Reducing residual cardiovascular risk: the relevance of raising high-density lipoprotein cholesterol in patients on cholesterol-lowering treatment

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Abstract

Reducing low-density lipoprotein cholesterol (LDL-C) with statin therapy represents the cornerstone of dyslipidaemia management in patients with cardiovascular disease, as reflected in current treatment guidelines. Yet even among statin-treated patients who achieve LDL-C targets (< 2.59 mmol/L [100 mg/dL]), the residual risk of further cardiovascular events remains unacceptably high. Although clinical studies indicate that intensive LDL-C lowering may provide some additional benefit, this does not suppress the excess cardiovascular risk sufficiently. This European Expert Panel therefore recognises that there is an unmet clinical need in the management of these patients. Additional intervention to modify other clinically important risk factors should be viewed as a priority.

A reduced level of high-density lipoprotein cholesterol (HDL-C) < 1.03 mmol/L (40 mg/dL) in men and < 1.29 mmol/L (50 mg/dL) in women is an important independent predictive factor for coronary heart disease. HDL-C levels are also predictive of cardiovascular risk in statin-treated patients, irrespective of their LDL-C levels. Therefore, HDL-C represents a logical therapeutic target for reducing cardiovascular risk further in statin-treated patients, including those who achieve LDL-C targets. Given that low HDL-C is common among dyslipidaemic patients with cardiovascular disease, a therapeutic strategy aiming at effectively raising HDL-C, while at the same time lowering LDL-C to target levels, would be expected to offer clinical benefit beyond that achieved through LDL-C reduction alone. Although both nicotinic acid and fibrates raise HDL-C, nicotinic acid has greater potency. Studies show that combination therapy with prolonged-release (PR) nicotinic acid and a statin has an acceptable tolerability profile, normalises an atherogenic lipoprotein profile, and is able to induce regression of atherosclerosis and reduce coronary risk in patients with established cardiovascular disease and suboptimal HDL-C levels.

In conclusion, this European Expert Panel recommends that combination therapy with a statin and an HDL-C raising agent, such as PR nicotinic acid, should be considered in these patients, who remain at high residual risk despite achieving target LDL-C levels with statin monotherapy. Ongoing studies are essential to confirm the clinical outcome benefits of this approach.

Introduction

Reduction of low-density lipoprotein cholesterol (LDL-C) with a statin (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor) represents the cornerstone of dyslipidaemia management in patients with established cardiovascular disease (CVD). A meta-analysis including 90,056 subjects in 14 randomised prospective trials conclusively demonstrated the efficacy and tolerability of statins, with a 21% proportional reduction in the incidence of major vascular events per 1.0 mmol/L LDL-C reduction (corresponding to about a 5.4% reduction in risk per 10 mg/dL reduction in LDL-C) during a mean of five years of treatment. However, even among those patients who achieve target LDL-C levels, the residual risk of further cardiovascular
events over the next five years remains high, at 65%–75% of the risk of control groups.4,5 The absolute risk of further cardiovascular events is also high. In the meta-analysis reported by Baigent et al.,4 14.1% of patients treated with a statin – nearly one in six patients – had further or recurrent cardiovascular events over a five-year period. This absolute risk was even higher in patients with pre-existing coronary heart disease (CHD) (21.2% risk) and in patients with high-density lipoprotein cholesterol (HDL-C) levels below 1.0 mmol/L.

### Table 1. Summary of key features and findings of recent intensive LDL-C lowering outcome studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatments</th>
<th>Subjects</th>
<th>Primary endpoint</th>
<th>Key findings</th>
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</thead>
<tbody>
<tr>
<td>PROVE-IT –TIMI 22</td>
<td>Atorvastatin 80 mg/d (n=2,099) vs. pravastatin 40 mg/d (n=2,063)</td>
<td>Patients hospitalised with acute coronary syndrome in last 10 days; baseline mean LDL-C 2.59 mmol/L</td>
<td>Composite of death, MI, documented unstable angina requiring rehospitalisation, stroke, revascularisation</td>
<td>Atorvastatin led to: ↓ 16% RR for primary endpoint, p=0.005 ↓ LDL-C to 1.6 mmol/L</td>
</tr>
<tr>
<td>TNT</td>
<td>Eight-week open-label treatment with atorvastatin 10 mg/d, then randomisation to atorvastatin 80 mg/d (n=4,995) vs. atorvastatin 10 mg/d (n=5,006)</td>
<td>Median follow-up 4.9 years</td>
<td>Patients with CHD and LDL-C &lt; 3.4 mmol/L</td>
<td>Atorvastatin 80 mg/d led to: ↓ 22% RR for primary endpoint, p&lt;0.001 ↓ 20% RR for major coronary events, p=0.002 ↓ LDL-C to 2.0 mmol/L</td>
</tr>
<tr>
<td>IDEAL</td>
<td>Atorvastatin 80 mg/d (n=4,439) vs. simvastatin 20 mg/d (n=4,449)</td>
<td>Median follow-up 4.8 years</td>
<td>Patients with prior MI and mean LDL-C 3.1 mmol/L</td>
<td>Atorvastatin 80 mg/d led to: ↓ 11% RR for primary endpoint, NS ↓ 13% RR for major cardiovascular events (defined as in TNT), p=0.02 ↓ LDL-C to 2.1 mmol/L</td>
</tr>
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</table>

