ABSTRACT

Purpose:

The HPS2-THRIVE trial among patients at high risk of vascular disease found that adding ER niacin-laropiprant to intensive statin-based LDL-lowering therapy had no benefit on cardiovascular outcomes. However, it 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 determine whether any types of participant 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 daily) 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 (i) time after randomization; (ii) severity; (iii) baseline characteristics; (iv) baseline risk of the adverse event of interest; and (v) risk of major vascular event.

Findings:

The hazard ratio for new onset diabetes with niacin/laropiprant was 1.32 (95% CI 1.16-1.51; p<0.001), which corresponded to an absolute excess of 4 people (95% CI 2-6) developing diabetes per thousand person-years in the study population as a whole. Among the 8299 participants with diabetes at baseline, the hazard ratio 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 hazard ratio for serious bleeding was 1.38 (95% CI 1.17-1.63; p<0.001) corresponding to an absolute excess of 2 (95% CI 1-3) per 1000 person-years; and for serious infection, it was 1.22 (95% CI 1.11-1.34; p<0.001) corresponding to an absolute excess of 4 (95% CI 2-6) per thousand person-years. The excess risks of these serious adverse events was larger in the first year after starting niacin-laropiprant than in later years (except for the excess of infection which did not appear to attenuate with time), and the risks of

non-fatal 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.

Implications:

Clinicians 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.

HPS2-THRIVE is registered on clinicaltrials.gov (NCT00461630).

Keywords: niacin, adverse effects, cardiovascular disease, infection, bleedingse

CONDENSED ABSTRACT

Niacin-laropiprant causes a wide-range of adverse effects including new-onset diabetes, bleeding and infection. The absolute excess these is similar in nearly all of the different types of participant studied, suggesting that there is no type of patient who can take niacin-laropiprant without being at increased risk of such outcomes.

Clinical perspectives

Competency in medical knowledge: Niacin-laropiprant causes a number of adverse effects, including new-onset diabetes mellitus, bleeding and infection.

Competency in patient care: Consideration should be given to these adverse effects before niacin is initiated and during any consultation with a patient currently receiving niacin.

INTRODUCTION

Despite current best practice (including intensive statin-based low density lipoprotein ~~LDL~~ cholesterol [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 high density lipoprotein cholesterol [HDL-C]) [3]. However, two 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 HPS2-THRIVE (Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events) trial not only confirmed previously recognised adverse effects of niacin (in particular, cutaneous reactions, gastrointestinal upset and disturbance of diabetes control) but it 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 D2 receptor (DP_1) antagonist. It is not possible to determine from the HPS2-THRIVE trial alone whether the harmful effects observed were due to niacin or laropiprant. However, similar effects with ER niacin given on its own were observed in the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes) 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 patient 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. As 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 have 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 – in whom 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 50-80 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 two phase pre-randomization run-in period. During the first phase, participants' background LDL lowering therapy was standardized to either simvastatin 40 mg daily or ezetimibe/simvastatin 10/40 mg daily; during the second phase they took active niacin-laropiprant (1000/20 mg daily for 4 weeks then increased to 2000/40 mg daily). Participants who did not report adverse events and who remained eligible were randomly assigned to receive niacin-laropiprant (2000/40 mg daily) or matching placebo. Following randomization, follow-up assessments were scheduled at 3 and 6 months and then every 6 months for an average of about 4 years at which all serious adverse events (SAE) were recorded. Non-serious adverse events 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 HbA1c ≥48 mmol/mol, fasting glucose ≥7.0 mmol/L or random (ie, <8 hours fasting) glucose >11.1 mmol/L. Disturbances in diabetic control included minor disturbances (eg, hyperglycaemia requiring hospitalisation for optimisation of blood glucose) and major disturbances (eg, ketoacidosis or hyperosmolar hyperglycaemic state). Infections and gastrointestinal events were defined as any SAE included in 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 pre-

specified criteria by physicians who were unaware of the study treatment assignment. Non-fatal SAEs, other than those included in the composite primary outcome major vascular event (MVE: non-fatal MI, coronary death, stroke or arterial revascularization) or pre-specified 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 (i) time after randomization (i.e. in the first and later years after randomization); (ii) severity (defined by requirement for hospitalisation and whether the SAE resulted in death or not); (iii) 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); (iv) baseline risk of the adverse event; and (v) baseline risk of MVE. All analyses were based on comparisons between all participants randomly assigned niacin-laropiprant versus all those assigned placebo (i.e., properly intention-to-treat analyses).

