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EDITORIAL

The difficult search for a 'partner' of statins in lipid-targeted prevention of vascular events: the re-emergence and fall of niacin

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This editorial refers to 'HPS2-THRIVE randomized placebo-controlled in 25 673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment'†, by The HPS2-THRIVE Collaborative Group, on page 1279

Current studies evaluating the efficacy and safety of lipid-targeted therapies to reduce cardiovascular events are being performed on the background of statin therapy, given the overwhelming evidence from numerous randomized clinical studies indicating a reduction of occlusive vascular events by statin therapy.[1]

Niacin: a lipid-modifying agent with a long history

Already in 1955 Dr Altschul and colleagues described that high doses of the vitamin B3 (niacin) reduced serum cholesterol levels (*Figure 1*).[2] Later, the Coronary Drug Project (CDP) sponsored by the National Heart and Lung Institute (published in 1975) tested the efficacy and safety of long-term therapy with a high dose of niacin (3 g/day) in men after myocardial infarction.[3] In the CDP there was no significant effect of niacin therapy on the primary endpoint, i.e. all-cause mortality, but a significant reduction in the rate of recurrent non-fatal myocardial infarction by 27% was observed.[3] The authors concluded that the 'Coronary Drug Project data yield no evidence that niacin influences mortality of survivors of myocardial infarction; this medication may be slightly beneficial in protecting persons to some degree against recurrent nonfatal myocardial infarction', that is to say the authors were not overly enthusiastic with respect to the efficacy of the compound to prevent major cardiovascular events. Already in this early study it became apparent that the adherence to niacin therapy was significantly reduced as compared with placebo, probably due to the well-known skin and gastrointestinal side effects of the compound.[3]

The niacin receptor GPR109A and niacin-induced flushing

The mechanisms underlying the effects of niacin on lipids are still not completely understood, but include a decreased lipolysis due to inhibition of the hormone-sensitive triglyceride lipase in adipocytes.[4] In 2003, the discovery of the niacin receptor, the G_i protein–coupled receptor GPR109A (HM74A in humans; PUMA-G in mice) was reported, that later allowed a better understanding of the mechanisms underlying the well-known niacin-associated flush.[5] These studies could show that niacin-induced flushing was mediated by the niacin receptor GPR109A, that was also thought to mediate the effects of niacin on lipids and on experimental atherosclerosis.[5–7] Furthermore, it was suggested that niacin-induced flushing involved the release of prostaglandin D(2) and prostaglandin E(2), and the respective prostaglandin D(2) and prostaglandin E(2) receptors,[5,6] resulting in the concept of a blockade of the prostaglandin D(2) receptor-1 to reduce niacin-induced flushing. Later, a clinical study in 1455 patients with dyslipidaemia focusing on niacin-induced 'flushing' suggested that the addition of the prostaglandin D(2) receptor-1 antagonist laropiprant to extended-release (ER) niacin significantly reduced niacin-associated flushing.[8] Moreover, Lukasova *et al.* suggested in experimental studies that niacin reduced the progression of atherosclerosis by direct stimulation of GPR109A on immune cells (e.g. macrophages) leading to reduced inflammatory activation independent of lipid-modifying effects.[7] A subsequent clinical study by Taylor *et al.* suggested that addition of ER niacin to long-term statin therapy resulted in a modest regression of carotid intima-

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media thickness in patients with coronary artery disease or risk equivalent.[9]

Clinical outcome trials of niacin in combination with statin therapy

More recently, two clinical outcome studies (AIM-HIGH and HPS2-THRIVE) have consequently been evaluating the effects of ER niacin therapy or the combination of ER niacin with laropiprant on cardiovascular events in addition to statin therapy.[10,11] The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes trial (AIM-HIGH) was aiming to evaluate the impact of raising HDL-cholesterol levels with niacin therapy (1.5–2 g/day) on cardiovascular events in subjects with similar LDL-cholesterol levels (achieved by higher statin doses and ezetimibe therapy in the comparator treatment arm).[11] In this study, the primary endpoint, a composite of the first event of death from coronary heart disease, non-fatal myocardial infarction, ischaemic stroke, hospitalization for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization, was not reached by niacin therapy in patients with established cardiovascular disease and an atherogenic dyslipidaemia.[11] In fact, the trial was stopped early because the boundary for futility had been crossed and a higher number of ischaemic strokes was observed in patients assigned to niacin.[11] However, the interpretation of the results of the trial with respect to niacin has been somewhat difficult due to the design, i.e. the fact that more placebo-treated patients required increases in the statin dose or addition of ezetimibe, which could have partly blunted a potential therapeutic benefit of niacin (*Figure 2*).