**Key:** PROVE-IT TIMI 22 = Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22; TNT = Treating to New Targets; IDEAL = Incremental Decrease in Endpoints Through Aggressive Lipid Lowering; MI = myocardial infarction; CHD = coronary heart disease; LDL-C = low-density lipoprotein cholesterol; RR = relative risk; NS = not significant.
lipoprotein cholesterol (HDL-C) levels < 0.9 mmol/L (18.2% risk). Changes in dyslipidaemia management strategies are urgently needed to suppress or reduce this residual excess cardiovascular risk.

**Does further LDL-C reduction produce additional benefit?**

One approach has involved intensive LDL-C lowering, as investigated in the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction (PROVE IT-TIMI 22) study, the Treating to New Targets' (TNT) study, and the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering (IDEAL) study. 8 These studies demonstrated that intensive LDL-C lowering to either < 2.1 mmol/L (80 mg/dL) (TNT, IDEAL) 8 or < 1.8 mmol/L (70 mg/dL) (PROVE-IT TIMI 22) was associated with some additional clinical benefit compared with statin therapy at standard doses (table 1). However, there was also an increased risk of elevated liver transaminases (> three times the upper limit of the normal range) in patients treated with intensive compared with conventional statin therapy, which ranged from three-fold in PROVE-IT TIMI 22 (3.3% vs. 1.1%) to ten-fold in IDEAL (0.41% vs. 0.04% for aspartate transaminase and 0.97% vs. 0.11% for alanine transaminase). 8

Moreover, the residual risk of further events among patients who received high-dose statin therapy remained high over the follow-up period of 3–5 years. 6,8 In the IDEAL study, treatment with atorvastatin 80 mg daily resulted in a five-year cumulative major coronary event rate of 9.3%, which was substantially higher than that reported by Baigent et al. 4 in untreated patients without established CHD (6.1%) (figure 1). In addition, the PROVE-IT TIMI 22 study showed that one in five patients with a history of acute coronary syndromes died within 30 months. 8

Most of the reduction in LDL-C levels is achieved at conventional statin doses. 9,10,12 The Statin Therapy for Elevated Lipid Levels compared Across doses to Rosuvastatin (STELAR) study compared the lipid-modifying effects of the recommended dose ranges for rosvastatin, atorvastatin, simvastatin and pravastatin. At the lowest clinically recommended doses, LDL-C reduction was 72–98% of that achieved at the highest doses. Increasing the dose of the statin (simvastatin or atorvastatin) from 40 mg to 80 mg only provided an additional 3–7% reduction in LDL-C. 10

**Do statins reduce other CHD risk factors?**

Statins have pleiotropic actions that may contribute to a reduction in cardiovascular risk, although this is difficult to demonstrate, based on clinical trial results. Statins reduce levels of C-reactive protein (CRP), an inflammatory mediator that has been shown to play a key role in the progression of atherosclerosis. 13 However, statin therapy has limited effects on other non- lipid inflammatory mediators, 11 and only modest effects on critically important lipids, including HDL-C. 7 For example, in the meta-analysis of 14 trials reported by Baigent et al., 7 statin-associated increases in HDL-C at one year ranged between 1% and 6%. Rosuvastatin is more effective in raising HDL-C levels than simvastatin or atorvastatin but even at the highest recommended dose of 40 mg/day it raises HDL-C levels by approximately 15%. 9,10,12

A longitudinal survey of population trends in lipid levels showed that, while statin therapy has significantly reduced levels of total cholesterol and LDL-C, treatment has had no impact on population plasma levels of HDL-C and triglycerides. 11 It is also noteworthy that low HDL-C levels and elevated triglycerides are associated with the metabolic syndrome, which is becoming increasingly prevalent in both developed and developing countries. 11,15

Thus, the available evidence indicates that the current focus on LDL-C lowering in dyslipidaemic patients with established CVD does not sufficiently suppress the residual risk of further events over the next 3–5 years, even among those patients who achieve target, or below target, LDL-C levels. There is a need to re-evaluate dyslipidaemia management beyond statin therapy, with additional intervention to target other important lipids, in an effort to reduce this residual cardiovascular risk.

