Serious Adverse Effects of Extended-release Niacin/Laropiprant: Results From the Heart Protection Study 2—Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) Trial

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ABSTRACT

Purpose: The Heart Protection Study 2—Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial of patients at high risk of vascular disease found that adding extended-release niacin-laropiprant to intensive statin-based LDL-lowering therapy had no benefit on cardiovascular outcomes. However, the trial also identified previously unrecognized serious adverse effects (including new-onset diabetes, bleeding, and infection). Our objective was to explore the safety profile of niacin-laropiprant and examine whether any patients were at lower (or higher) risk of its adverse effects.

Methods: HPS2-THRIVE was a randomized, double-blind trial of niacin-laropiprant (2000/40 mg/d) versus placebo among 25,673 patients at high risk of vascular disease. Information on all serious adverse events was collected during a median of 3.9 years of study treatment. Effects of niacin-laropiprant on new-onset diabetes, disturbances of diabetes control, bleeding, infection, and gastrointestinal upset were estimated by (1) time after randomization, (2) severity, (3) baseline characteristics, (4) baseline risk of the adverse event of interest, and (5) risk of major vascular event.

Findings: The hazard ratio (HR) for new-onset diabetes with niacin/laropiprant was 1.32 (95% CI, 1.16−1.51; $P < .001$), which corresponded to an absolute excess of 4 people (95% CI, 2−6) developing diabetes per 1000 person-years in the study population as a whole. Among the 8299 participants with diabetes at baseline, the HR for serious disturbances in diabetes control was 1.56 (95% CI, 1.35−1.80), corresponding to an absolute excess of 12 (95% CI, 8−16) per 1000 person-years. The HR was 1.38 (95% CI, 1.17−1.63; $P < .001$) for serious bleeding, corresponding to an absolute excess of 2 (95% CI, 1−3) per 1000 person-years and 1.22 (95% CI, 1.11−1.34; $P < .001$) for serious infection, corresponding to an absolute excess of 4 (95% CI, 2−6) per 1000 person-years. The excess risks of these serious adverse events were larger in the first year after starting niacin-laropiprant therapy than in later years (except for the excess of infection, which did not appear to attenuate with time), and the risks of nonfatal and fatal events were similarly increased. The absolute excesses of each of these adverse effects were similar regardless of the baseline risk of the outcome.

* Members of the HPS2-THRIVE Collaborative Group are listed in the Supplementary Appendix.

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Implications: Practitioners or patients considering the use of niacin (in addition to, or instead of, a statin) despite the lack of evidence of cardiovascular benefits (at least when added to effective statin therapy) should take account of the significant risks of these serious adverse effects when making such decisions. ClinicalTrials.gov identifier: NCT00461630. (*Clin Ther*. 2019;41:1767–1777) © 2019 Published by Elsevier Inc.

Key words: adverse effects, bleeding, cardiovascular disease, infection, niacin.

INTRODUCTION

Despite current best practice (including intensive statin-based LDL-C reduction), patients with atherosclerotic disease remain at significant risk of future occlusive vascular events.[1,2] Niacin has been recommended to reduce this residual risk because of its apparently beneficial effects on the lipid profile (including lowering LDL-C, triglycerides, and lipoprotein(a) and increasing HDL-C).[3] However, 2 randomized trials have found that, despite these effects, niacin does not reduce the risk of vascular events when added to intensive statin-based LDL-lowering therapy.[4,5] Furthermore, the large Heart Protection Study 2—Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial not only confirmed previously recognized adverse effects of niacin (in particular, cutaneous reactions, gastrointestinal upset, and disturbance of diabetes control) but also identified previously unrecognized serious adverse effects (including new-onset diabetes mellitus, bleeding, and infection). As a consequence, the US Food and Drug Administration has withdrawn the indication for niacin to be used in combination with a statin.[6]

HPS2-THRIVE tested extended-release (ER) niacin with laropiprant (niacin/laropiprant), a prostaglandin D_2 receptor antagonist. It is not possible to determine from the HPS2-THRIVE trial alone whether the harmful effects observed were attributable to niacin or laropiprant. However, similar effects with ER niacin given on its own were observed in the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial.[7] In combination, therefore, these trials strongly suggest that niacin was responsible for the adverse effects that were observed.