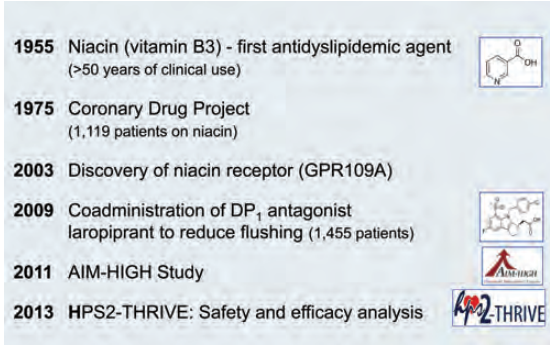

Figure 1 Niacin (vitamin B3)—a lipid-modifying agent with a long history.

The substantially larger Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) study has now evaluated the combination of ER-niacin (2 g/day) with the prostaglandin D(2) receptor-1 antagonist laropiprant (40 mg) in 25 673 patients with pre-existing occlusive vascular disease.[10] The sponsor of the trial has recently communicated that the study did not meet its primary endpoint of reduction of major vascular events, although the detailed data presentation is still expected. Within this large-scale clinical study, a careful analysis of the side effects was pre-specified, in particular with respect to muscle and liver outcomes and reasons for stopping study treatment that is reported in the *European Heart Journal*. The addition of ER niacin/laropiprant to 40 mg simvastatin therapy (and ezetimibe in some participants) increased the risk of definite myopathy. The risk of myopathy on the combination therapy was substantially more pronounced in Chinese patients as compared with European patients, indicating that the safety of a drug in one region and in Caucasians cannot necessarily be translated to other regions, such as Asia.[10] Interestingly, although the name of the trial focuses on the HDL-cholesterol-raising effects of niacin, there was also a 19.9% reduction of LDL-cholesterol levels and a 19.5% reduction of triglycerides already in the run-in phase, and niacin is also known to lower the proatherogenic lipoprotein(a). The vascular effects of HDL have been observed to be highly heterogenous, e.g. the endothelial-protective properties of HDL are impaired in patients with coronary disease or diabetes as compared with healthy subjects,[12–15] which may represent one mechanisms limiting beneficial effects of HDL-cholesterol-raising therapies in these patients. The above observations of

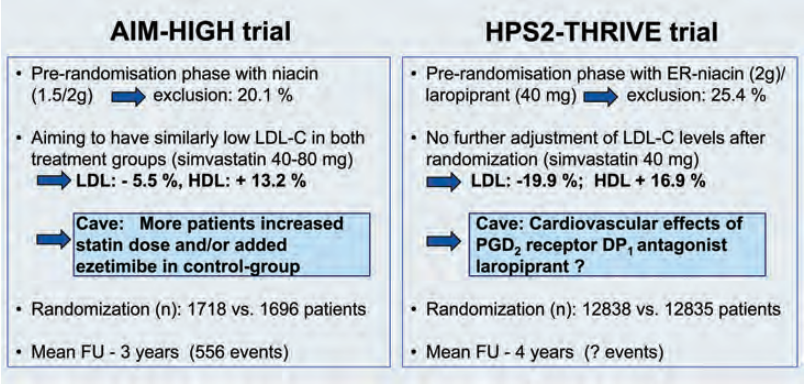

Figure 2 Comparison of the AIM-HIGH and the HPS2-THRIVE trial. C, cholesterol; ER, extended release; FU, follow-up.

