Modified-release nicotinic acid for dyslipidaemia: novel formulation improves tolerability and optimises efficacy

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Abstract

Data from epidemiological and intervention studies have conclusively shown that a low level of high-density lipoprotein cholesterol (HDL-C) is an important risk factor for cardiovascular disease. Increasing low HDL-C levels produces risk reduction comparable with that observed with decreasing low-density lipoprotein cholesterol (LDL-C) in the major statin trials. The latter have shown that, even with effective statin therapy, there is still an unacceptably high residual risk of major coronary events. A substantial proportion of patients with coronary heart disease (CHD) with acceptable levels of LDL-C will have low levels of HDL-C and increased serum triglycerides. Of the available lipid-modifying treatments, nicotinic acid is the most potent agent for increasing HDL-C (by about 30% from baseline). In addition, it effectively decreases triglycerides and has a relatively modest effect in decreasing LDL-C. Modified-release nicotinic acid has been developed to overcome the poor tolerability associated with earlier formulations while maintaining the efficacy of immediate-release nicotinic acid. Modified-release nicotinic acid is effective and safe for the treatment of dyslipidaemia, including the atherogenic dyslipidaemia associated with type 2 diabetes and the metabolic syndrome. Combination therapy with modified-release nicotinic acid and a statin offers complementary therapeutic benefits, as well as reducing the progression of, or even regressing, atherosclerosis. This strategy can represent an important advance for clinical management of at-risk patients with dyslipidaemia.

Key words: nicotinic acid, high-density lipoprotein cholesterol, dyslipidaemia, type 2 diabetes, combination lipid modifying therapy.

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Introduction

High-density lipoprotein cholesterol (HDL-C) is recognised as an independent risk factor for cardiovascular disease. Epidemiological data have demonstrated an inverse relationship between serum HDL-C and risk of coronary artery disease (CAD).[1-3] For every 1% decrease in HDL-C there was a 2–3% increase in the risk of CAD, independent of low-density lipoprotein cholesterol (LDL-C) and triglyceride concentrations.[4] Recent data also indicate that the association between HDL-C and mortality from CAD and stroke is even valid in elderly patients (aged at least 85 years).[5] Lipid-modifying intervention studies, principally the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT), demonstrated that, in patients with desirable levels of LDL-C, raising low HDL-C levels by 6% led to a relative risk reduction of 24% in the combined outcome of death from CAD, non-fatal myocardial infarction (MI) and confirmed stroke.[6] Multivariate analysis showed that only the increase in HDL-C was associated with a significantly lower risk of CAD events.[7]

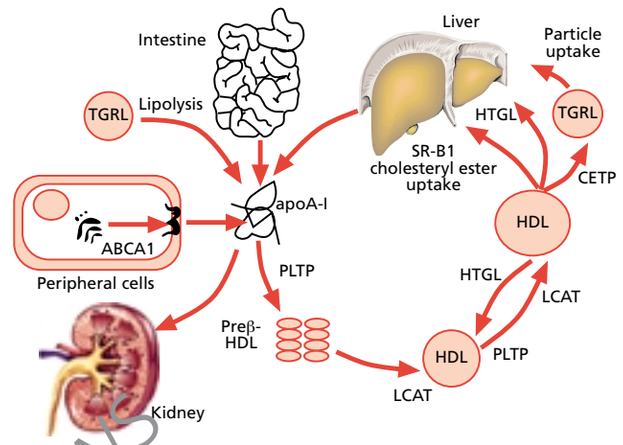
Although LDL-C is still the primary focus of lipid modifying treatment, the importance of low HDL-C as an independent risk factor for CAD is already recognised in current guidelines.[8,9] Most patients with CAD have multiple lipid abnormalities. In a study by the VA-HIT group, involving analysis of samples from 8,500 men with coronary heart disease (CHD), 87% had elevated LDL-C lev-

els, 33% had high triglycerides and 64% had low HDL-C; moreover, low HDL-C (with desirable levels of LDL-C) may occur in up to 40% of patients with CHD.[10]

Atherogenic dyslipidaemia, specifically decreased levels of HDL-C associated with increased levels of triglyceride-rich lipoprotein remnants derived from chylomicrons and very low-density lipoproteins (VLDL), is characteristic of the metabolic syndrome. Although LDL-C levels may not be elevated, the subtype of LDL is predominantly small and dense, which is regarded as more atherogenic. This particular dyslipidaemia, as well as other characteristics of the metabolic syndrome such as abdominal obesity and insulin resistance, are common in South Asians living in the UK, a group that has a significantly increased risk of cardiovascular disease.[11,12] This makes clinical management of these patients a particular challenge for clinicians.