It is uncertain whether certain types of patients are at higher or lower risks of the harmful effects of niacin. Furthermore, the predictors of outcomes, such as bleeding (in the absence of a recent acute coronary syndrome or atrial fibrillation) and infection, among patients with atherosclerotic disease are not well known. Because some physicians and patients may still wish to continue to use niacin, knowledge of the risk factors for the harmful effects of niacin and whether the risks of these adverse effects vary by those risk factors may be clinically useful. We used the HPS2-THRIVE trial database to investigate whether there are subgroups of patients, in particular those at high risk of vascular disease or with a dyslipidaemia (low HDL-C/high triglycerides), who may be more likely to be considered for niacin therapy because the harmful effects of niacin are less significant.

METHODS

Study Participants and Procedures

The design and methods of the HPS2-THRIVE trial have been described previously.[5,8] In brief, men and women aged 5 to 80 years were eligible if they had a history of myocardial infarction, cerebrovascular or peripheral arterial disease, or diabetes mellitus with evidence of symptomatic coronary disease. Patients were excluded if they had clinically significant hepatic, renal, muscle-related, or other disease. Willing and eligible patients entered a 2-phase pre-randomization run-in period. During the first phase, participants' background LDL-lowering therapy was standardized to either simvastatin 40 mg/d or ezetimibe/simvastatin 10/40 mg/d; during the second phase they took active niacin-laropiprant (1000/20 mg/d for 4 weeks then increased to 2000/40 mg/d). Participants who did not report adverse events and who remained eligible were randomly assigned to receive niacin-laropiprant (2000/40 mg/d) or matching placebo. After randomization, follow-up assessments were scheduled at 3 and 6 months and then every 6 months for a mean of approximately 4 years at which all SAEs were recorded. Non-SAEs were not recorded unless they were considered to be the reason for stopping the study treatment.

Study Outcomes

New-onset diabetes was defined based on self-report by the participant or new use of hypoglycaemic medication. The definition of baseline diabetes also included glycosylated haemoglobin ≥48 mmol/mol, fasting glucose ≥7.0 mmol/L, or random (ie, <8 h fasting) glucose >11.1 mmol/L. Disturbances in diabetic control included minor disturbances (eg, hyperglycemia requiring hospitalization for optimization of blood glucose) and major disturbances (eg, ketoacidosis or hyperosmolar hyperglycaemic state). Infections and gastrointestinal events were defined as any SAE included in the *Medical Dictionary for Regulatory Activities* (MedDRA version 14.0) system organ classes infection and infestation and gastrointestinal disorder (excluding any bleeding events), respectively. Bleeding was defined as any SAE included in the MedDRA haemorrhage standard medical query. If the SAE resulted in death, further information was requested from the local study site for central adjudication according to prespecified criteria by physicians who were unaware of the study treatment assignment. Nonfatal SAEs, other than those included in the composite primary outcome major vascular event (MVE: nonfatal myocardial infarction, coronary death, stroke, or arterial revascularization) or prespecified safety outcomes (myopathy and hepatitis), were not adjudicated.

Statistical Analysis

The effects of niacin/laropiprant on new-onset diabetes, bleeding, and infection (separately) were examined by (1) time after randomization (ie, in the first and later years after randomization), (2) severity (defined by requirement for hospitalization and whether the SAE resulted in death or not); (3) subgroups of participant derived from baseline characteristics (as defined in the main trial data analysis plan[8] with the addition of individuals with the combination of HDL-C <0.9 mmol/L and triglycerides >1.7 mmol/L), (4) baseline risk of the adverse event, and (5) baseline risk of MVE. All analyses were based on comparisons between all participants randomly assigned niacin/laropiprant versus all those assigned placebo (ie, properly intention-to-treat analyses).

To develop baseline risk scores for harmful effects and MVEs, Cox proportional hazards regression models with stepwise model selection were used to identify significant baseline predictors of each relevant outcome (using a P threshold of 0.01), with randomized treatment allocation always included in the model. These independent risk factors were then used to construct a joint model that estimated each patient's risk of the outcome. The baseline characteristics considered and the variables selected for inclusion in each joint risk factor model are given in Supplemental Table I. Tertiles of the risk score (based on numbers of events rather than participants) were used to determine higher-, middle-, and lower-risk groups shown in the figures.