**Dyslipidaemia is not a single defect**

There is now conclusive evidence that dyslipidaemia is not a single defect. The Apolipoprotein-related Mortality Risk Study (AMORIS), 16 a prospective study in a very large cohort in Sweden, was among the first to highlight the ratio of apolipoprotein B to apolipoprotein A (apoB to apoA) as the strongest risk factor for fatal myocardial infarction (MI). Subsequently INTERHEART, 17 a global case-control study of acute MI involving 52 countries, demonstrated that the imbalance between atherogenic lipids (apoB, indicative of LDL-C levels) and atheroprotective lipids (apoA-I, indicative of HDL-C levels) is the most important risk factor for MI. This finding was applicable to both men and women, and to
younger and older individuals. This single parameter accounted for up to 54% of the overall population-attributable cardiovascular risk. A recent analysis of the AMORIS study has extended the predictive value of the ApoB/ApoA-I ratio to the risk of fatal stroke. In contrast, LDL-C alone has not been consistently associated with increased risk of stroke.

Epidemiological studies such as the Framingham Study and the Prospective Cardiovascular Münster (PROCAM) study have established that a low level of HDL-C (< 1.03 mmol/L [40 mg/dL] in men and < 1.29 mmol/L [50 mg/dL] in women) constitutes a predictive and independent risk factor for CHD. In the PROCAM study many subjects also had elevated triglycerides. Meta-analysis of four large prospective studies (the Framingham Study, Lipid Research Clinics Prevalence Mortality Follow-up Study, Coronary Primary Prevention Trial and Multiple Risk Factor Intervention Trial) consistently showed that for every 0.026 mmol/L (1 mg/dL) decrease in plasma levels of HDL-C there was a 2–3% increase in the risk of CHD; this was independent of other risk factors, including plasma LDL-C. However, as numerous lifestyle factors which are common in the population (such as smoking, physical inactivity and obesity) also adversely affect HDL-C, the possibility cannot be discounted that low HDL-C may reflect poor lifestyle.

By comparison, evidence indicates that every 0.026 mmol/L (1 mg/dL) increase in LDL-C appears to increase the risk of CVD by 1%. Most recently, in a primary care follow-up study in patients with and without CVD, many of them with diabetes and the metabolic syndrome, who were recruited following lipid sampling where LDL-C did not predict future risk, a 0.26 mmol/L (10 mg/dL) increase in HDL-C was associated with an 11% reduction in CHD events.

Why may raising HDL-C be the most important next step in reducing cardiovascular risk?

Findings from INTERHEART imply that, even in patients with low LDL-C levels, if the level of HDL-C is not sufficiently high there remains an increased risk of further progression of atherosclerosis and further clinical events. This can be explained on the basis of an imbalance between deposition and removal of cholesterol in the arterial wall. Atherogenic cholesterol-rich lipoproteins containing apoB100 (very low-density lipoproteins [VLDL], VLDL remnants, intermediate-density lipoproteins [IDL] and LDL) penetrate the arterial wall at sites of endothelial dysfunction, and if plasma concentrations exceed a threshold level, they accumulate and undergo modification, including oxidation. Oxidised LDLs promote a cascade of atherogenic and pro-inflammatory events that favour development of atherosclerotic plaque, with cholesterol accumulation and formation of macrophage foam cells.

In contrast, HDL exerts several vasculoprotective, anti-inflammatory, and thus anti-atherosclerotic, actions (figure 2). In addition, and most importantly, HDL facilitates efflux of cellular cholesterol from macrophage foam cells and peripheral tissues, which is then transported to the liver for recycling or elimination from the body in the process of reverse cholesterol transport. After transfer to HDL in the extracellular space, cholesterol is delivered to the liver either directly, in a process involving binding of HDL to scavenger receptors, or indirectly, via the lipoprotein lipase pathway. This results in the cholesterol being converted to bile acids and eliminated from the body via the gut. Further, HDL facilitates reverse cholesterol transport from the liver to the liver by the production of lipoprotein lipase, which hydrolyses triglycerides to fatty acids and monoglycerides, which are then re-esterified by the liver and used to form VLDL, which is then secreted into the circulation. This process is repeated several times, such that HDL ultimately delivers cholesterol to the liver for elimination as bile acids.

