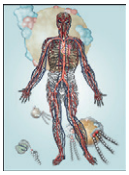

thematic review

Thematic Review Series: New Lipid and Lipoprotein Targets for the Treatment of Cardiometabolic Diseases

Niacin, an old drug with a new twist

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Abstract Niacin (nicotinic acid) has been used for decades as a lipid-lowering drug. The clinical use of niacin to treat dyslipidemic conditions is limited by its side effects. Niacin, along with fibrates, are the only approved drugs which elevate high density lipoprotein cholesterol (HDLc) along with its effects on low density lipoprotein cholesterol (LDLc) and triglycerides. Whether niacin has a beneficial role in lowering cardiovascular risk on the background of well-controlled LDLc has not been established. In fact, it remains unclear whether niacin, either in the setting of well-controlled LDLc or in combination with other lipid-lowering agents, confers any therapeutic benefit and if so, by which mechanism. The results of recent trials reject the hypothesis that simply raising HDLc is cardioprotective. However, in the case of the clinical trials, structural limitations of trial design complicate their interpretation. This is also true of the most recent Heart Protection Study 2-Treatment of HDLc to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial in which niacin is combined with an antagonist of the D prostanoid (DP) receptor. Human genetic studies have also questioned the relationship between cardiovascular benefit and HDLc. It remains to be determined whether niacin may have clinical utility in particular subgroups, such as statin intolerant patients with hypercholesterolemia or those who cannot achieve a sufficient reduction in LDLc. It also is unclear whether a potentially beneficial effect of niacin is confounded by DP antagonism in HPS2-THRIVE.—Song, W-L., and G. A. FitzGerald. **Niacin, an old drug with a new twist. *J. Lipid Res.* 2013.** 54: **2586–2594.**

Supplementary key words cholesterol • prostaglandin • cardiovascular

Niacin is also known as vitamin B3. Chronic dietary deficiency of niacin can cause pellagra (1). It is a precursor to NAD+/NADH and NADP+/NADPH, both of which play essential metabolic roles in living cells (2). Niacin has been used for more than half a century in the treatment of dyslipidemia. When Altschul, Hoffer, and Stephen (3) discovered that niacin could lower plasma levels of cholesterol, it was the only approved drug with such an effect (1). It has proven to be an attractive option for those intolerant of statin treatment. It has been demonstrated to reduce risk of atherosclerotic cardiovascular disease (4). The clinical use of niacin has been markedly limited by cutaneous flushing. The molecular target of niacin responsible for lipid metabolic changes and flushing was unknown until 2003 (5–7), when the niacin receptor, namely HM74A in humans and PUMA-G in mice, was discovered. The niacin receptor, also known as GPR109A, was shown to be activated by niacin and to mediate its antilipolytic effect as well as the flushing effect (8–10). Interest in niacin has risen because there is still significant residual risk in patients with intensive statin therapy (11). However, recent outcome trials (11, 12) failed to show niacin's benefit on top of statin therapy in lipid-targeted approaches to reduce major cardiovascular events in high-risk patients. In this review we will summarize the pharmacology of niacin, with a particular emphasis on recent outcome trials, including discussion of their limitations.

NIACIN'S LIPID EFFECTS

Niacin has long been shown to have effects on lipids (13). Niacin increases high density lipoprotein cholesterol (HDLc), but reduces low density lipoprotein cholesterol (LDLc), VLDL cholesterol, and triglycerides (TGs) (14). Niacin also decreases the plasma concentration of lipoprotein a [Lp(a)],

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Abbreviations: AIM-HIGH, Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes; CDP, Coronary Drug Project; CETP, cholesteryl ester transfer protein; DP, D prostanoid receptor; ERN, extended-release niacin; HDLc, high density lipoprotein cholesterol; HPS2-THRIVE, Heart Protection Study 2-Treatment of HDLc to Reduce the Incidence of Vascular Events; IMT, intima-media thickness; LDLc, low density lipoprotein cholesterol; Lp(a), lipoprotein a; LRPT, laropiprant; PGD_2, prostaglandin D_2; PGE_2, prostaglandin E_2; PPARγ, peroxisome proliferator-activated receptor γ; TG, triglyceride; TP, T prostanoid receptor; VLDLc, very low density lipoprotein cholesterol.