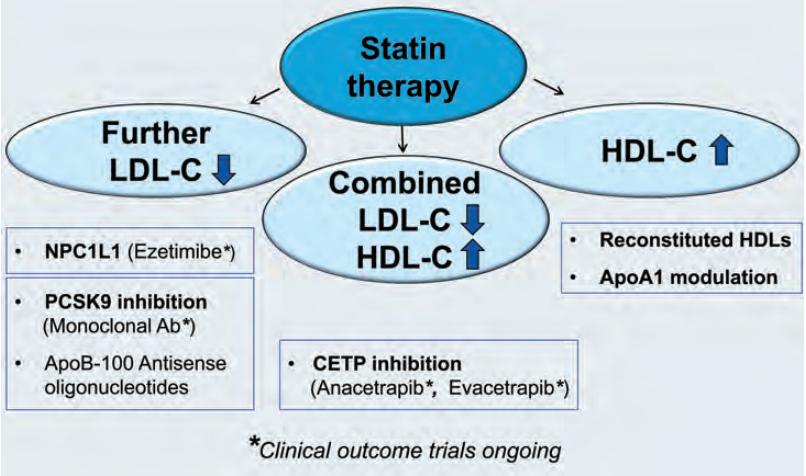

Figure 3 Strategies of ongoing clinical trials to examine which lipid-targeted therapy should be added to statin treatment in patients with high vascular risk. Ab, antibody; C, cholesterol; CETP, cholesteryl ester transfer protein.

substantially lowered LDL-cholesterol levels, however, raise important questions as to why niacin/laropiprant did not reduce major cardiovascular events.

Cardiovascular biology of the prostaglandin D(2) receptor-1?

The question arises of whether the prostaglandin D(2) receptor-1 antagonist laropiprant, that was used to reduce niacin-induced flushing, is really biologically inert with respect to atherosclerosis and thrombosis, in particular since little is known about the cardiovascular biology of prostaglandin D(2). Interestingly, a recent experimental study has observed that prostaglandin D(2) receptor-1 deletion in mice augmented aneurysm formation and accelerated atherogenesis and thrombogenesis, and these authors suggested that niacin-induced prostaglandin D(2) release may function as a constraint on platelets during niacin therapy.[16] The effects of inhibition of the prostaglandin D(2) receptor-1 by laropiprant on thrombosis and atherosclerosis in humans *in vivo* are probably difficult to predict and complex, since it has been observed that on the one hand laropiprant at low concentrations prevented the inhibitory effects of prostaglandin D(2) on platelet function, including effects on platelet aggregation and thrombus formation, but on the other hand laropiprant at higher concentrations attenuated platelet activation induced by thromboxane and inhibited thrombus formation.[17] Similarly, the effects of prostaglandin D(2) receptor-1 inhibition on atherosclerotic plaque formation in mouse models have not been consistent, with accelerated atherosclerosis in some, but not all atherosclerotic mouse models.[18]

Where do we go from here?

Given the disappointing efficacy results of the two recent clinical outcome studies of ER niacin in addition to statin therapy and the increased risk of myopathy observed in the HPS2-THRIVE study, niacin has failed as a valuable 'partner' of statin therapy in lipid-targeted approaches to reduce major cardiovascular events further in high-risk patients. There are, however, several large-scale clinical trials under way that focus either on further LDL-cholesterol reduction by inhibition of intestinal absorption (IMPROVE-IT) or PCSK9 antagonism (e.g. ODYSSEY), on combined LDL-cholesterol lowering and HDL-cholesterol raising by potent cholesteryl ester transfer protein inhibition with anacetrapib (HPS3-TIMI55) or evacetrapib (ACCELERATE), or on short-term HDL raising by infusion (*Figure 3*).

At present, statin therapy has been clearly shown to reduce vascular events effectively and is reasonably well tolerated in most patients. We will still have to wait for the results of the above ongoing studies to see whether another lipid-targeted intervention can further reduce vascular events in addition to statin therapy. At the same time, other therapeutic strategies targeting mechanisms known to be involved in the progression of atherosclerotic vascular disease, such as anti-inflammatory therapies (low-dose methotrexate; interferon-1β antibody),[19,20] have been initiated to determine whether such treatment strategies can further reduce cardiovascular events in addition to statin therapy with an acceptable safety profile.

Conflict of interest: U.L. has received speaker fees or research grants from Merck, Roche, and Pfizer.

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