The absolute excess of particular adverse events attributable to niacin/laropiprant was defined as the difference between the 2 treatment arms in the number of events as a proportion of person-years at risk, expressed as events per 1000 person-years. Hazard ratios (HRs) describing proportional effects of niacin/laropiprant (and interactions between individual baseline characteristics and randomized treatment) were estimated by Cox proportional hazards regression models based on the first occurrence of each event after randomization. Tests for trend and heterogeneity were used to explore whether the effect of treatment varied by the various groups or categories examined. No formal correction for multiple testing was made, but P values were not to be considered significant unless $P < 0.01$ because of the post hoc nature of these analyses and the number of analyses conducted.

RESULTS

Between January 2007 and May 2010, a total of 51,698 patients were screened and 42,424 entered the prerandomization run-in (of whom 6365 entered the active niacin/laropiprant phase directly). A total of 4055 of the 36,059 participants (11%) who entered the LDL standardization phase withdrew compared with 12,696 of the 38,369 (33%) who entered the active niacin/laropiprant phase. A total of 25,673 participants were randomized and followed up for a mean of 3.6 years (median, 3.9 years).[5] Mean study adherence to niacin/laropiprant was 77.7% (ie, the proportion who reported taking most of their study treatment at each study visit). A total of 25.4% of participants assigned to receive niacin/laropiprant discontinued use of the study drug compared with 16.6% of those assigned to take

placebo ($P < 0.001$; Supplemental Table II). Further details of the run-in period and baseline characteristics have been published elsewhere.[8]

New-Onset Diabetes Mellitus

Among the 17,374 participants without diabetes mellitus at baseline, 494 (1.64% per year) of those assigned niacin/laropiprant developed new-onset diabetes compared with 376 (1.23% per year) of those assigned placebo (Table I); this finding corresponds to a one-third proportional increase (HR, 1.33; 95% CI, 1.16−1.52; $P < 0.001$) and an absolute excess of 4 people (95% CI, 2−6) per 1000 person-years developing diabetes in the study population as a whole. The proportional effect was greater in the first year of treatment (HR, 2.02; 95% CI, 1.58−2.58) than in later years (HR, 1.09; 95% CI, 0.93−1.28; P for heterogeneity <0.001).

After allowance for multiple comparisons, the proportional effect of niacin/laropiprant was broadly similar in the different types of participant studied (including those with low HDL-C and high triglycerides), with the exception of subgroups defined by adiposity (Supplemental Figure 1). In univariate analyses, there was evidence of an interaction ($P < 0.001$) with body mass index (BMI) and, more weakly, with waist circumference ($P = 0.01$): for each 5-kg/m^2 *greater* BMI, there was a 14% (95% CI, 10%−18%) proportional *reduction* in the relative risk of new-onset diabetes associated with assignment to niacin/laropiprant. Among participants with BMI <25 kg/m^2 (mean, 23.1 kg/m^2), 98 (4.2%) of those assigned niacin/laropiprant developed new-onset diabetes compared with 48 (2.0%) of those assigned placebo (HR, 2.09; 95% CI, 1.48−2.96). By contrast, among participants with

Table I. Effects of niacin/laropiprant on new-onset diabetes by time and disturbances in diabetic control by description, severity, and time.