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which has been suggested to play an independent role in the pathogenesis of coronary heart disease (15, 16).

Effect on LDL and VLDL

Niacin's lipid effects are poorly understood. It was believed that niacin acts as an inhibitor of FFA mobilization from adipocytes (17–19). Carlson and Oro (17) found that niacin lowered the arterial plasma concentration of FFAs in fasting humans within minutes. This effect is dose dependent (20) and is not desensitized after 6 months of regular treatment (21), in contrast with niacin's flushing effect which undergoes tachyphylaxis within a week (22). This suppression of plasma FFAs reduced the supply of substrate for the hepatic synthesis of TGs, VLDL and LDL particles (23). However, the suppression of FFAs is niacin receptor dependent but the lipid effect is not, which is inconsistent with the FFA hypothesis (24). Niacin can also inhibit diacylglycerol acyltransferase 2 in liver, accelerating the intracellular degradation of apoprotein B, which results in decreased hepatic VLDL and TG synthesis (25, 26) (**Fig. 1**).

Effects on HDL

Several mechanisms by which niacin may increase HDLc have been proposed. The most popular one is based on the FFA hypothesis. Decreased FFA mobilization from adipocytes directly results in decreased TG concentrations in VLDLs and LDLs (27). Generally, there is a strong negative correlation between plasma TG levels and the concentration of HDLc, related to the cholesteryl ester exchange between VLDLs and HDLs mediated by cholesteryl ester transfer protein (CETP). Inhibition of FFA mobilization from adipocytes depletes TGs in VLDLs and LDLs, which, in turn, reduces the exchange of cholesterol esters and TGs, resulting in an increase in plasma HDLc levels (Fig. 1). This suggests that niacin acts like a CETP inhibitor. Interestingly, both CETP inhibitors and niacin cause an elevation of the HDL2 fraction (28). However, CETP inhibition and niacin have different effects on the ability of HDLs to promote net cholesterol efflux. Niacin treatment caused a moderate increase in the ability of HDLs to promote net cholesterol efflux, whereas inhibition of CETP, at least with anacetrapib, led to a more dramatic increase in association with enhanced particle functionality at higher HDLc concentrations (29). A recent study of the niacin receptor also casts doubt on this once popular hypothesis (24).

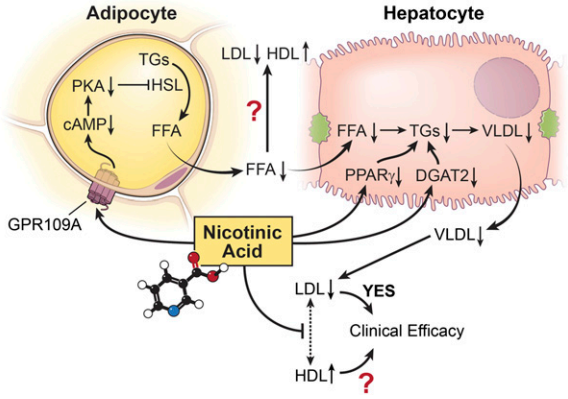

Fig. 1. FFA hypothesis of niacin's lipid effects. Niacin acts on its receptor GPR109A on adipocytes, lowering cAMP and protein kinase A levels. PKA phosphorylates hormone sensitive lipase (HSL). Therefore, niacin decreases *HSL* and TG hydrolysis in adipocytes, which causes a suppressed level of plasma FFAs. This suppression of plasma FFAs reduces the supply of substrate for the hepatic synthesis of TGs and VLDL and LDL particles. Niacin can also inhibit diacylglycerol acyltransferase 2 (DGAT2) and reduce hepatic expression of the PPARγ in liver, which results in decreased hepatic VLDL and TG synthesis. Suppressed levels of VLDLs and LDLs reduce the exchange of cholesterol esters and TGs between LDLs and HDLs, resulting in an increase in plasma HDLc levels. Suppression of FFAs is niacin receptor dependent, but the lipid effect is not, which casts doubt on this FFA hypothesis.