In order to develop baseline risk scores for harmful effects and for MVE, Cox proportional hazards models with stepwise model selection were used to identify significant baseline predictors of each relevant outcome (using a p-value 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 which estimated each individual's risk of the outcome. The baseline characteristics considered and the variables selected for inclusion in each joint risk factor model are shown in webtable 1. Tertiles of the risk score (based on numbers of events rather than participants) were used to determine higher, mid, and lower risk groups shown in the figures.

The absolute excess of some particular adverse event due to niacin-laropiprant was defined as the difference between the two treatment arms in the number of events as a proportion of person years at risk, expressed as events per 1000 person years. Hazard ratios describing proportional effects of niacin-laropiprant (and interactions between individual baseline characteristics and randomized treatment) were estimated by Cox proportional hazards models based on the first occurrence of each

particular event after randomization. Tests for trend and heterogeneity were used to explore whether the effect of treatment varied by the various groups/categories examined. No formal correction for multiple testing was made, but p values were not to be considered significant unless $p<0.01$ due to the *post hoc* nature of these analyses and the number of analyses conducted.

RESULTS

Between January 2007 and May 2010, 51,698 patients were screened and 42,424 entered the pre-randomization run-in (of whom 6365 entered the active niacin-laropiprant phase directly). 4055 of the 36,059 participants (11%) who entered the LDL standardization phase withdrew compared to 12,696 of the 38,369 (33%) who entered the active niacin-laropiprant phase. 25,673 participants were randomized and followed for a mean of 3.6 years (median 3.9 years).[5] Study average adherence to niacin-laropiprant was 77.7% (i.e. the proportion reporting taking most of their study treatment at each study visit). 25.4% of participants assigned niacin-laropiprant discontinued the study drug compared to 16.6% of those assigned placebo (p<0.001; see webtable 2). 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 [py]) of those assigned niacin-laropiprant developed new-onset diabetes compared to 376 (1.23% py) of those assigned placebo (table 1); this corresponds to a one-third proportional increase (hazard ratio [HR] 1.33; 95% CI 1.16-1.52; p<0.001) and an absolute excess of 4 people (95% CI 2-6) per thousand 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/high triglycerides), with the exception of subgroups defined by adiposity (webfigure 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 to 48 (2.0%) of those assigned

placebo (HR 2.09; 95% CI 1.48-2.96). By contrast, among participants with 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 (webtable 1). 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 to 25.9% in highest risk group (figure 1A). 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 1A), or among participants with low baseline HDL-C/high triglycerides (webfigure 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 having serious disturbances of diabetes control, corresponding to an absolute excess of 12 people (95% CI 8-16; table 1) 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 (0.71% py) participants assigned niacin-laropiprant had at least one bleeding SAE during follow-up versus 238 (0.52% py) assigned 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 2) per 1000 person-years. Most bleeds were intracranial (including haemorrhagic stroke) or gastrointestinal, but there was little evidence that the proportional effects of niacin-laropiprant varied at different sites (p for heterogeneity = 0.18).

About 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] versus 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 (webfigure 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/high triglycerides (webfigure 2B).

Infection

Overall 1031 (2.32% py) participants assigned niacin-laropiprant versus 853 (1.90% py) assigned placebo had at least one 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 3) per thousand person-years. The most common sites of infection were lower respiratory and urinary, with little evidence that the proportional effect varied by site of infection (p for heterogeneity = 0.20; table 3). 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 (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] versus 3 [95% CI 1-6] per thousand per year).

The proportional effect of niacin-laropiprant on infection was similar in different types of participant (webfigure 4). However, the absolute effect did not appear to vary by baseline risk of infection or MVE (figure 1C) or baseline low HDL-C/high triglycerides (webfigure 2C).