Of the classes of drugs currently approved for treatment of dyslipidaemia, nicotinic acid (niacin) is the most effective in raising levels of HDL-C, while at the same time reducing levels of LDL-C and triglycerides. Nicotinic acid is also the only lipid-modifying agent that has been shown to reduce levels of lipoprotein (a) (Lp[a]), a genetic variant of plasma LDL, an important indicator of risk of CHD.[13] As a result, nicotinic acid has gained increasing attention for the treatment of dyslipidaemia, either alone or in combination with other lipid-lowering agents.[9]

Figure 1. Schematic representation of reverse cholesterol transport



Key: CETP = cholesterol ester transfer protein; HTGL = hepatic triglyceride lipase; LCAT = lecithin-cholesterol acyltransferase; PLTP = phospholipid transfer protein; SR-BI = scavenger receptor B1; TGRL = triglyceride-rich lipoprotein

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Mechanism of action of nicotinic acid

Although observational studies have convincingly demonstrated the important role of HDL-C in protecting against cardiovascular disease, the mechanisms of this function are far from clear. Currently, one of the main mechanisms by which HDL-C is thought to protect against atherosclerosis is reverse cholesterol transport (RCT), in which excess cholesterol is transported via HDL-C from peripheral tissues to the liver and then excreted either directly or after conversion to bile acids (see figure 1). Three main pathways are thought to mediate the removal of cholesterol from cells: passive diffusion; a pathway involving scavenger receptor type B1, the main HDL receptor on hepatocytes, which leads to removal of cholesterol ester in the HDL particle; and the ABCA1 transporter pathway involving apolipoprotein A-I (apoA-I) on the HDL particle, which acts as an acceptor for cholesterol effluxed from peripheral cells.[14,15]

HDL-C may also have protective effects on endothelial function as well as countering LDL oxidation, an important event in the initiation and development of atherosclerosis[15] although the mechanisms and clinical relevance of these effects have not yet been elucidated.

Although the mechanism by which nicotinic acid increases HDL-C is unclear, the pathway involving binding to apoA-I on the HDL particle is thought to be the primary target of nicotinic acid. Nicotinic acid decreases the rate of removal of apoA-I by the liver but does not appear to affect the rate of synthesis of this protein; as a result, HDL particles can persist for extended periods leading to an increase in HDL levels. Nicotinic acid also decreases the activity of hepatic triglyceride lipase, leading to an increase in the amount of HDL2, which is thought to be cardioprotective.[16]

Nicotinic acid reduces the pool of free fatty acids leading to inhibition of triglyceride synthesis in the liver[17,18] and increases the rate of VLDL breakdown, which together result in a reduction in triglyceride levels. Nicotinic acid also reduces the rate of mobilisation of free fatty acids from adipose tissue to the liver, leading to reduction in hepatic synthesis of VLDL, and as VLDLs are precursors to LDL, reduction in levels of LDL-C.[19] Although the mechanism by which nicotinic acid decreases Lp(a) is currently not known, it is not directly related to the decrease in LDL-C as neither statins nor fibrates decrease Lp(a).

Inflammatory cells play a key role in the process of atherogenesis and influence plaque stability. Elevated levels of C-reactive protein (CRP), a protein produced in the liver during inflammation, have been identified as an indicator of increased risk of cardiovascular events, including MI and stroke.[20] CRP may itself play a role in atherogenesis. Nicotinic acid has been shown to reduce levels of CRP in one study,[21] which may be indicative of reduction in the inflammatory responses associated with atherogenesis.

Development of modified-release nicotinic acid

Clinical data support the use of nicotinic acid for secondary prevention. The Coronary Drug Project[22] was a long-term study involving 8,341 men with previous MI, treated with five different lipid-modifying regimens including nicotinic acid (immediate-release formulation). After six years, treatment with nicotinic acid reduced the incidence of non-fatal MI by 26% and cerebrovascular events by 24% compared with placebo, although there was no significant effect on mortality. Follow-up data after 15 years demonstrated a significant reduction in mortality with nico-

tinic acid (11% *vs.* placebo, p<0.001).[23] Additionally, the Stockholm Ischaemic Heart Disease Secondary Prevention Study[24] demonstrated a significant reduction in total mortality (by 26%, p<0.05) and CHD mortality (by 36%, p<0.01) with the combination of immediate-release nicotinic acid and clofibrate. The magnitude of the benefit of HDL-C lowering with nicotinic acid, in terms of reduction of cardiovascular morbidity and mortality, was comparable with that observed with LDL-C lowering with statin therapy.