Another mechanism proposed is that niacin reduces hepatic expression of the peroxisome proliferator-activated receptor γ (PPARγ) coactivator-1β and apolipoprotein C-III (apoC-III) (30), which results in accelerated clearance of triglyceride-rich lipoproteins (31). This, in turn, would elevate HDLc as less cholesterol would be transferred via CETP. This model is supported by the observation that niacin-induced augmentation of HDLc in animal models requires the presence of CETP (32). It has also been found that niacin selectively increases apoA-I-containing HDL particles through inhibition of their uptake and catabolism by hepatocytes (25, 33, 34). However, these effects were observed at niacin concentrations far higher than those attained during chronic treatment with niacin (35).

Effects on Lp(a)

Genetic and epidemiologic studies indicate that high Lp(a) is an independent risk factor for myocardial infarction and stroke (36–40). Statins and other lipid-lowering medications do not affect elevated plasma concentrations of Lp(a) (41). By contrast, treatment with 4 g of niacin for 5–7 weeks reduces plasma concentrations of Lp(a) by nearly 40% (15). While no outcome studies have addressed this possibility, it is not clear whether niacin as an intervention would result in a favorable clinical outcome in patients with high Lp(a) levels.

Niacin receptor

Several pharmaceutical companies began developing selective agonists of GPR109A (42–47). Walters et al. (48) suggested that the effects of niacin on FFAs and flushing could be segregated. Thus, β-arrestin1-null mice displayed reduced cutaneous flushing in response to niacin, although the improvement in serum FFA levels was retained and was similar to that observed in wild-type mice. A partial agonist was developed in an effect to mimic niacin's lipid efficacy bypassing its flushing side effect (49).

However, the effects of niacin on HDLc seem unrelated to either GPR109A or FFA suppression (24). In CETP transgenic mice, niacin increases HDLc and decreases LDLc and TGs. This effect is not abolished by deletion of GPR109A. In humans, two GPR109A agonists lower FFAs acutely; however, neither had the expected effects on serum lipids (24, 49). In addition, chronic FFA suppression via GPR109A agonism is not attained either by niacin or other agonists.

Is simply raising HDLc level cardioprotective?

Recent outcome trials (11, 12, 50) and a study of human genetics (51) have questioned the HDL hypothesis (52). Epidemiological data reveal a strong inverse relationship between cardiovascular risk and HDLc (52). However, given the many potential confounding factors, such as exercise, which might elevate HDLc and be causative of this relationship by other mechanisms, a beneficial effect from pharmacological manipulation of HDLc could never be assumed from such evidence. Perhaps the strongest argument against this theory is the study of Voight et al. (51) in which polymorphisms related to elevations of plasma LDLc were associated directly with the risk of myocardial infarction, whereas an inverse relationship with variants related to elevations of plasma HDLc was not apparent. Multiple lipid-independent effects of niacin have been proposed. There is growing evidence that niacin restrains inflammation, independent of its effects on HDLc (53–56). Niacin retards atherogenesis in hyperlipidemic mice in the absence of significant changes in lipids. This effect may in part reflect a GPR109A-mediated restraint of immune cell infiltration of the vessel wall (54). Niacin may influence the inflammatory process by a variety of mechanisms including the expression of cell adhesion molecules (57), nuclear and scavenger receptors (58, 59), and the release of adipokines (60, 61) and bioactive lipids (62, 63).