Variable0	Niacin/laropiprant, No. (%)	Placebo, No. (%)	Hazard Ratio (95% CI)	Absolute Excess per 1000 Participants per Year (95% CI)
Randomized participants	12,838	12,835	—	—
New-onset diabetes mellitus nondiabetic at randomization	8704	8670	—	—
Time from randomization				
<1 year	193 (2.26)	96 (1.12)	2.02 (1.58−2.58)	11 (8 to 15)
≥1 year	301 (1.39)	280 (1.28)	1.09 (0.93−1.28)	1 (−1 to 3)
Any new-onset diabetes	494 (1.64)	376 (1.23)	1.33 (1.16−1.52)	4 (2 to 6)
Disturbances in diabetic control				
Diabetic at randomization	4134	4165	—	—
Description of event				
Minor hyperglycemic disturbance	361 (2.59)	242 (1.66)	1.56 (1.32−1.83)	9 (6 to 13)
Major hyperglycemic disturbance	42 (0.28)	12 (0.08)	3.56 (1.88−6.77)	2 (1 to 3)
Hypoglycemia	46 (0.31)	31 (0.21)	1.51 (0.96−2.38)	1 (−0 to 2)
Other diabetic disturbance	44 (0.30)	48 (0.32)	0.93 (0.62−1.40)	−0 (−1 to 1)
Time from randomization				
<1 year	219 (5.51)	83 (2.03)	2.71 (2.11−3.49)	35 (27 to 43)
≥1 year	241 (2.48)	228 (2.19)	1.13 (0.94−1.35)	3 (−1 to 7)
Any diabetic disturbance	460 (3.36)	311 (2.14)	1.56 (1.35−1.80)	12 (8 to 16)

BMI ≥30 kg/m^2 (mean, 33.1 kg/m^2), there were 165 (8.6%) versus 148 (8.1%) cases (HR, 1.06; 95% CI, 0.85−1.32).

Various independent predictors (identified by stepwise selection) were associated with the risk of new-onset diabetes (Supplemental Table I). A risk score based on these variables was strongly predictive of new-onset diabetes and differentiated participant groups well: rate of new-onset diabetes among placebo-allocated participants in the lowest-risk group was 1.7% compared with 25.9% in highest-risk group (Figure). However, after allowance for multiple comparisons, the absolute effects of niacin/laropiprant on new-onset diabetes did not differ by baseline risk of new-onset diabetes or of MVE (Figure) or among participants with low baseline HDL-C and high triglycerides (Supplemental Figure 2A).

Disturbances of Diabetes Control

Among the 8299 participants known to have diabetes at baseline, niacin/laropiprant was associated with a 56% proportional increase (HR, 1.56; 95% CI, 1.35−1.80) in individuals with serious disturbances of diabetes control, corresponding to an absolute excess of 12 people (95% CI, 8−16) (Table I) per 1000 person-years in the overall study population. Most of the absolute excess was in minor disturbances, although the proportional effect on major disturbances appeared larger. The proportional effects were also larger in the first year after treatment started than in later years (P for heterogeneity <0.001).

Bleeding

Overall, 326 participants (0.71% per year) assigned to receive niacin/laropiprant had at least 1 bleeding SAE during follow-up versus 238 (0.52% per year) assigned to receive placebo, corresponding to a 38% proportional increase (HR, 1.38; 95% CI, 1.17−1.63; $P < 0.001$) and an absolute excess of 2 people (95% CI, 1−3) (Table II) per 1000 person-years. Most bleeds were intracranial (including hemorrhagic stroke) or gastrointestinal, but there was little evidence that the proportional effects of niacin/laropiprant varied at different sites (P for heterogeneity = 0.18).

Approximately one-fifth of these bleeds were fatal, and the proportional effect of niacin/laropiprant did not appear to differ by severity of bleeding (P for heterogeneity = 0.64). The proportional effect appeared to be greater during the first year after treatment started (HR, 2.00; 95% CI, 1.42−2.83) than in later years (HR, 1.22; 95% CI, 1.01−1.48; P for heterogeneity = 0.01), and the absolute excess was also larger (albeit the difference was not statistically definite) in the first year than in subsequent years (4 [95% CI, 2−6] vs 1 [95% CI, 0−3] per 1000 per year (P for heterogeneity = 0.02).

The proportional effect of niacin/laropiprant on bleeding was similar in different types of participant (Supplemental Figure 3). Although the risk score discriminated participants based on their risk of bleeding, the absolute effect of niacin/laropiprant did not vary by baseline risk of bleeding or MVE (Figure 1B) or baseline low HDL-C and high triglycerides (Supplemental Figure 2B).