Despite these benefits, problems relating to the tolerability of immediate-release nicotinic acid, in particular cutaneous flushing, limited its use. Up to 25% of patients in clinical trials discontinued treatment due to flushing.[25] Sustained-release formulations were developed to circumvent this problem; however, some of these preparations were associated with an increased incidence and severity of hepatotoxicity, a problem which had also been described with the immediate-release formulation.[25,26] Additionally, considerable interindividual variability in the HDL-C response has been observed with some sustained-release preparations.[27]

These side effects are attributable to the metabolism of nicotinic acid. Nicotinic acid is metabolised either via conjugation with glycine to form nicotinuric acid, or via a series of oxidation-reduction reactions that ultimately result in the production of nicotinamide and pyrimidines. The former is associated with flushing, whereas the latter is associated with hepatotoxicity.[28]

A modified-release formulation was specifically developed to optimise the release rate of nicotinic acid over 8–12 hours, thereby improving tolerability compared with sustained-release nicotinic acid, while maintaining its efficacy.[1] Modified-release nicotinic acid administered once-daily in the evening or at bedtime is associated with a lower rate of flushing than immediate-release nicotinic acid, and a lower risk of hepatotoxicity compared with that reported with sustained-release nicotinic acid.[25] Additionally, the HDL-C raising efficacy is fully maintained.[19]

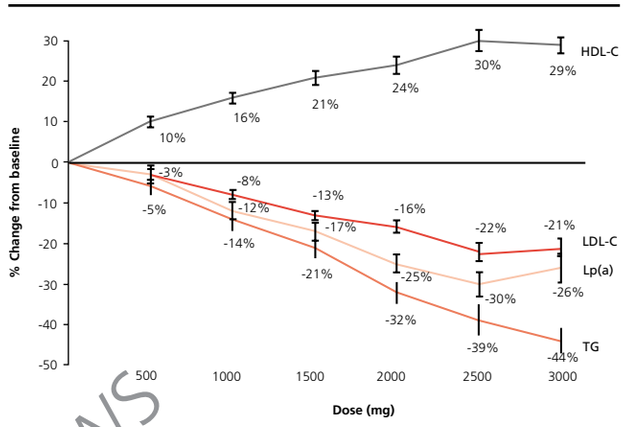
Clinical efficacy

The efficacy and tolerability of modified-release nicotinic acid for treatment of dyslipidaemia, either as monotherapy or in combination with other lipid-lowering agents, has been investigated in a series of trials involving over 8,700 patients, over 500 of whom received treatment for over two years.

Modified-release nicotinic acid monotherapy

Pivotal studies show that modified-release nicotinic acid monotherapy increases HDL-C in a dose-related manner by up to 30% (figure 2).[29-31] In one study[29] involving 122 patients with primary dyslipidaemia, HDL-C levels increased by 17% with 1 g daily modified-release nicotinic acid and by 23% with 2 g daily, administered over 12 weeks; the higher dose also decreased LDL-C by 14%, Lp(a) by 27% and triglycerides by 29%. A dose-ranging study[30] showed that significant increases in HDL-C were first evident at 500 mg daily, reaching 30% with larger doses. Administration of modified-release nicotinic acid (median dose 2 g daily) in 517 patients with primary hypercholesterolaemia

Figure 2. Overview of dose-related changes in HDL-C, LDL-C, Lp(a) and TG with modified-release nicotinic acid. (Combined data from pivotal studies)



Key: HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein (a); TG = triglycerides

produced a consistently large increase in HDL-C which was sustained in the long term (26% at 48 weeks and 28% at 96 weeks); treatment effects on other lipid components were also sustained at 96 weeks (decreases of 40% in triglycerides, 20% in LDL-C and 40% in Lp[a]).[31] Moreover, in a direct comparative trial in patients with isolated low HDL-C,[32] modified-release nicotinic acid 2 g daily was significantly more effective than gemfibrozil 600 mg twice-daily in raising HDL-C (26% *vs.* 13%, respectively).