However, there are abundant data supporting the possibility that HDL function may be the more relevant issue to cardioprotection than the HDLc levels per se (64, 65). Several experiments on genetically manipulated mouse models are consistent with the suggestion that apolipoprotein A-I (apoA-I) promoting reverse cholesterol transport from macrophages in vivo with resultant attenuation of atherogenesis (66–68). Furthermore, infusion of apoA-I in animal models and also in humans has been reported to reduce lesion burden (69–71). However, despite their promise, these results have yet to be confirmed by the results of clinical outcome trials.

SIDE EFFECTS

Flushing

Niacin-induced flushing is characterized by redness and warmth due to vasodilation of dermal blood vessels, and is associated with a sensation of tingling and burning. It lasts typically for an hour. Most patients (~70%) receiving niacin experience flushing and about 20% of niacin-treated subjects drop out of clinical trials for this reason (14, 72). Morrow and colleagues first noted that prostaglandin D_2 (PGD_2) played a central role in the flushing that constrains the use of niacin (73, 74). In mice, niacin-induced flushing results from an early phase of COX-1-dependent formation of PGD_2 and prostaglandin E_2 (PGE_2) in Langerhans cells, followed by delayed COX-2-dependent production of PGE_2 by keratinocytes (10). However, niacin also evokes COX-1-derived PGD_2 release from platelets in both mice and humans (61). It seems likely that niacin-induced flushing is mediated by prostaglandins produced initially by bone marrow-derived cells such as platelets and dendritic cells (Langerhans), perhaps contributing to subsequent induction of COX-2-dependent lipids by dermal or epidermal cells. During chronic drug administration, niacin-induced flushing and prostaglandin release are subject to tachyphylaxis within a week (22, 75).

Reduction of niacin-induced flushing by pretreatment with aspirin is well established (76). However, despite complete suppression of niacin-evoked PGD_2 release by low doses of aspirin (81 mg/day), there are still significant residual symptoms of flushing, even after pretreatment with higher doses (325 and 650 mg) (62, 77, 78) of aspirin which would suppress residual prostaglandin formation. A recent study has shown that aspirin only blocks vasodilation in hairy but not in glabrous skin (79). These findings raised the question of whether niacin-induced flushing is mediated solely by prostaglandins.

PGD_2 mediates niacin-evoked flushing via its D prostanoid (DP)1 receptor. Antagonism of DP1 suppresses niacin-induced vasodilation significantly in mice and humans (80). For example, laropiprant (LRPT) (74), a DP1 antagonist, reduces flushing induced by niacin (81–84) without affecting niacin's effects on lipids. This combination was developed as Cordaptive® in the USA and Tredaptive® in Europe. The combination was approved in Europe in 2008, while the US Food and Drug Administration requested more safety data before approval of the drug combination in the USA (85–90). Interestingly, despite tachyphylaxis of niacin-induced PGD_2 within a week (75), LRPT's anti-flushing effect is reportedly sustained for months (82, 83). These observations are confusing. First, prostaglandins other than PGD_2 may contribute to flushing, as has been shown in mice (10). Such compounds might resist the rapid tachyphylaxis observed with PGD_2. However, if this is the case, why is the efficacy of LRPT sustained? It has been reported to block, at concentrations attained clinically, T prostanoid (TP) receptors, albeit at higher concentrations than DP1, but not the I or E prostanoid receptors, more likely relevant to vasodilation. Thus, the combination might disrupt prostanoid-independent mechanisms of niacin-induced flushing. One approach to addressing this possibility would be to compare the relative efficacy of prostanoid suppression with higher doses of aspirin with that of LRPT in restraining niacin-induced flushing.

Diabetes

Niacin has long been known to reduce insulin sensitivity (12, 91). The recent Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial (see below) also found that in the niacin/LRPT group, diabetic complications (typically hyperglycemia) were about twice as common as in the control group as a reason for dropping out of the trial (0.9% vs. 0.4%) (12). A proposed mechanism is the rebound increase in FFA levels following the transient FFA suppression induced by niacin (92), although this has been disputed (17).