Infection

Overall, 1031 participants (2.32% per year) assigned to receive niacin/laropiprant versus 853 (1.90% per year) assigned to receive placebo had at least 1 infection reported as a SAE during follow-up, corresponding to a 22% proportional increase (HR, 1.22; 95% CI, 1.11−1.34; $P < 0.001$) and an absolute excess of 4 people (95% CI, 2−6) (Table III) per 1000 person-years. The most common sites of infection were the lower respiratory tract and urinary tract, with little evidence that the proportional effect varied by site of infection (P for heterogeneity = 0.20) (Table III). Only 5% of the infections resulted in death, and again there was little evidence that the proportional effect of niacin/laropiprant varied by severity of infection (P for heterogeneity = 0.51). The proportional effects appeared to be similar in the first year after treatment started (HR, 1.34; 95% CI, 1.13−1.59) and in later years (HR, 1.18; 95% CI, 1.06−1.31; P for heterogeneity = 0.21), as were the absolute effects (absolute excess 6 [95% CI, 3−10] vs 3 [95% CI, 1−6] per 1000 per year).

The proportional effect of niacin/laropiprant on infection was similar in different types of participants (Supplemental Figure 4). However, the absolute effect did not appear to vary by baseline risk of infection or MVE (Figure) or baseline low HDL-C and high triglycerides (Supplemental Figure 2C).