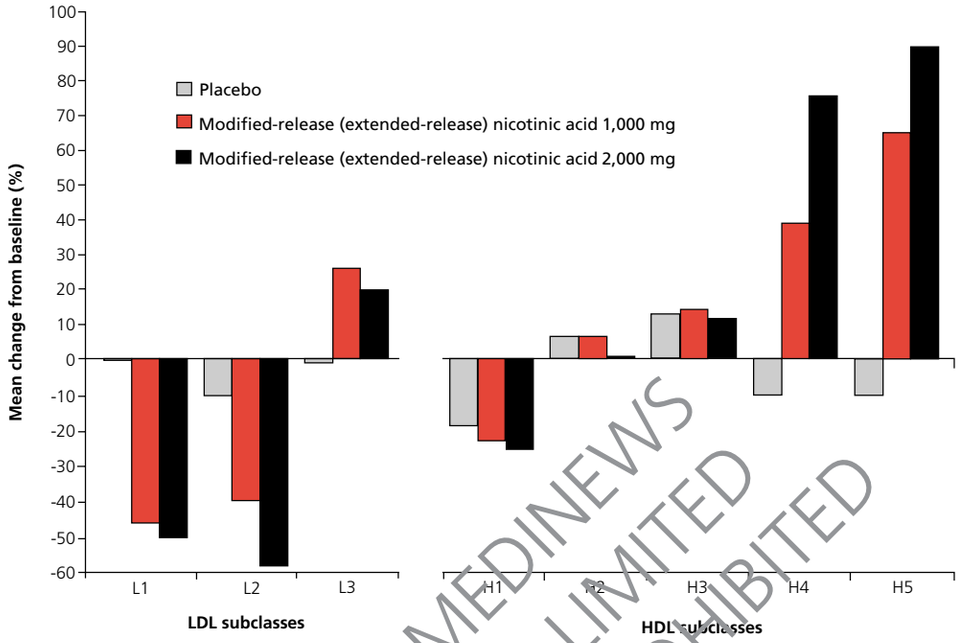
Patients treated with modified-release nicotinic acid 1–2 g daily showed beneficial effects on the lipoprotein subclasses, specifically increases in the cardioprotective larger HDL particles (H5 and H4), and decreases in the more atherogenic, small, dense LDL particles (figure 3).[29,33] These findings were consistent with the effects of immediate-release nicotinic acid on the lipid subclasses,[34,35] and may account for the observed beneficial effects of nicotinic acid on cardiovascular mortality and morbidity.[23]

Combination therapy with modified-release nicotinic acid

Patients with dyslipidaemia frequently do not achieve lipid goals. In one extensive review,[36] up to 40% of patients failed to meet lipid targets as set by the Adult Treatment Panel (ATP) III guidelines, and such guidelines may become even more rigorous. In a separate retrospective analysis[37] over one-half of patients required combination lipid-modifying therapy in order to achieve lipid goals.

The combination of modified-release nicotinic acid and a statin appears to be logical given the potential for complementary therapeutic benefits. The statins – as a class – are the most effective agents for reducing LDL-C, but have only a moderate effect on reducing triglycerides and even more modest effects on

Figure 3. Effect of modified-release (extended-release) nicotinic acid on the distribution of LDL and HDL subclasses



Key: HDL = high-density lipoprotein; LDL = low-density lipoprotein

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increasing HDL-C.[8] Moreover, while there is substantial LDL-C reduction at lower doses, there is less incremental benefit as dosage is increased, with only a 6% reduction in LDL-C for every doubling of the statin dose.[38] Additionally, higher doses of statins can be associated with more serious side effects such as liver and especially muscle toxicity.