Figure 2. Anti-atherogenic activities exerted by HDL. Adapted with permission from Nofer et al.
receptor B1 (SR-B1), or via an indirect pathway involving cholesterol ester transfer protein (CETP)-mediated transfer of HDL cholesteryl esters to the VLDL/LDL fraction, and subsequent receptor-mediated uptake of LDL. Raising HDL promotes the efflux of cholesterol from foam cells, thereby inhibiting progression (or even promoting regression) of atherosclerosis, and in turn reducing cardiovascular risk. HDL also has other important actions that contribute to reduction in risk, including inhibition of the oxidative modification of atherogenic lipoproteins, vascular inflammation and thrombosis, and endothelium-stabilising effects.

Clinical evidence supports this rationale. A study involving 60 patients with a history of coronary atherosclerosis demonstrated a significant direct linear correlation between levels of LDL-C and progression of atherosclerosis (p < 0.0001) but a significant inverse relationship between HDL-C levels and plaque progression (p < 0.02). These correlations remained significant when only those patients taking statin therapy were evaluated. The increase in plaque cross-sectional area correlated with established cardiovascular risk scores and with an increased frequency of cardiovascular events. Findings from a small study in patients with acute coronary syndromes further support the atheroprotective effects of raising HDL-C. Here, weekly infusion for five weeks with recombinant lipoproteins of apoA-I Milano (a variant of apoAI) complexed with phospholipid produced significant and rapid regression (by 4.2%) of the atheroma burden in the coronary arteries, as assessed by intravascular ultrasound imaging. Follow-up data from the Tromsø study, a large population-based prospective study, also showed that high levels of HDL-C were associated with reduced plaque growth in subjects with pre-existing carotid atherosclerosis.

The atheroprotective potential of raising HDL-C levels seems to translate into improved clinical outcome in patients with CVD, as demonstrated by major studies and reviewed in a recent consensus paper. In the Coronary Drug Project, which involved 8,341 men with previous MI treatment with nicotinic acid for six years reduced the incidence of non-fatal MI by 26% and cerebrovascular events by 24% compared with placebo. Follow-up nine years after the end of the study demonstrated a significant 11% reduction in mortality compared with placebo (p < 0.001).

Subsequently, the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT), involving 2,531 men with known CHD, low HDL-C (mean baseline HDL-C 0.83 mmol/L [32 mg/dL]) and moderate LDL-C levels (mean baseline LDL-C 2.87 mmol/L [111 mg/dL]), demonstrated the benefit of increasing HDL-C (and reducing triglycerides) in reducing coronary risk. After one year, gemfibrozil treatment led to a 6% increase in HDL-C levels and a 31% decrease in fasting triglyceride levels compared with placebo, with no appreciable change in LDL-C levels. Lipid changes remained globally unchanged during the entire study duration. After a median follow-up of 5.1 years, gemfibrozil treatment produced significant reductions in the primary combined endpoint of CHD death or non-fatal MI (by 22%), non-fatal MI alone (by 22%) and stroke (by 27%), as well as a 22% reduction in CHD mortality. Subsequent analysis of the relationship between on-treatment lipid values and outcome in VA-HIT showed that the increase in HDL-C was the only treatment effect shown to correlate significantly with reduction in CHD risk.

Is low HDL-C a frequent component of the residual cardiovascular risk in statin-treated patients?

Low HDL-C is a common finding in patients with CVD. In the third National Health and Nutrition Examination Survey (NHANES) in the USA, low HDL-C was reported in 35% of men (< 1.03 mmol/L [40 mg/dL]) and 39% of women (< 1.29 mmol/L [50 mg/dL]). The prevalence of low HDL-C may be even higher in some Asian populations, affecting up to 65–70% of individuals in the Philippines and Asian Indian women. However, the extent to which low HDL-C in certain populations is genetic or environmental in origin is at present unknown. More recently, a pan-European survey involving 8,545 patients on lipid-modifying therapy (85% on statins) demonstrated a prevalence of low HDL-C (using the same criteria specified above) of 33% in men and 40% in women (figure 3). Very low levels of HDL-C (< 0.90 mmol/L [35 mg/dL]) occurred in 14% of patients treated with lipid-modifying therapy.

New data demonstrate that low HDL-C levels are predictive of cardiovascular risk in statin-treated patients. Analysis by Baigent et al. of 14 statin studies showed that patients with a low level of HDL-C (0.9 mmol/L [35 mg/dL]) had up to 60% higher risk of further cardiovascular events than patients with higher HDL-C levels (> 1.1 mmol/L [42.5 mg/dL]) (figure 4). Statin treatment did not affect this excess risk.