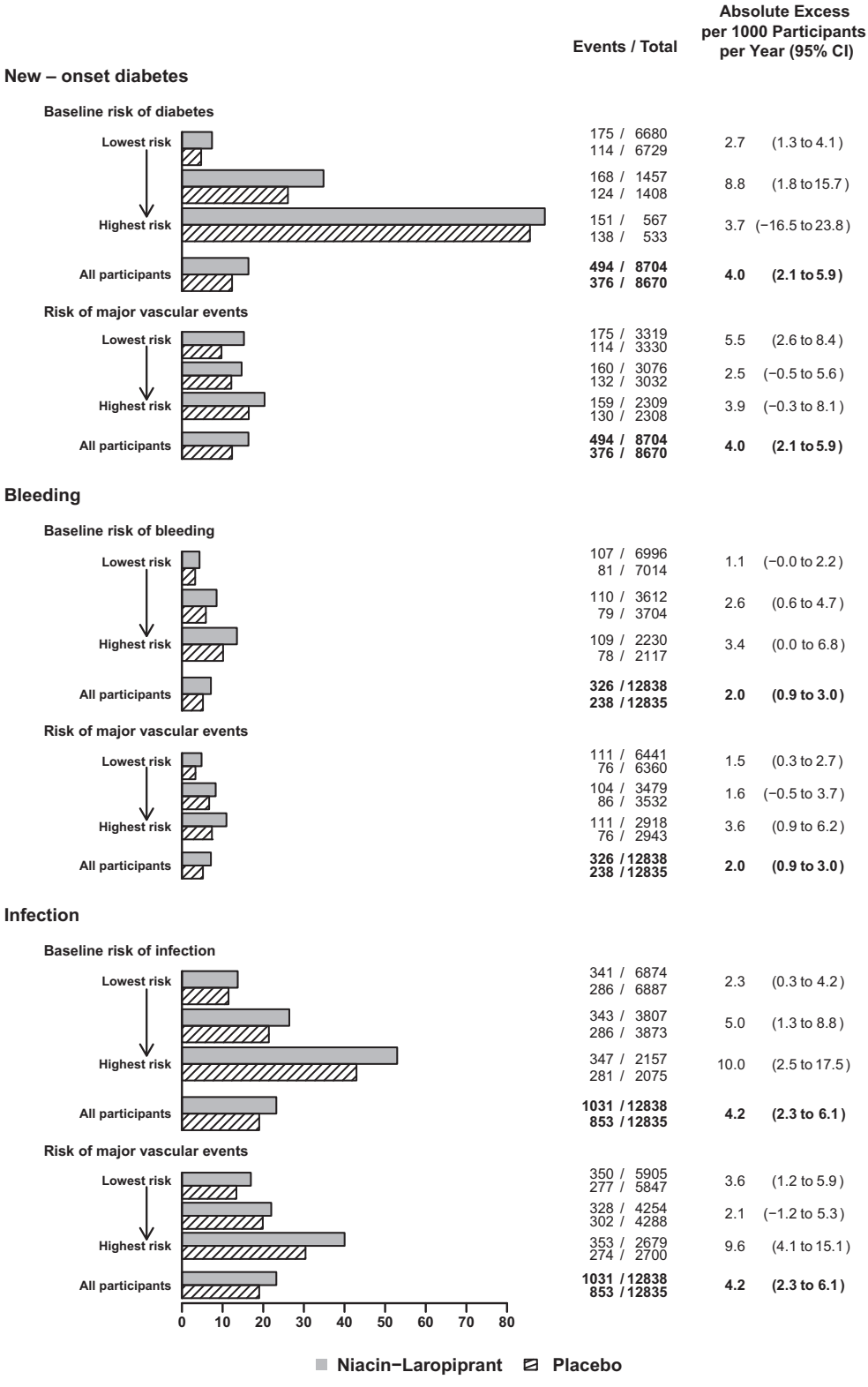

Figure. Effects of niacin/laropiprant on new-onset diabetes, bleeding, and infection by risk.

Table II. Effects of niacin/laropiprant on bleeding by site, severity, and time.

Variable	Niacin/laropiprant, No. (%)	Placebo, No. (%)	Hazard Ratio (95% CI)	Absolute Excess per 1000 Participants per Year (95% CI)
Randomized	12,838	12,835	—	—
Description of event				
Gastrointestinal	109 (0.24)	71 (0.15)	1.54 (1.14–2.08)	1 (0 to 1)
Intracranial	139 (0.30)	119 (0.26)	1.17 (0.92–1.50)	0 (–0 to 1)
Other	82 (0.18)	49 (0.11)	1.68 (1.18–2.39)	1 (0 to 1)
Severity				
Nonfatal	286 (0.63)	198 (0.43)	1.45 (1.21–1.74)	2 (1 to 3)
Fatal	60 (0.13)	49 (0.11)	1.23 (0.84–1.79)	0 (–0 to 1)
Time from randomization				
<1 year	96 (0.75)	48 (0.38)	2.00 (1.42–2.83)	4 (2 to 6)
≥1 year	230 (0.70)	190 (0.57)	1.22 (1.01–1.48)	1 (0 to 2)
Any bleeding SAE	326 (0.71)	238 (0.52)	1.38 (1.17–1.63)	2 (1 to 3)

SAE = serious adverse effect.

Table III. Effects of niacin/laropiprant on infection by site, severity, and time.

Variable	Niacin/laropiprant, No. (%)	Placebo, No. (%)	Hazard Ratio (95% CI)	Absolute Excess per 1000 Participants per Year (95% CI)
Randomized	12,838	12,835	—	—
Description of event				
Lower respiratory tract	547 (1.21)	471 (1.03%)	1.17 (1.03–1.32)	2 (0 to 3)
Urinary tract	114 (0.25)	107 (0.23%)	1.07 (0.82–1.39)	0 (–0 to 1)
Abdominal GI	82 (0.18)	65 (0.14%)	1.27 (0.91–1.75)	0 (–0 to 1)
Skin	67 (0.15)	40 (0.09%)	1.68 (1.14–2.49)	1 (0 to 1)
Other	306 (0.67)	223 (0.49%)	1.38 (1.16–1.64)	2 (1 to 3)
Severity				
Nonfatal	994 (2.24)	825 (1.84%)	1.22 (1.11–1.33)	4 (2 to 6)
Fatal	52 (0.11)	43 (0.09%)	1.21 (0.81–1.82)	0 (–0 to 1)
Time from randomization				
<1 year	311 (2.47)	233 (1.84%)	1.34 (1.13–1.59)	6 (3 to 10)
≥1 year	720 (2.27)	620 (1.93%)	1.18 (1.06–1.31)	3 (1 to 6)
Any infection	1031 (2.32)	853 (1.90%)	1.22 (1.11–1.34)	4 (2 to 6)

GI = gastrointestinal.