The efficacy of combination therapy with nicotinic acid and a statin is well established. In one study,[39] long-term combination therapy with modified-release nicotinic acid (median dose 2 g daily at bedtime) and a statin (lovastatin, pravastatin or simvastatin) increased HDL-C by 26% and reduced total cholesterol by 23%, LDL-C by 32%, triglycerides by 30% and Lp(a) by 19%. Modified-release nicotinic acid was safe and highly effective in improving lipid parameters when added to a stable dose of a statin.[40] Moreover, improvements in lipid parameters were sustained with long-term administration of combination nicotinic acid/lovastatin therapy, with increases in HDL-C by 41% and decreases in LDL-C and triglycerides by 47% and 41%, respectively, at 12 months.[41]

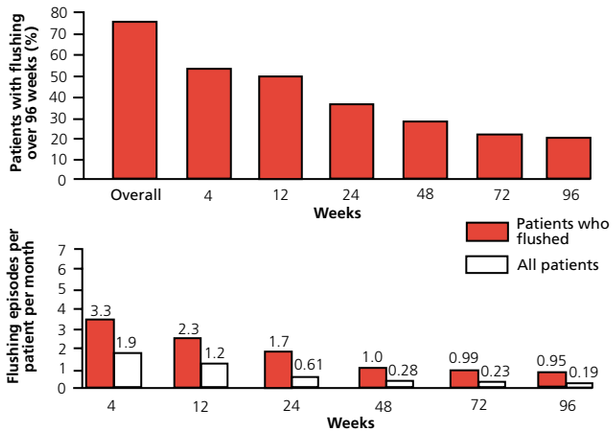
As patients treated with statins are often maintained on starting doses without titration,[42] the relative lipid-modifying efficacy of starting doses of combination nicotinic acid/lovastatin therapy was compared with standard doses of atorvastatin and simvastatin monotherapy.[43] After 12 weeks, the starting dose of the combination was significantly more effective than either atorvastatin or simvastatin in increasing HDL-C (19% *vs.* 4% and 8%, p<0.005) and decreasing triglycerides (32% *vs.* 23%, p<0.05 and 6%, p<0.001).

The clinical benefits of combining nicotinic acid and a statin are supported by the HDL Atherosclerosis Treatment Study (HATS).[44] Patients were treated with combination therapy with nicotinic acid and simvastatin, either with or without antioxidant vitamins. Treatment with the combination resulted in a 60–90% reduction in the incidence of major coronary events (i.e., death from coronary causes, confirmed MI, stroke or revascularisation for worsening symptoms) compared with placebo. Moreover, treatment with nicotinic acid/simvastatin resulted in significant angiographic regression of stenosis by 0.4% on average, compared with progression of 3.9% on placebo, (p<0.001). The HATS investigators concluded that combination nicotinic acid/simvastatin therapy represented a substantial advance over current clinical practice for the substantial proportion of patients with CHD and low HDL-C (about 40%),[8,9] who rarely receive therapy directed at both HDL-C and LDL-C. Incidentally, the antioxidant vitamins had no beneficial effect.

Type 2 diabetes and metabolic syndrome

Type 2 diabetes mellitus is closely associated with various risk factors, collectively termed the metabolic syndrome, which together increase the risk of cardiovascular disease by two-to-

Figure 4. Occurrence and frequency of flushing during long-term treatment with modified-release (extended-release) nicotinic acid



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four-fold.[45] This syndrome is characterised by atherogenic dyslipidaemia, specifically moderately elevated plasma triglycerides, elevated small dense LDL-C and low levels of HDL-C. The nature of the atherogenic dyslipidaemia associated with diabetes makes nicotinic acid appear a logical choice for correcting these abnormalities but its use has been avoided in patients with diabetes, due to reports of hyperglycaemia with immediate-release nicotinic acid.[46]

Recent data show that modified-release nicotinic acid can be safely used in patients with controlled type 2 diabetes. In the Assessment of Diabetes control and Evaluation of the Efficacy of Niaspan Trial (ADVENT),[21] 148 patients with type 2 diabetes (fasting blood glucose ≤ 200 mg/dL, glycated haemoglobin [HbA_{1C}] ≤ 9%) and dyslipidaemia, were treated with modified-release nicotinic acid (1–1.5 g daily). There was a dose-related increase in HDL-C at both doses (19% and 24%, respectively) and decrease in triglycerides (13% and 28%). An initial rise in fasting blood glucose levels occurred in both nicotinic acid-treated groups but there were no significant differences after four months treatment relative to placebo. Effects on glycaemic control were manageable by adjusting the dose of antiglycaemic medication. Additionally, data from the Coronary Drug Project,[47] showed that reductions in non-fatal MI and total mortality were unaffected by baseline fasting or one-hour blood glucose. Patients with the highest fasting blood glucose (≥ 126 mg/dL) derived the greatest benefit in terms of reduction in the incidence of non-fatal MI compared with placebo (58%).