Furthermore, data from a population-based cohort study showed that, among patients taking lipid-lowering treatment who had not been hospitalised previously for CVD, an increase in HDL-C independently predicted reduced cardiovascular risk.

These data indicate that HDL-C levels are an important consideration in dyslipidaemic patients with CVD, even those intensively managed with high-dose statin therapy, and raising
suboptimal HDL-C levels in these patients could be expected to provide additional clinical benefit.

In the recently reported study – A Study To Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID) – an open-label, single-arm, blinded endpoint study, treatment with rosuvastatin (40 mg/day) for two years reduced LDL-C levels by 53% and raised HDL-C levels by 14.7% in patients who had undergone coronary angiography and had evidence of coronary artery disease. These lipid changes were associated with a modest but significant reduction in total atheroma volume (6.8% median reduction; median change -12.5 mm³ [95% CI -15.1 to -10.5 mm³], p<0.001), as assessed by intravascular ultrasound imaging. Unfortunately, this study did not include a control group.

By comparison, in the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study, which had virtually the same design as the ASTEROID study except that it did include a comparative group, treatment with atorvastatin 80 mg/day for 18 months was associated with a similar magnitude of reduction in LDL-C levels (by 46.3%), but only a minimal rise in HDL-C (2.9% vs. 5.6% in the group receiving pravastatin 40 mg/day). The median relative baseline to total atheroma volume of 0.4% with atorvastatin was not statistically significant, although it compared favourably with an increase of 2.7% observed with pravastatin therapy, p=0.02. These studies raise the question of what threshold level is required for HDL-C raising (relative to LDL-C) in order to induce significant plaque regression.

Clinical impact of combination therapy
A therapeutic strategy aimed at raising HDL-C while lowering LDL-C with a statin, thus favourably affecting cholesterol metabolism at the arterial wall and leading to plaque regression and improved clinical outcome, might be desirable. This concept was explored in studies before the advent of statins. In the Stockholm Ischaemic Heart Disease Secondary Prevention Study involving 555 patients, treatment with a combination of gemfibrozil and nicotinic acid achieved cholesterol and triglyceride reductions of 13% and 19%, respectively, and showed a 36% CHD mortality reduction (p<0.01). More recently, the Air Force Regression Study (AFREGS) showed that raising HDL-C by 35% using a combination of nicotinic acid and gemfibrozil, allied with LDL-C lowering by 21% with a bile acid sequestrant, reduced progression of atherosclerosis in 143 patients and was associated with a (non-significant) 50% reduction in CHD events. However, there was still a need to show benefit for nicotinic acid on top of statin therapy as statins are first-line therapy for CVD. Some analyses have suggested that patients with lower HDL-C levels benefit more in absolute terms in the statin trials; others have suggested that the benefits of statin therapy are independent of HDL-C.

Recent studies such as the HDL-Atherosclerosis Treatment Study (HATS) and the Arterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol study (ARBITER) have investigated the clinical value of this strategy. HATS...
evaluated the impact of treatment with the combination of nicotinic acid (mean dose 2.4±2.0 g/day) and simvastatin (mean dose 13±6 mg/day) for three years in 160 patients with CHD and low levels of HDL-C (<35 mg/dL [0.91 mmol/L] in men and <40 mg/dL [1.03 mmol/L] in women). Combination therapy produced up to 90% reduction in major cardiovascular events compared with placebo (figure 5) although it should be noted that, because of the relatively small number of patients included, the 95% confidence intervals are wide.46 There was significant angiographic regression of stenosis by 0.4% on average (vs. baseline) with combination therapy, compared with progression of 3.9% on placebo (figure 5).

Subsequently, ARBITER 2 demonstrated the benefits of combining prolonged-release (PR) nicotinic acid (final dose 1,000 mg/day) and a statin (mean dose 37 mg/day) compared with a statin alone in 167 patients with known CHD and mean baseline lipid levels of 2.3 mmol/L (89 mg/dL) for LDL-C, 1.03 mmol/L (40 mg/dL) for HDL-C and 1.84 mmol/L (161 mg/dL) for triglycerides.47 The primary endpoint in ARBITER 2 was the change in carotid intima-media thickness (CIMT), as assessed by B-mode ultrasonography, a recognised and valid surrogate cardiovascular endpoint.47