DISCUSSION

Niacin/laropiprant causes a wide range of SAEs, including new-onset diabetes, disturbances in diabetic control, bleeding, infection, and gastrointestinal events. These SAEs are in addition to the larger number of non-SAEs and effects on statin-associated myopathy.[5,8] The harmful effects of niacin/laropiprant described here appear to be consistent in different types of participants (with the exception of an interaction between adiposity and the effect on new-onset diabetes). Specifically, after identifying risk factors for each outcome of interest and combining these into a risk score, the absolute effect of niacin/laropiprant was similar regardless of baseline risk of the harmful effect in question. Therefore, although it was possible to identify a subgroup of participants at lower risk of the particular adverse event, it was not possible to identify a subgroup among whom the harmful effects of niacin/laropiprant were smaller. Furthermore, there was no evidence that participants at high risk of vascular events or with a low HDL-C/high triglyceride dyslipidemia (either of which might be considered an indication for niacin therapy) were at lower absolute risk of these harmful effects of niacin.

Niacin's effects on gastrointestinal events and disturbances of diabetes control are well established.[9] However, it is not possible to determine from the HPS2-THRIVE data alone whether the effects of niacin/laropiprant observed on the previously unknown harmful effects (new-onset diabetes, bleeding, and infection) were attributable to the ER niacin or the laropiprant. However, previous trials of niacin alone suggest that it was the ER niacin component that was responsible for the effects observed. For example, a meta-analysis investigating the effects of niacin alone on the development of new-onset diabetes found a 38% (95% CI, 16%−65%) increased risk of new-onset diabetes,[10] which is similar to the 33% (95% CI, 16%−52%) proportional increase that was observed in HPS2-THRIVE. Although insulin resistance (and consequently the risk of diabetes) increases with adiposity,[11] the HPS2-THRIVE results suggest that the adverse effect of niacin on new-onset diabetes reduces with increasing adiposity, which was not expected. The effects of niacin on insulin resistance and glucose homeostasis are not fully understood.[12,13] Genetic studies have suggested that genetic variants associated with lower LDL-C are associated with an increased risk of diabetes mellitus.[14] However, treatments that reduce LDL-C have discordant effects on the risk of diabetes (statins increase the risk modestly,[15] whereas cholesterol ester transfer protein inhibitors reduce the risk[16]) and the effect size observed in HPS2-THRIVE are disproportionately large compared with the reduction in LDL-C. The effect in HPS2-THRIVE was largely confined to the first year after the start of treatment, perhaps because the effects on glucose metabolism attenuate with time. Adherence to niacin-laropiprant also decreased with time, which may also explain the apparent attenuation of effect during follow-up.

The effects on bleeding observed in HPS2-THRIVE are also consistent with those observed in previous trials of niacin alone. For example, in the Coronary Drug Project (CDP), which compared immediate release niacin 3 g/d (n = 1119) wity placebo (n = 2789) in male survivors of a myocardial infarction,[9] there was a nonsignificant excess of black tarry stools (presumably melena attributable to gastrointestinal bleeding) among participants assigned to receive niacin.[9] The AIM-HIGH trial was much smaller than HPS2-THRIVE and did not have the statistical power to detect the effect on serious bleeds that was observed in HPS2-THRIVE. Therefore, although the proportional effect on SAEs attributable to bleeding (crude risk ratio, 1.19; 95% CI, 0.82−1.73) in the AIM-HIGH trial is consistent with that in HPS2-THRIVE (HR, 1.38; 95% CI, 1.17−1.63), there were too few such SAEs in AIM-HIGH for this difference (59 [3.4%] in the niacin group vs 49 [2.9%] in the placebo group; $P = 0.36$) to be statistically significant.[7] However, when both serious and nonserious bleeding adverse events recorded in AIM-HIGH are considered (174 [10.1%] assigned to receive niacin vs 137 [8.1%] assigned to receive placebo), a significant excess was found with niacin (crude risk ratio, 1.25; 95% CI, 1.01−1.55; $P = 0.04$). The wide variety of sites at which bleeding was in excess suggests that niacin induces a generalized bleeding diathesis. Niacin is known to reduce the platelet count by approximately 10%[17] and to inhibit platelet aggregation[18] and reduces the concentrations of circulating coagulation factors and inhibiting thrombus formation *in vitro*. In addition, niacin

exacerbates peptic ulcer disease,[19] and although patients with a recent diagnosis of a peptic ulcer were excluded from HPS2-THRIVE, some of the excess in gastrointestinal bleeding may have been among people with undiagnosed peptic ulcers.