Safety and tolerability

Modified-release nicotinic acid was generally well tolerated in clinical trials. Although flushing was the most common side effect, occurring in 88% of patients in placebo-controlled clinical studies (Kos Pharmaceuticals, data on file), the severity and frequency of this event was substantially lower than with immediate-release nicotinic acid. Moreover, data from a long-term treatment study[31] showed that the frequency of flushing decreased progressively with continued treatment. In this study, an average of 3.3 flushing episodes occurred during the first month on treatment compared with less than one episode per month by week 48 (figure 4). Taking the dose at bedtime with a low-fat snack, avoiding hot drinks, spicy food and alcohol prior to dosing and taking aspirin or a non-steroidal anti-inflammatory agent helps to minimise the frequency and severity of flushing. Obviously the last of these could not be recommended for long-term administration in the absence of other indications.

In a long-term study, less than 1% of patients treated with modified-release nicotinic acid discontinued treatment due to asymptomatic elevation in hepatic transaminases of more than three-fold the upper limit of the laboratory reference range (Data on file, Kos Pharmaceuticals). Reports from studies involving treatment with modified-release nicotinic acid and lovastatin showed no evidence of drug-related myopathy (defined as myalgia and elevated creatine kinase > 10-fold the upper limit of the reference range) or hepatotoxicity, although this had been a concern with combination therapy involving statins.[41,43] In fact, this problem largely concerns combination therapy with the atypical fibrate gemfibrozil.[42,49]

Treatment with nicotinic acid, either modified-release or immediate-release formulations, has been associated with hyperuricaemia,[19] so it should be used with caution in patients with gout, pre-existing hyperuricaemia or those receiving other treatments that might increase serum uric acid levels.

Conclusions

Data from epidemiological and interventional studies have confirmed the importance of HDL-C as an independent risk factor for cardiovascular disease. Although statin therapy is effective in reducing LDL-C and has more modest effects on hypertriglyceridaemia, it has limited efficacy in increasing HDL-C. Up to 40% of patients fail to achieve the lipid targets set in current guidelines.[8,9]

Nicotinic acid is the most potent available agent for raising HDL-C, increasing levels by as much as 30%, and is also effective in reducing LDL-C, triglycerides and, uniquely, Lp(a). Modified-release nicotinic acid has equivalent efficacy to immediate-release nicotinic acid but with an improved tolerability profile, in particular a lower incidence of flushing. In contrast to the experience with earlier modified-release formulations, changes in liver enzymes occurred rarely.

Treatment with modified-release nicotinic acid therapy is therefore a useful treatment option in patients with mixed dyslipidaemia and, possibly, in patients with very low HDL-C levels and otherwise normal lipid profiles. The combination of modified-release nicotinic acid/statin therapy has been shown to have complementary lipid-modulating effects, and is safe and effective even in patients with diabetic dyslipidaemia, despite earlier

Key messages

- Epidemiological and intervention studies have established that HDL-C is an independent risk factor for CHD. The benefit associated with increasing low HDL-C is comparable with that observed with decreasing LDL-C in the major statin trials
- A substantial proportion of patients with CHD have normal or moderately elevated levels of LDL-C but low HDL-C, often with hypertriglyceridaemia. Therapy targeting these abnormalities is appropriate in these patients
- Nicotinic acid is the most potent available agent for increasing HDL-C and has important effects on other lipid components, including a reduction of LDL-C and triglycerides
- A modified-release nicotinic acid with improved tolerability compared with earlier formulations has been shown to be safe while increasing HDL-C by as much as 30%. Modified-release nicotinic acid has been shown to be an appropriate treatment for dyslipidaemia associated with type 2 diabetes and the metabolic syndrome
- The combination of modified-release nicotinic acid with a statin offers complementary lipid-modulating effects, and confers regression of atherosclerosis and reduction in the incidence of major coronary events. Combination nicotinic acid/statin therapy represents an important strategy for the clinical management of many patients with an increased CHD risk

concerns about hyperglycaemia. Combination nicotinic acid/statin therapy therefore represents an important advance for the clinical management of patients with dyslipidaemia of several types.

Conflict of interest

Dr Michael Schachter has been a member of a Merck advisory panel dealing with Niaspan®. He has also acted in a similar capacity for Bristol Myers Squibb, AstraZeneca and Schering Plough with respect to lipid-lowering drugs.

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