DISCUSSION

Niacin-laropiprant causes a wide range of serious adverse effects, including new-onset diabetes, disturbances in diabetic control, bleeding, infection and gastrointestinal events. These are in addition to the larger number of non-serious adverse effects and effects on statin-associated myopathy [5, 8]. The harmful effects of niacin-laropiprant described here appear to be consistent in different types of participant (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, whereas 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 either at high risk of vascular events or with a low HDL-C/high triglyceride dyslipidaemia (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 due 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 which 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 is disproportionately large compared to 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 fell with time so this 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 daily (n=1119) versus placebo (n=2789) in male survivors of a myocardial infarction [9], there was a non-significant excess of "black tarry stools" (presumably melaena due to gastrointestinal bleeding) among participants assigned 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. So, although the proportional effect on SAEs due 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 versus 49 [2.9%] in the placebo group; p=0.36) to be statistically significant [7]. However, when both serious and non-serious bleeding adverse events recorded in AIM-HIGH are considered (174 [10.1%] assigned niacin 137 [8.1%] assigned placebo), there was found to be a significant excess 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. It is known to reduce the platelet count by about 10% [17] and to inhibit platelet aggregation [18], as well as reducing the concentrations of circulating coagulation factors and inhibitings thrombus formation *in vitro* . In addition, niacin has been found to exacerbate 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%] versus 32/2695 [1.2%]; p<0.001), perhaps reflecting an excess of urinary tract infections [9]. AIM-HIGH provides clearer supporting evidence for the effect on infection observed in HPS2-THRIVE: with significant excesses in both serious infections (139 [8.1%] in the niacin group versus 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 non-serious infections (674 [39.2%] versus 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 or not [22]; a previous lack of side-effects does not guarantee they will not occur in the future.

It is of note that the harmful effects detected by the randomised comparisons within HPS2-THRIVE were not detected by the expedited reporting required by regulatory authorities of any suspected unexpected serious adverse events (SUSARs) that were recorded in the trial [23]. This observation reinforces the point that such non-randomised pharmacovigilance data (whether from trials or from post-marketing 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 serious adverse events (such as the 20-40% proportional increases in bleeding and infection in HPS2-THRIVE), despite attempts to use non-randomised 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 dyslipidaemia. However, niacin was not found to be effective at reducing the risk of vascular events (at least in the presence of effective statin therapy) either in the subgroup of over 4000 patients in HPS2-THRIVE with low HDL-C levels and high triglyceride, or in the AIM-HIGH population which selected specifically for such patients. Nor do the results in these trials 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 US, 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 and this 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 pre-randomization run-in phase with niacin-laropiprant treatment that was intended to exclude individuals who could not tolerate it for at least two months. One-third of the people who started this run-in phase withdrew prior to randomization, with the commonest reasons being related to skin, gastrointestinal and diabetes-related adverse events [8]. The analyses presented here are, therefore, restricted to people able to tolerate niacin short-term and, as a consequence, the absolute excesses that were observed may underestimate the adverse effects of starting niacin 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, as 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 which 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 different patients. Consequently, clinicians or patients wishing to continue using niacin should consider the potential impact of these harmful effects in determining whether using niacin is worth the risk.

Acknowledgments:

The most important acknowledgement is to the participants in the study and to the collaborators. HPS2-THRIVE was funded by a grant to Oxford University from Merck (manufacturers of niacin-laropiprant, simvastatin and ezetimibe), but the study was designed, and has been conducted, analysed, interpreted and reported, independently by the Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU) at the University of Oxford which is the regulatory sponsor for the trial. CTSU receives funding from the UK Medical Research Council, the British Heart Foundation and Cancer Research UK. Jemma Hopewell acknowledges support from the British Heart Foundation (grant number FS/14/55/30806).

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REFERENCES

1. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC, Jr., Sperling L, Virani SS and Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology*. 2018:25709.

2. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Z, Riccardi G, Taskinen MR, Tokgozoglu L, Verschuren WMM, Vlachopoulos C, Wood DA, Zamorano JL, Cooney MT and Group ESCSD. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. *Eur Heart J*. 2016;37:2999-3058.

3. Catapano AL, Reiner Z, De Backer G, Graham I, Taskinen MR, Wiklund O, Agewall S, Alegria E, Chapman MJ, Durrington P, Erdine S, Halcox J, Hobbs R, Kjekshus J, Perrone Filardi P, Riccardi G, Storey RF and Wood D. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Atherosclerosis*. 2011;217 Suppl 1:S1-44.