After 12 months, treatment with combination therapy led to a 21% increase in HDL-C (together with a 13% decrease in triglycerides), and these lipid changes were associated with a lack of progression of CIMT. By contrast, patients treated with a statin alone had no change in CIMT and a 5% decrease in triglycerides, associated with a statistically significant increase in mean CIMT (p<0.001), indicative of progression of atherosclerosis.48 Although ARBITER 2 was not powered to evaluate clinical outcomes, the frequency of clinical cardiovascular events tended to be higher among patients treated with statin alone compared with those treated with the combination therapy (9.6% vs. 3.8%, p=0.20).48

In an open-label extension study (ARBITER 3),49 130 patients who completed ARBITER 2 either continued on or were switched to the combination therapy for a further 12 months. Treatment with combination therapy for 12 to 24 months was associated with a 23% increase in HDL-C (by 0.24 mmol/L [9.3 mg/dL], p<0.001). Furthermore, continued treatment with this combination therapy induced regression of atherosclerosis, as measured by a significant decrease in CIMT from baseline to 12 or 24 months (for those patients who were switched from placebo to combination therapy or those who continued on combination therapy after ARBITER 2, respectively) (figure 6).48

**What pharmacological options are currently available for raising HDL-C in combination with a statin?**

Non-pharmacological approaches, including stopping smoking, losing weight, moderate alcohol consumption and exercise, have all been shown to have a beneficial effect on raising HDL-C levels in patients with or at risk of premature CHD and with a low level of HDL-C.49-51 Moderate weight loss (by 5–10%) combined with exercise significantly decreases triglycerides and increases HDL-C levels, and improves cardiovascular risk factors.52 There is also some clinical trial evidence to support a role for omega-3 polyunsaturated fatty acids.53 Although such lifestyle interventions are important, the majority of patients will also require pharmacological treatment in order to approach HDL-C levels that are associated with low risk.

Realistically, in order to achieve target HDL-C levels in most statin-treated patients with CVD and suboptimal HDL-C levels, pharmacological agents capable of raising HDL-C by 20–30% are required. Currently available therapeutic options for raising HDL-C include fibrates (peroxisome proliferator-activated receptor [PPARα agonists) and nicotinic acid (table 2). Is there any evidence that the combination of either of these agents with a statin can provide further clinical benefit in this patient group?

### Fibrates

Fibrates typically increase levels of HDL-C by 5–15%,54 while reducing plasma triglycerides by 30–50% and LDL-C by up to 15–20%, depending on the underlying lipid abnormality and baseline lipid phenotype.55,56 Recent meta-analysis including data from 53 trials using fibrates reported a mean increase in HDL-C of 10% and reduction in triglycerides and LDL-C of 36% and 8%, respectively.57 Evidence is accumulating that demonstrates the effects of combination fibrate/statin therapy on the lipoprotein profile,58-61 but there are as yet no large prospective studies eval-

### Table 2. Currently licensed therapeutic options for raising high-density lipoprotein cholesterol (HDL-C)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Increase in HDL-C (%) at clinically recommended doses</th>
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</thead>
<tbody>
<tr>
<td>Fibrates</td>
<td>10–15%,54 mean 10%57</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>mean 16%57</td>
</tr>
<tr>
<td>Prolonged-release nicotinic acid</td>
<td>26%48</td>
</tr>
</tbody>
</table>

* First 12 months’ treatment either in ARBITER 2 or ARBITER 3

**Figure 6. Regression of atherosclerosis, as measured by the change in carotid intima-media thickness (CIMT), after 12 or 24 months of combination treatment with prolonged-release nicotinic acid and statin. Data derived from Taylor et al.46 and Taylor et al.49**
ultating the impact of this combination on clinical outcome. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study\textsuperscript{62} was specifically designed to evaluate the effect of fenofibrate monotherapy in 9,795 patients with type 2 diabetes, recruited in both primary and secondary prevention settings. There was significant drop-in statin use in both placebo and fenofibrate treatment arms during the study, although this was more marked in the placebo group (17\% vs. 8\%).\textsuperscript{62} The decision to initiate statin therapy was not prospectively defined but instead was based on the individual investigator's clinical judgement. As a result, data relating to combination fenofibrate/statin therapy come from a selected subgroup of the study population.

In FIELD, the increase in HDL-C observed with fenofibrate therapy was substantially smaller than anticipated. At four months, treatment with fenofibrate led to reductions in plasma LDL-C (by 12\%) and triglyceride concentrations (by 29\%), but only a 5\% increase in HDL-C, relative to placebo. Further, the difference in HDL-C levels between the two groups lessened over time: at the end of the five-year follow-up period, fenofibrate treatment was associated with only a 2\% increase in HDL-C levels, relative to placebo.\textsuperscript{62} The finding of a relatively rapid loss of HDL-C-raising activity with fenofibrate over time in FIELD contradicts clinical experience and is discordant with findings from other studies with prolonged fenofibrate administration, during which increases in HDL-C were well maintained over time.\textsuperscript{63,64} It is possible that the low incidence of mixed dyslipidaemia in type 2 diabetes patients in this study (only 38\% of patients had both low HDL-C and elevated triglycerides)\textsuperscript{62} may have been a confounding factor.