Despite niacin's impact on insulin sensitivity, the cardiovascular benefits from niacin were similar in patients with or without impaired glucose tolerance in the Coronary Drug Project (CDP) (93). Statins present a similar case. Despite

their cardioprotective effects, also evident in diabetic patients, statins have been associated with an increased risk of diabetes (94, 95). Statins and niacin may be interacting with other risk factors to reveal a predisposition to diabetes (96).

Gastrointestinal

Gastritis-like symptoms such as heartburn, indigestion, nausea, diarrhea, or stomach pain can occur after niacin administration. This has been widely observed in experimental and outcome studies (11, 97). The mechanism for these gastrointestinal symptoms is not clear. Niacin can also cause hepatotoxicity (98, 99), which may be more common when the drug is administered in a sustained-release form (99, 100). It has been suggested that this effect may be mediated by niacin's metabolites (101).

Gout

Niacin can also occasionally increase plasma uric acid levels and induce gout (102). This effect may be due to the inhibition effect of niacin on uricase, an oxidizing enzyme of uric acid (103), or due to a decrease in uric acid excretion (104).

RANDOMIZED CONTROLLED TRIALS

The CDP

The CDP (105) was the first clinical trial to show the cardiovascular benefits of any lipid-modifying agent. It was conducted between 1966 and 1975 to assess the long-term efficacy and safety of five lipid-influencing drugs in 8,341 men aged 30 to 64 years with electrocardiogram-documented previous myocardial infarction. Patients were randomized to placebo or clofibrate, dextrothyroxine, two doses of oral estrogen, or to niacin (3,000 mg/day). The two estrogen regimens and dextrothyroxine were discontinued early because of adverse effects. Hence, only the effects of clofibrate and niacin were examined. Clofibrate yielded no evidence of efficacy. Niacin treatment showed modest benefit in decreasing definite nonfatal recurrent myocardial infarction (10.2 vs. 13.8%), but no decrease in total mortality. However, a follow-up study revealed that 9 years after termination of the CDP study, patients originally randomized to niacin had a mortality rate 11% lower than those originally randomized to placebo. Presumably, patients stopped taking the drug after an average of 6.2 years in the trial (106). The cumulative motility rate curves didn't start to diverge until ~65 months post treatment, raising the possibility that drug-related impact on mortality might be delayed. However, as this comparison no longer fell within the structure of a randomized trial, it did no more than frame a hypothesis.

Surrogate endpoint trials

There have been a few trials assessing niacin efficacy utilizing surrogate endpoints. All are small and some of them were not designed to study niacin efficacy. A couple of them also had prespecified clinical endpoints, although probably none of them were suitably controlled or powered (107–113).

The open-labeled Stockholm trial followed the CDP trial. Patients with prior myocardial infarction were randomized to receive either placebo (N = 276) or the combination of clofibrate and nicotinic acid (N = 279) (107). The concentrations of both serum cholesterol and TGs were lowered by 13 and 19%, on average, respectively, in the treatment versus control groups. The combination resulted in an average 26% reduction in mortality, but with greater effect in those patients with hypertriglyceridemia. However, aside from its open-label design, this trial was far underpowered to assess mortality.

In the Familial Atherosclerosis Treatment Study (FATS) (108), male patients (N = 146) with angiographic evidence of coronary artery disease and elevated apoB levels were treated with either lovastatin-colestipol, niacin-colestipol, or placebo. Lovastatin-colestipol reduced the frequency of the progression of coronary lesions, increased the frequency of regression, and reduced the incidence of cardiovascular events. It was based on a methodology utilizing angiocatheterization. Experienced observers blindly assessed the change in the severity of coronary disease both visually and quantitatively. Again, this was underpowered to assess clinical outcomes.