4. The AIM-HIGH Investigators, Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, McBride R, Teo K and Weintraub W. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *The New England journal of medicine*. 2011;365:2255-67.

5. HPS2-THRIVE Collaborative Group. Effects of extended-release niacin with laropiprant in high-risk patients. *The New England journal of medicine*. 2014;371:203-12.

6. Food & Drug Administration. 2016.

7. Paromov VM and Morton RE. Lipid transfer inhibitor protein defines the participation of high density lipoprotein subfractions in lipid transfer reactions mediated by cholesterol ester transfer protein (CETP). *The Journal of biological chemistry*. 2003;278:40859-66.

8. HPS2-THRIVE Collaborative Group. HPS2-THRIVE randomized placebo-controlled trial in 25 673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment. *Eur Heart J*. 2013;34:1279-91.

9. Clofibrate and niacin in coronary heart disease. *JAMA : the journal of the American Medical Association*. 1975;231:360-81.

10. Goldie C, Taylor AJ, Nguyen P, McCoy C, Zhao X-Q and Preiss D. Niacin therapy and the risk of new-onset diabetes: a meta-analysis of randomized controlled trials. *Heart*. 2015.

11. Wajchenberg BL. Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. *Endocr Rev*. 2000;21:697-738.

12. Poynten AM, Gan SK, Kriketos AD, O'Sullivan A, Kelly JJ, Ellis BA, Chisholm DJ and Campbell LV. Nicotinic acid-induced insulin resistance is related to increased circulating fatty acids and fat oxidation but not muscle lipid content. *Metabolism*. 2003;52:699-704.

13. Choi S, Yoon H, Oh KS, Oh YT, Kim YI, Kang I and Youn JH. Widespread effects of nicotinic acid on gene expression in insulin-sensitive tissues: implications for unwanted effects of nicotinic acid treatment. *Metabolism*. 2010;60:134-44.

14. White J, Swerdlow DI, Preiss D, Fairhurst-Hunter Z, Keating BJ, Asselbergs FW, Sattar N, Humphries SE, Hingorani AD and Holmes MV. Association of Lipid Fractions With Risks for Coronary Artery Disease and Diabetes. *JAMA Cardiology*. 2016;1:692-699.

15. Swerdlow DI, Preiss D, Kuchenbaecker KB, Holmes MV, Engmann JE, Shah T, Sofat R, Stender S, Johnson PC, Scott RA, Leusink M, Verweij N, Sharp SJ, Guo Y, Giambartolomei C, Chung C, Peasey A, Amuzu A, Li K, Palmen J, Howard P, Cooper JA, Drenos F, Li YR, Lowe G, Gallacher J, Stewart MC, Tzoulaki I, Buxbaum SG, van der AD, Forouhi NG, Onland-Moret NC, van der Schouw YT, Schnabel RB, Hubacek JA, Kubinova R, Baceviciene M, Tamosiunas A, Pajak A, Topor-Madry R, Stepaniak U, Malyutina S, Baldassarre D, Sennblad B, Tremoli E, de Faire U, Veglia F, Ford I, Jukema JW, Westendorp RG, de Borst GJ, de Jong PA, Algra A, Spiering W, Maitland-van der Zee AH, Klungel OH, de Boer A, Doevendans PA, Eaton CB, Robinson JG, Duggan D, Consortium D, Consortium M, InterAct C, Kjekshus J, Downs JR, Gotto AM, Keech AC, Marchioli R, Tognoni G, Sever PS, Poulter NR, Waters DD, Pedersen TR, Amarenco P, Nakamura H, McMurray JJ, Lewsey JD, Chasman DI, Ridker PM, Maggioni AP, Tavazzi L, Ray KK, Seshasai SR, Manson JE, Price JF, Whincup PH, Morris RW, Lawlor DA, Smith GD, Ben-Shlomo Y, Schreiner PJ, Fornage M, Siscovick DS, Cushman M, Kumari M, Wareham NJ, Verschuren WM, Redline S, Patel SR, Whittaker JC, Hamsten A, Delaney JA, Dale C, Gaunt TR, Wong A, Kuh D, Hardy R, Kathiresan S, Castillo BA, van der Harst P, Brunner EJ, Tybjaerg-Hansen A, Marmot MG, Krauss RM, Tsai M, Coresh J, Hoogeveen RC, Psaty BM, Lange LA, Hakonarson H, Dudbridge F, Humphries SE, Talmud PJ, Kivimaki M, Timpson NJ, Langenberg C, Asselbergs FW, Voevoda M, Bobak M, Pikhart H, Wilson JG, Reiner AP, Keating BJ, Hingorani AD and Sattar N. HMG-coenzyme A reductase inhibition, type 2 diabetes, and bodyweight: evidence from genetic analysis and randomised trials. *Lancet*. 2015;385:351-61.