FIELD failed to demonstrate a significant treatment effect with fenofibrate on the primary endpoint of first non-fatal MI or CHD death (reduction by 11\%, p=0.76), although there was significant reduction in the secondary endpoint of total cardiovascular events (reduction by 10\%, p=0.032).\textsuperscript{62} There was a trend for greater cardiovascular benefit in the subgroup of patients with low HDL-C (< 1.03 mmol/L [40 mg/dL]) in men and < 1.29 mmol/L [100 mg/dL] in women, providing further support for the importance of raising HDL-C in improving outcome.\textsuperscript{33,67} Subgroup analyses showed that significant treatment benefits on clinical outcome were solely confined to the primary prevention group (78\% of the study population).\textsuperscript{62} The findings of FIELD do not definitively prove a role for fenofibrate (either as monotherapy or in combination with a statin) in significantly reducing coronary risk in patients with type 2 diabetes at high risk or with established CVD.\textsuperscript{60}

Outcome data are awaited from the ongoing Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, to determine whether the use of fibrate/statin combination therapy produces greater coronary benefit than either agent used alone. This randomised, multicentre study is designed to test three medical strategies independently (intensive glycaemia and blood pressure, as well as combination fibrate plus statin therapy vs. statin monotherapy) in 10,000 patients with type 2 diabetes and a history of clinical CVD or at high risk for cardiovascular events. The primary study endpoint is first occurrence of a major cardiovascular event (non-fatal MI, non-fatal stroke or cardiovascular death) after randomisation.\textsuperscript{66}

![Figure 7. Changes in lipoprotein levels after 16 weeks' treatment with combination therapy with prolonged-release nicotinic acid and lovastatin, or monotherapy with atorvastatin or simvastatin. Data from Bays et al.\textsuperscript{76}](image)

**Nicotinic acid**

Nicotinic acid is the most potent agent currently available for raising HDL-C.\textsuperscript{33,67} A PR formulation has been developed to obviate the problems with hepatotoxicity associated with sustained-release nicotinic acid and to reduce the vasodilatory flushing associated with immediate-release nicotinic acid.\textsuperscript{65} Increases in HDL-C of up to 26\%, and decreases of LDL-C and triglycerides of up to 16\% and 35\%, respectively, have been reported in dyslipidaemic patients treated with clinically recommended doses of PR nicotinic acid (1,000–2,000 mg/day).\textsuperscript{75-79} The pharmacology, efficacy and tolerability of nicotinic acid have been reviewed extensively in recent publications.\textsuperscript{33,67,71}

Flushing, the main side effect of therapy, occurs significantly less frequently with PR nicotinic acid than with immediate-release nicotinic acid.\textsuperscript{71} Also, tolerance to flushing does develop over time.\textsuperscript{71} It has been proposed that combination with other agents may minimise flushing; this is the subject of ongoing investigations such as the Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) study.\textsuperscript{72} Extensive data from clinical trials and post-marketing safety surveillance indicate a very low incidence (< 1\%) of elevated liver function enzymes with PR nicotinic acid, when given either alone or in combination with a statin\textsuperscript{73} and no increase in the incidence of myopathy (when used in combination with a statin) compared with statin therapy alone.\textsuperscript{74}

Expert consensus clearly supports a role for raising HDL-C with nicotinic acid in order to reduce cardiovascular risk.\textsuperscript{71} Clinical studies\textsuperscript{75-79} have demonstrated that the combination of nicotinic acid and a statin markedly improves an atherogenic lipoprotein profile. In one long-term study involving 814 patients with dyslipidaemia, treatment with the combination of PR nicotinic acid (2,000 mg/day) and lovastatin (40 mg/day) for up to 52 weeks increased HDL-C by 41\%, and...
Table 3. Summary of the AIM-HIGH study