In the HDL Atherosclerosis Treatment Study (HATS) (109), patients (N = 160) with prior coronary events and low HDL (mean 32 mg/dl) and LDL (mean 130 mg/dl) were randomized to treatment with simvastatin-niacin or placebo, with or without antioxidants. Simvastatin-niacin decreased LDLc by 42% and increased HDLc by 26% on average, compared with placebo. Angiographically, the average coronary stenosis progressed by 0.4% in the simvastatin-niacin group versus 3.9% in the placebo group. In addition, there were fewer clinical events in the simvastatin-niacin group than in the placebo group (9 vs. 1).

The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2 study (110) tested first the incremental impact of adding niacin to background statin therapy. Patients (N = 167) with known coronary heart disease and low HDLc (<45) were treated with niacin (1,000 mg) or placebo on top of a statin. Niacin significantly reduced the rate of progression of carotid intima-media thickness (IMT), although only in subjects without insulin resistance. A follow-up open-labeled observation found regression of IMT in the niacin group (111).

The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis (ARBITER 6-HALTS) trial was designed to compare the effect of niacin and ezetimibe on the progression of IMT, on the background of statin therapy (112). Patients who had coronary heart disease or a coronary heart disease risk equivalent with low LDL (<100 mg/dl) and moderate HDL (HDL <50 mg/dl in male and <55 mg/dl in female) were randomized to niacin or ezetimibe treatment. While niacin and ezetimibe had divergent effects on HDLc, a greater reduction in LDLc was attained with ezetimibe. Despite this, progression of atherosclerosis, as reflected by the IMT, was only observed in the patients receiving niacin, leading to premature termination of this study.

The Oxford Niaspan study treated patients (N = 71) with coronary heart disease or risk equivalent with low LDL (~85 mg/dl) and low HDL (~38 mg/dl) with either niacin (2,000 mg) or placebo, on top of statin (113). At 12 months, regression was observed in the niacin group versus progression in the placebo group.

Aside from the variable fidelity of the surrogate endpoints in predicting clinical outcomes (114), these studies suffer from a series of limitations ranging from open-label design to being seriously underpowered to assess clinical outcomes which nonetheless are both reported and interpreted.

Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes trial

The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial was designed to compare niacin versus placebo in patients with established atherosclerotic disease on statin therapy (11). The primary endpoint was the composite of the first event of death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalization (for >23 h) for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization.

Patients with established cardiovascular disease with low LDLc (mean 71 mg/dl) and low HDLc (34 mg/dl) entered an open-label niacin run-in phase. Patients in whom a dose of at least 1,500 mg of niacin per day was associated with a tolerable side-effect profile were randomly assigned to niacin or matching placebo. Patients in the active treatment group received niacin at a dose of 1,500 to 2,000 mg per day plus simvastatin. Patients in the placebo group received simvastatin plus a small dose (50 mg) of immediate-release niacin to induce flushing and to facilitate blinding of patients and observers to drug induced flushing. In both groups, the dose of simvastatin could be adjusted and subjects could receive ezetimibe to achieve and maintain the LDLc within a prespecified target range.

AIM-HIGH was ended after a mean follow-up of 3 years, when an interim analysis suggested the futility of the comparison. There was no incremental benefit of niacin in reducing cardiovascular events, despite significant increases in HDLc and decreases in TG levels in the niacin-treated group.

The outcome and design of the AIM-HIGH trial prompted considerable controversy. The design of the trial allowed liberal use of hypolipidemic agents other than niacin in both groups and, as a consequence, there was unbalanced use of both statins (25% on 80 mg statin in the placebo group vs. 18% in the niacin group) and ezetimibe (22% in the placebo group vs. 10% in the niacin group).

This study was attempting to answer the question of whether once LDLc is reduced, is there an incremental benefit from raising HDLc? However, the absolute difference in HDLc achieved by niacin was only 4 mg/dl (42 vs. 38 mg/dl). This was largely because of a paradoxical increase in HDLc in the placebo group, which might be a result of higher statin doses or of the small doses of immediate-release niacin.

