level of 253 mg per deciliter (6.54 mmol per liter).<sup>19</sup> Lipid fractions were not measured in the CDP, but it can be estimated that the LDL cholesterol level was reduced by at least 30 mg per deciliter (0.78 mmol per liter) and the HDL cholesterol level was increased by approximately 5 mg per deciliter (0.13 mmol per liter). On the basis of the statin trials and observational epidemiologic studies,<sup>1,2</sup> such changes in lipid levels might produce a reduction in risk of 15 to 20%, which is compatible with the 19% reduction in myocardial infarction or coronary death observed in the CDP. By contrast, in the AIM-HIGH trial,<sup>8</sup> adding niacin to effective LDL



cholesterol-lowering therapy reduced the LDL cholesterol level by only 5 mg per deciliter and increased the HDL cholesterol level by 5 mg per deciliter. Such changes in lipid levels would be expected to reduce the relative risk of major vascular events by less than 10%, which is also compatible with the observed result in that trial.

In HPS2-THRIVE, niacin-laropiprant was associated with highly significant increases in the rates of various serious adverse events, including some already known to be caused by niacin (i.e., diabetes-related, gastrointestinal, musculoskeletal, and skin-related disorders).<sup>8,19,20</sup> For example, new diagnoses of diabetes were increased by one third, corresponding to 13 new cases per 1000 patients treated for approximately 4 years (or 18 new cases per 1000 patients if a glycated hemoglobin level of more than 48 mmol per mole is included in the definition). In addition, among the participants with diabetes at baseline, serious complications associated with glucose control (most of which resulted in hospitalization) occurred in 37 patients per 1000, a finding that counters previous reassurances about the safety of niacin in persons with diabetes.<sup>21-23</sup>

Most of the excess of serious musculoskeletal adverse events with niacin-laropiprant was due to myopathy. The absolute risk of myopathy in the placebo group was much higher in China than in Europe, and the relative risk with niacin-laropiprant versus placebo was 5.2 in China, as compared with 1.5 in Europe. Consequently, as reported previously,<sup>11</sup> the absolute excess of myopathy associated with adding niacin-laropiprant to statin-based LDL cholesterol-lowering therapy was more than 10 times as great among participants in China as among those in Europe: 50 cases per 10,000 participants versus 3 cases per 10,000 participants annually.

The observed excess of serious infections — an excess of 14 cases per 1000 participants assigned to receive niacin-laropiprant for 4 years — had not been expected. It is not possible to determine the separate contributions of niacin and laropiprant (with potential mechanistic explanations for both drugs<sup>24,25</sup>) from the results of HPS2-THRIVE alone. However, in the AIM-HIGH trial, niacin alone was associated with a significant increase in the risk of serious infection (139 patients in the niacin group [8.1%] vs. 98 in the placebo group [5.8%],  $P=0.008$ ).<sup>26</sup> Moreover, the larger numbers of events of any severity attributed to infection in the AIM-HIGH

trial (674 participants in the niacin group [39.2%] vs. 593 in the placebo group [35.0%];  $P=0.01$ ) provide an even more robust demonstration of this hazard.<sup>26</sup>

In HPS2-THRIVE, the unexpected excess of serious bleeding events — an excess of 7 cases per 1000 participants treated with niacin-laropiprant for 4 years — was distributed across gastrointestinal, intracranial, and other sites. Niacin is known to reduce platelet counts<sup>27</sup> (Table S4 in Supplementary Appendix 1) and affect clotting,<sup>28-31</sup> but potential mechanisms for bleeding have also been proposed for laropiprant.<sup>32-34</sup> In the smaller AIM-HIGH trial, there were relatively few serious bleeding-related events, and the excess with niacin alone was not significant (59 participants in the niacin group [3.4%] and 49 in the placebo group [2.9%],  $P=0.36$ ).<sup>26</sup> However, the result is consistent with the excess in HPS2-THRIVE, and there was a significant excess in the larger numbers of bleeding events of any severity recorded in the AIM-HIGH trial (174 participants in the niacin group [10.1%] vs. 137 in the placebo group [8.1%],  $P=0.04$ ).<sup>26</sup>

In conclusion, we evaluated the effects of extended-release niacin combined with laropiprant, as compared with placebo, in 25,673 adults with atherosclerotic vascular disease. Treatment with extended-release niacin-laropiprant did not significantly reduce the risk of major vascular events but did significantly increase the risk of serious adverse events. In light of the consistency of the results with those from previous trials of niacin alone, we believe that the findings from HPS2-THRIVE are likely to be generalizable to all high-dose niacin formulations. Although niacin might still be relevant for particular patient groups (e.g., patients at high risk for vascular events who have high levels of LDL cholesterol), any potential benefits should be considered in the context of the observed hazards.

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