- Multicentre, randomised, double-blind, parallel-group comparison of PR nicotinic acid + simvastatin vs. simvastatin
- Men and women ≥ 45 years with documented vascular disease (coronary artery disease, cerebrovascular or carotid disease or symptomatic peripheral arterial disease) AND atherogenic dyslipidaemia, defined as LDL-C < 4.14 mmol/L (160 mg/dL), HDL-C < 1.03 mmol/L (40 mg/dL) in men and < 1.29 mmol/L (50 mg/dL) in women, and triglycerides > 1.7 mmol/L (150 mg/dL) AND < 4.5 mmol/L (400 mg/dL)
- Estimated recruitment of 3,300 subjects
- Study duration six years
- Primary endpoint: composite of cardiovascular death, non-fatal MI, non-haemorrhagic stroke and hospitalisation for high-risk acute coronary syndrome with objective evidence of ischaemia (troponin-positive or ST-segment deviation)
- Secondary endpoint: cardiovascular death, non-fatal MI and non-haemorrhagic stroke

Key: PR = Prolonged-release; AIM-HIGH = Atherothrombosis Intervention in Metabolic Syndrome with low HDL-C/High Triglyceride and Impact on Global Health Outcomes; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; MI = myocardial infarction

Future options

Future alternative approaches to raising HDL-C levels may include the CETP inhibitors: torcetrapib and JTT-704 are probably the most advanced in development. Preliminary clinical studies have demonstrated that the CETP inhibitors effectively raise HDL-C, either as monotherapy or in combination with atorvastatin. However, data are required on the effect of CETP inhibition on surrogate endpoints for atherosclerosis, such as CIMT and intravascular ultrasound evaluation of coronary artery disease. The results of major outcome studies involving cardiovascular endpoints will be essential in confirming the efficacy and longer-term safety of these agents. Antagonists of the cannabinoid receptor 1 (such as rimonabant) may have a role in raising HDL-C in patients with metabolic syndrome, although further study of their long-term efficacy and safety, particularly in combination with a statin, is required. Other novel agents currently under investigation include apo A-I mimetics, apo A-I Milano, liver X receptor agonists, farnesoid X receptor agonists and lysosphingolipid mimetics. Of these, apo A-I Milano is most clinically advanced, with encouraging preliminary results. Large-scale trials with appropriate clinical endpoints are awaited.

Conclusion: a call for action

Clearly, reduction of LDL-C levels with statin therapy has an important role in reducing cardiovascular risk, as reflected in current treatment guidelines. However, among dyslipidaemic patients with established CVD who achieve target – or below target – LDL-C levels, statin therapy alone appears to be insufficient in suppressing the high level of residual risk of further cardiovascular events (which remains at 50–75% of that of control groups). Furthermore, absolute cardiovascular risk remains high; nearly one in six patients treated with statin monotherapy experiences further cardiovascular events over a five-year period and one in five patients with a history of acute coronary syndrome who is treated with a statin dies within 30 months.

This unacceptably high cardiovascular risk appears to be driven by the presence of other lipid abnormalities. A low HDL-C level is overwhelmingly established as an important independent predictor of CHD risk and is also predictive of increased cardiovascular risk in statin-treated patients who achieve LDL-C targets. Moreover, low HDL-C is common despite statin treatment. In a Pan-European survey, 33% of men and 40% of women on statin therapy had low HDL-C levels, as defined by current treatment guidelines.

This European Expert Panel recognises that there is an unmet clinical need in the management of dyslipidaemic patients with CVD and suboptimal HDL-C levels. Statin therapy alone, while effective in lowering LDL-C levels, fails to raise HDL-C levels satisfactorily. Therapeutic intervention aimed at raising HDL-C effectively, while at the same time lowering LDL-C to target levels, would be expected to suppress, or at least to reduce significantly, the high residual (and absolute) cardiovascular risk in this patient group.

Therefore, in the opinion of this European Expert Panel:

- Intervention to raise HDL-C, in addition to LDL-C lowering with a statin, should be a priority in the many dyslipidaemic patients with established CVD and suboptimal HDL-C levels.
Clinical evidence shows that a dual strategy aimed at raising HDL-C, in addition to reducing LDL-C to target levels, is able to induce regression of atherosclerosis and to reduce cardiovascular risk.

Of the available options for raising HDL-C, PR nicotinic acid is the most potent agent currently available, increasing HDL-C by about 26% at clinically recommended doses.10 Evidence from clinical trials indicates that the combination of PR nicotinic acid and a statin also has good tolerability.11

In conclusion, this European Expert Panel recommends that combination therapy with a statin and an agent that effectively raises HDL-C, such as PR nicotinic acid, should be considered in patients with established CVD and sub-optimal HDL-C levels, who remain at high residual risk despite achieving target LDL-C levels with statin monotherapy. There is clearly a need for outcome studies to test this hypothesis fully, which is being addressed by the ongoing AIM-HIGH study.

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**References**