Besides achieving such a modest change in HDLc, the follow up time of 3 years post randomization might have been too short to see a benefit in mortality. For example, the ultimate mortality benefit from statins was not apparent in the 4S (Scandinavian Simvastatin Survival Study) study after 3 years of dosing (115), nor was the divergence in mortality rates in the posthoc analysis of the CDP . For these reasons, the apparently null effect afforded by the results of AIM HIGH left many questions unanswered.

HPS2-THRIVE

The HPS2-THRIVE trial hoped to answer these outstanding questions. It was much larger than the antecedent clinical trials (25,673 patients) and suitably powered to detect a reasonable expectation of benefit. However, this was a trial to assess the usefulness of a drug combination, extended-release niacin (ERN) (2 g) and the DP1 antagonist, LRPT (40 mg), in the reduction of major vascular events (composite of nonfatal myocardial infarction, coronary heart disease death, stroke, or arterial revascularization) (12). The study was not designed to answer the questions of how either drug alone acted or how they compared with the combination.

Prior to randomization, patients diagnosed with occlusive arterial disease received standardized open-labeled LDLc lowering therapy with simvastatin 40 mg (± ezetimibe) daily (to a total cholesterol target of 135 mg/dl). The ability to remain compliant with ERN/LRPT for about 1 month was then assessed in 38,369 patients. About one-third were excluded (mainly due to combination drug-related side effects). A total of 25,673 patients were randomized between ERN/LRPT daily versus placebo on a background of 38,369 and were followed for a median of 3.9 years.

Average baseline lipids were LDLc (63 mg/dl), HDLc (44 mg/dl), and TGs (125 mg/dl). ERN/LRPT treatment reduced LDLc by an average 10 md/dl, and increased HDLc by 6 mg/dl. The primary endpoint was no different between the two groups (relative risk 0.96, [confidence interval 0.90–1.03]) (116).

After 3.9 years of follow-up, 25.4% of the participants allocated active ERN/LRPT had stopped their treatment compared with 16.6% of those on placebo. The most common medical reasons for stopping ERN/LRPT were previously recognized side effects of niacin, such as flushing, gastrointestinal complaints, and the onset of diabetes. Other reasons for stopping the drug combination had not previously been ascribed to niacin. These included myopathy, infection, and bleeding (12).

Myopathy. Myopathy is a common side effect of statins (117). It had never been recognized as a common side effect of niacin. However, in the HPS2-THRIVE study, the risk of myopathy was increased four times (0.16%/year vs. 0.04%/year) by adding ERN/LRPT to simvastatin (40 mg daily) (12), particularly in Chinese patients which comprised 42.6% of subjects, and whose myopathy rates on simvastatin are also higher than in Europeans (0.13% vs. 0.04%) (12).

Infection. Similar to myopathy, infection had never been recognized as a side effect of niacin. However, in the

HPS2-THRIVE study, treatment with niacin resulted in a 1.4% (8.0% in treatment group vs. 6.6% in placebo group) higher risk of infection (116). PGD_2, acting through DP1, has been known to have potent anti-inflammatory effects, especially relating to resolution of acute inflammatory processes (118, 119). Whether LRPT contributed to the excess infection in the HPS2-THRIVE study is unclear.

Bleeding. In the HPS2-THRIVE study, treatment with niacin/LRPT resulted in 0.7% (2.54% in treatment group vs. 1.85% in placebo group) higher risk of bleeding (116), including an increased risk of hemorrhagic stroke. It is unclear whether this relates to niacin, LRPT, or the combination. Niacin decreases the synthesis of plasminogen activator inhibitor 1 and potentiates fibrinolysis (120). Another study found that niacin reduces fibrinogen and a prothrombin fragment (121). However, higher bleeding events with niacin were not observed in previous large trials like CDP and AIM-HIGH. LRPT antagonizes the TP receptor at concentrations higher than those that antagonize DP1. Deletion of TP in mice predisposes them to bleeding; however, it is unknown whether TP antagonism was asymmetrically attained due to variability in kinetics and consequent drug exposure in patients receiving niacin/LRPT who suffered bleeding episodes.