16. Barter PJ, Rye KA, Tardif JC, Waters DD, Boekholdt SM, Breazna A and Kastelein JJ. Effect of torcetrapib on glucose, insulin, and hemoglobin A1c in subjects in the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial. *Circulation*. 2011;124:555-62.

17. Maccubbin D, Bays HE, Olsson AG, Elinoff V, Elis A, Mitchel Y, Sirah W, Betteridge A, Reyes R, Yu Q, Kuznetsova O, McCrary Sisk C, Pasternak RC and Paolini JF. Lipid-modifying efficacy and tolerability of extended-release niacin/laropiprant in patients with primary hypercholesterolaemia or mixed dyslipidaemia. *Int J Clin Practice*. 2008;62:1959-1970.

18. Chesney CM, Elam MB, Herd JA, Davis KB, Garg R, Hunninghake D, Kennedy JW and Applegate WB. Effect of niacin, warfarin, and antioxidant therapy on coagulation parameters in patients with peripheral arterial disease in the Arterial Disease Multiple Intervention Trial (ADMIT). *American heart journal*. 2000;140:631-6.

19. Mosher LR. Nicotinic acid side effects and toxicity: a review. *Am J Psychiatry*. 1970;126:1290-6.

20. Digby JE, Martinez F, Jefferson A, Ruparelia N, Chai J, Wamil M, Greaves DR and Choudhury RP. Anti-inflammatory effects of nicotinic acid in human monocytes are mediated by GPR109A dependent mechanisms. *Arteriosclerosis, thrombosis, and vascular biology*. 2012;32:669-76.

21. Singh N, Gurav A, Sivaprakasam S, Brady E, Padia R, Shi H, Thangaraju M, Prasad PD, Manicassamy S, Munn DH, Lee JR, Offermanns S and Ganapathy V. Activation of Gpr109a, receptor

for niacin and the commensal metabolite butyrate, suppresses colonic inflammation and carcinogenesis. *Immunity*. 2014;40:128-39.

22. Jackevicius CA, Tu JV, Ko DT, de Leon N and Krumholz HM. Use of niacin in the United States and Canada. *JAMA Internal Medicine*. 2013:1-3.

23. Reith C, Landray M, Devereaux PJ, Bosch J, Granger CB, Baigent C, Califf RM, Collins R and Yusuf S. Randomized clinical trials--removing unnecessary obstacles. *The New England journal of medicine*. 2013;369:1061-5.

24. Eknoyan G, Wacksman SJ, Glueck HI and Will JJ. Platelet function in renal failure. *The New England journal of medicine*. 1969;280:677-81.

25. Alsheikh-Ali AA and Karas RH. Safety of lovastatin/extended release niacin compared with lovastatin alone, atorvastatin alone, pravastatin alone, and simvastatin alone (from the United States Food and Drug Administration adverse event reporting system). *Am J Cardiol*. 2007;99:379-81.

26. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR, Committee FS and Investigators. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *The New England journal of medicine*. 2017;376:1713-1722.