Infection was another previously unrecognized harmful effect of niacin. Information on infections was not collected during the CDP, but dysuria was significantly more common among niacin-allocated participants (31/1073 [2.9%] vs 32/2695 [1.2%]; $P < 0.001$), perhaps reflecting an excess of urinary tract infections.[9] AIM-HIGH provides clearer supporting evidence of the effect on infection observed in HPS2-THRIVE: with significant excesses in both serious infections (139 [8.1%] in the niacin group vs 98 [5.8%] in the placebo group; crude risk ratio, 1.40; 95% CI, 1.09−1.80) and in the combination of serious and nonserious infections (674 [39.2%] vs 593 [35.0%]; crude risk ratio, 1.12; 95% CI, 1.03−1.23).[7] Niacin produces only a modest reduction in the white cell count,[9] but it suppresses monocyte activation *in vivo* via the GPR109A receptor, resulting in reduced cytokine production after lipopolysaccharide stimulation.[20] In animal models, niacin induces immunosuppressive T regulatory cells,[21] and its anti-inflammatory effects may be undesirably immunosuppressive, impairing the response to infection. The effect of niacin/laropiprant on infections did not appear to attenuate with time, which is relevant for patients already receiving niacin who may be considering whether to continue taking the drug[22]; a previous lack of adverse effects does not guarantee they will not occur in the future.

Notably, the harmful effects detected by the randomized comparisons within HPS2-THRIVE were not detected by the expedited reporting required by regulatory authorities of any suspected unexpected SAEs that were recorded in the trial.[23] This observation reinforces the point that such nonrandomized pharmacovigilance data (whether from trials or from postmarketing surveillance) are typically only of value for detecting large increases in rare outcomes (such as the excess of statin-related myopathy that was seen when statin therapy was used in combination with ER niacin in China[8,24]) and not for detecting reliably more moderate effects on relatively common SAEs (such as the 20%−40% proportional increases in bleeding and infection in HPS2-THRIVE), despite attempts to use nonrandomized observational data for such purposes.[25]

Niacin has been specifically recommended for patients who have the combination of low HDL-C levels and high triglyceride levels because it is partially effective at correcting this dyslipidemia. However, niacin was not found to be effective at reducing the risk of vascular events (at least in the presence of effective statin therapy) in the subgroup of >4000 patients in HPS2-THRIVE with low HDL-C and high triglyceride levels or in the AIM-HIGH population, which selected specifically for such patients. In addition, the results of these trials do not indicate that niacin is less hazardous among such patients or among other patients at high vascular risk who might also be encouraged to take niacin. Although niacin is no longer licensed for use in combination with statins in the United States, it may still be considered for patients who do not wish to take statins. In such circumstances, the absolute LDL-C reduction with niacin is likely to be larger, which might be expected to yield a larger benefit. However, the present analyses indicate that the absolute excess of adverse effects would still be clinically significant. It may, therefore, be more prudent to consider using some other LDL-C−lowering therapies (such as ezetimibe or, for patients at particularly high risk, PCSK9 inhibitors).[26]

A limitation of these analyses is the prerandomization run-in phase with niacin/laropiprant treatment that was intended to exclude individuals who could not tolerate it for at least 2 months. One-third of the people who started this run-in phase withdrew before randomization, with the most common reasons being related to skin, gastrointestinal, and diabetes-related adverse events.[8] The analyses presented here are, therefore, restricted to people able to tolerate short-term niacin treatment, and as a consequence, the absolute excesses that were observed may underestimate the adverse effects of starting niacin treatment in routine care. In addition, despite the addition of laropiprant, it is possible that some participants still experienced flushing and were therefore aware of their treatment assignment, which could have made them more likely to report adverse effects. However, because the major adverse effects

described here were not previously known to be associated with niacin therapy, this is not likely to bias these assessments.

In conclusion, a number of previously unrecognized harmful effects, namely, new-onset diabetes, bleeding, and infection, were observed in HPS2-THRIVE and appear to have been caused largely (if not wholly) by the niacin component of the study treatment. The absolute excesses of these and other adverse effects appeared to be similar in a wide variety of patients. Consequently, practitioners or patients wishing to continue using niacin should consider the potential implications of these harmful effects in determining whether using niacin is worth the risk.

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CONFLICTS OF INTEREST

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinthera.2019.06.012.

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