HPS2-THRIVE was a much larger trial than its antecedents. Besides its effects on HDLc and LDLc, the combination reduced Lp(a) and TGs and reduced average systolic blood pressure by 2 mmHg. These effects might be expected to result in differences that could translate into an ~17% reduction in vascular events by ERN/LRPT, based on previous observational studies and randomized trials (12, 122). On the other hand, such assumptions are based on trials in which patients had higher baseline levels of LDLc than in HPS2-THRIVE, so the room for an LDLc-based improvement in outcomes would be expected to be diminished.

Recently (62), we found that PGD_2, like prostaglandin I_2, may function as a limiting homeostatic response to thrombogenic and hypertensive stimuli and may have particular relevance as a constraint on platelets during niacin therapy (61). Moreover, DP1 antagonism may restrain the anti-inflammatory effects and hence the putative atheroprotective benefit of niacin (54); it may further undermine the efficacy of niacin by failing to mediate direct platelet-inhibitory effects or by removing a restraint on niacin-evoked platelet thromboxane A_2 formation, which increases dramatically (~80-fold) after niacin administration. DP1 deletion in mice augments aneurysm formation and the hypertensive response to angiotensin II, and modestly accelerates atherogenesis (62, 123). However, the design of HPS2-THRIVE does not let us draw conclusions about whether concomitant DP1 antagonism limited any actual benefit from niacin with respect to cardiovascular outcomes, as control groups administered niacin or LRPT alone were not included in this study.

Similarly, it is impossible to assign cause for some of the unexpected adverse effects to one or the other component of the combination. As mentioned, bleeding may have derived from TP antagonism in some patients by LRPT, and it is biologically plausible that DP1 antagonism could have contributed to the excessive and infection observed in the combination, as there is some evidence that PGD_2 contributes to resolution of inflammation (118, 119). On the other hand, although bleeding and infection were not reported as adverse effects of niacin in AIM-HIGH, post hoc analysis of the data by some has reported an excess of infections. Either way, a definitive conclusion cannot be reached from concordance with a post hoc analysis of another trial; HPS2-THRIVE was a trial of niacin/LRPT, not of niacin.

CONCLUSIONS

HPS2-THRIVE is a well-designed and powered clinical trial that has provided a definitive answer as to the efficacy/adverse response profile of a combination of niacin with a DP1 antagonist. However, it is impossible to parse with confidence the differential impact of the two elements of this combination. At face value, the results of this study and AIM-HIGH are concordant with HPS2-THRIVE and fail to support the hypothesis that raising HDLc by niacin would confer any cardiovascular benefit. However, the increment in HDLc was very modest in AIM-HIGH, which was relatively underpowered by comparison with HPS2-THRIVE; it also included niacin in the control group, albeit at a lower dose, and it was prematurely concluded. Adding to this impression, and perhaps more persuasive with respect to HDLc, is the study of human genetics, where variants associated with rising levels of HDLc are not related inversely to cardiovascular risk. However, even here, controversy lingers around the nature of the HDL that is elevated and, with respect to niacin, potentially beneficial mechanisms of action that have nothing to do with raising HDLc.

How will this all play out? To some degree, the results of ongoing trials of CETP inhibitors will influence the HDL discussion. Further, the impact of novel therapeutics, such as inhibitors of PCSK9, may shift the goal posts. Such results are likely to determine whether the performance of a sufficiently large and well-controlled study of niacin in more defined populations, say those relatively resistant to benefit from statins, seems like a cost-effective initiative to a commercial sponsor. Such pragmatic reasoning may drive the progressive abandonment of niacin, a drug that has long been a mainstay of cardiovascular therapy, while we still poorly understand its many potentially relevant mechanisms of action and have an incomplete picture of its clinical utility.

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