447 **FIGURE LEGEND**

448 **Figure 1** Effects of niacin−laropiprant on new−onset diabetes, bleeding and infection by risk.
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TABLES

Table 1: Effects of niacin-laropiprant on (A) new-onset diabetes by time; (B) Disturbances in diabetic control by description, severity and time

	Niacin-laropiprant N (%)	Placebo N (%)	Hazard ratio (95% CI)	Absolute excess per 1000 participants per year (95% CI)
Randomized participants	12838	12835		
(A) New-onset diabetes mellitus				
Non-diabetic at randomization	8704	8670		
Time from randomization				
<1 year	193 (2.26%)	96 (1.12%)	2.02 (1.58-2.58)	11 (8, 15)
≥ 1 year	301 (1.39%)	280 (1.28%)	1.09 (0.93-1.28)	1 (-1, 3)
Any new-onset diabetes	494 (1.64%)	376 (1.23%)	1.33 (1.16-1.52)	4 (2, 6)
(B) Disturbances in diabetic control				
Diabetic at randomization	4134	4165		
Description of event				
Minor hyperglycaemic disturbance	361 (2.59%)	242 (1.66%)	1.56 (1.32-1.83)	9 (6, 13)
Major hyperglycaemic disturbance	42 (0.28%)	12 (0.08%)	3.56 (1.88-6.77)	2 (1, 3)
Hypoglycaemia	46 (0.31%)	31 (0.21%)	1.51 (0.96-2.38)	1 (-0, 2)
Other diabetic disturbance	44 (0.30%)	48 (0.32%)	0.93 (0.62-1.40)	-0 (-1, 1)
Time from randomization				
<1 year	219 (5.51%)	83 (2.03%)	2.71 (2.11-3.49)	35 (27, 43)
≥1 year	241 (2.48%)	228 (2.19%)	1.13 (0.94-1.35)	3 (-1, 7)
Any diabetic disturbance	460 (3.36%)	311 (2.14%)	1.56 (1.35-1.80)	12 (8, 16)

457 **Table 2: Effects of niacin-laropiprant on bleeding by site, severity and time**
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	Niacin-laropiprant N (%)	Placebo N (%)	Hazard ratio (95% CI)	Absolute excess per 1000 participants per year (95% CI)
Randomized participants	12838	12835		
Description of event				
Gastrointestinal bleeding	109 (0.24%)	71 (0.15%)	1.54 (1.14-2.08)	1 (0, 1)
Intracranial	139 (0.30%)	119 (0.26%)	1.17 (0.92-1.50)	0 (-0, 1)
Other	82 (0.18%)	49 (0.11%)	1.68 (1.18-2.39)	1 (0, 1)
Severity				
Non-Fatal	286 (0.63%)	198 (0.43%)	1.45 (1.21-1.74)	2 (1, 3)
Fatal	60 (0.13%)	49 (0.11%)	1.23 (0.84-1.79)	0 (-0, 1)
Time from randomization				
<1 year	96 (0.75%)	48 (0.38%)	2.00 (1.42-2.83)	4 (2, 6)
≥ 1 year	230 (0.70%)	190 (0.57%)	1.22 (1.01-1.48)	1 (0, 2)
Any bleeding SAE	326 (0.71%)	238 (0.52%)	1.38 (1.17-1.63)	2 (1, 3)

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461 **Table 3: Effects of niacin-laropiprant on infection by site, severity and time**
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	Niacin-laropiprant N (%)	Placebo N (%)	Hazard ratio (95% CI)	Absolute excess per 1000 participants per year (95% CI)
Randomized participants	12838	12835		
Description of event				
Lower respiratory	547 (1.21%)	471 (1.03%)	1.17 (1.03-1.32)	2 (0, 3)
Urinary tract	114 (0.25%)	107 (0.23%)	1.07 (0.82-1.39)	0 (-0, 1)
Abdominal GI	82 (0.18%)	65 (0.14%)	1.27 (0.91-1.75)	0 (-0, 1)
Skin	67 (0.15%)	40 (0.09%)	1.68 (1.14-2.49)	1 (0, 1)
Other	306 (0.67%)	223 (0.49%)	1.38 (1.16-1.64)	2 (1, 3)
Severity				
Non-Fatal	994 (2.24%)	825 (1.84%)	1.22 (1.11-1.33)	4 (2, 6)
Fatal	52 (0.11%)	43 (0.09%)	1.21 (0.81-1.82)	0 (-0, 1)
Time from randomization				
<1 year	311 (2.47%)	233 (1.84%)	1.34 (1.13-1.59)	6 (3, 10)
≥1 year	720 (2.27%)	620 (1.93%)	1.18 (1.06-1.31)	3 (1, 6)
Any infection	1031 (2.32%)	853 (1.90%)	1.22 (1.11-1.34)	4 (2, 6)

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