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REVIEW ARTICLE

Beyond the Statins: New Therapeutic Perspectives in Cardiovascular Disease Prevention

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Summary. **Reduction of low-density lipoprotein cholesterol (LDL-C) with statin therapy is currently identified in treatment guidelines as the primary focus for patients with or at risk of coronary heart disease (CHD). Yet despite effective statin therapy there is still an unacceptably high residual coronary risk. A substantial proportion of patients with CHD have mixed dyslipidemia, including low levels of high-density lipoprotein cholesterol (HDL-C), an independent and predictive risk factor for CHD. Although effective in reducing LDL-C, statin therapy has only modest effects in raising HDL-C. Fibrate therapy is an alternative lipid-modifying strategy, and is effective in reducing CHD mortality and morbidity, with the magnitude of clinical benefit similar to statin therapy. Multi-drug therapy with complementary mechanisms of action has been proposed as a means of improving lipid-modifying efficacy. Nicotinic acid is the most potent agent for increasing HDL-C and also substantially reduces LDL-C and triglycerides. Addition of nicotinic acid to statin therapy would be a logical management approach, given the potential for complementary therapeutic benefit. The clinical benefits of this combination are supported by the results of the HDL Atherosclerosis Treatment Study, which showed reduction of 60–90% in the incidence of major coronary events when both agents were administered. In addition, combination treatment led to angiographic regression of stenosis, compared with placebo, rather than slowed progression as previously reported with statin monotherapy. Given that the prevalence of low HDL-C, particularly amongst individuals with CHD, is higher than previously anticipated, combining nicotinic acid and a statin represents an innovative approach to further reducing CHD risk.**

Key Words. **high-density lipoprotein cholesterol, statin, nicotinic acid, combination lipid-modifying therapy**

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (i.e., statins) are well established in the treatment of coronary heart disease (CHD). Extensive evidence from large prospective clinical trials (4S, CARE, LIPID, AFCAPS/TexCAPS, WOSCOPS) [1–5] has shown that the statins are highly effective in reducing the incidence of coronary events and improving survival in patients with or at risk of CHD. Overall, these trials showed that statin therapy reduced the relative risk of coronary events by 24–37% [1–5] as well as reducing all-cause mortality by up to 30% [2,3]. Moreover, statin therapy reduced the risk of coronary events in patients with a prior myocardial infarction (MI) [1,2] or unstable angina [2]. The mechanism of these benefits is attributable to reduction in low-density lipoprotein cholesterol (LDL-C) by statin therapy, resulting in reduced plaque regression and/or stabilization. As a result, current treatment guidelines [6,7] focus on statin therapy for reduction of LDL-C in individuals with CHD.

However, statin therapy does have a number of limitations. Firstly, meta-analysis of combined data from the three pravastatin studies (CARE, LIPID and WOSCOPS) [8] comprising a total of 19,768 patients indicated that there was little evidence of any benefit associated with statin therapy in patients with low LDL-C levels (<125 mg/dL, [3.5 mmol/L]). Further subgroup analysis [9] showed that these patients were more likely to be diabetic and have lower plasma levels of high-density lipoprotein cholesterol (HDL-C) and higher triglyceride levels, both of which are associated with increased risk of CHD, than patients with LDL-C $\geq$ 125 mg/dL. Low HDL-C, in particular, has been conclusively established as a predictive and independent risk factor for CHD, based on data from population studies [10,11] as well as clinical endpoint studies [12,13]. Increasing the statin dose may not provide significant additional benefit in these patients due to the curvilinear dose-response relationship established for the statins [14].

Moreover, retrospective analyses of data from the major statin trials [8,15] showed that the remaining residual coronary risk in patients treated with a statin is significant. Based on data from the CARE [1] and LIPID [2] studies, between 28 and 33 patients would need to be treated with pravastatin for 5 years to prevent one major coronary event (CHD death or nonfatal MI). Data from the Heart Protection Study [16] showed

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that even in patients with low baseline LDL-C levels (<120 mg/dL [3 mmol/L]) treated with statin therapy, the 10-year risk of a further major coronary event remained unacceptably high (about 35%), indicating the need to consider other therapy that goes beyond LDL-C lowering to optimize the management of CHD risk.

Lipid Targets Beyond LDL-C Lowering

A substantial number of patients with CHD exhibit mixed dyslipidemic phenotypes. For example, the results of analyses of samples from 8,500 men with established CHD screened by the Veterans Affairs HDL Intervention Trial Study Group (VA-HIT) [17], showed that while 87% of patients had elevated LDL-C levels, 33% also had hypertriglyceridemia and 64% had low plasma levels of HDL-C. The relatively high prevalence of low HDL-C amongst individuals with CHD is also supported by data from the Framingham Study [18], in which 57% of men who developed CHD had low HDL-C (<40 mg/dL [1.0 mmol/L]). Epidemiological evidence also supports a high prevalence of low HDL-C in the general population, with estimates of 16–18% in men and 4–5% of women [11,19,20].

A low HDL-C (as well as hypertriglyceridemia), together with elevated triglyceride and very low-density lipoprotein levels and a dense LDL phenotype [21], is also common amongst patients with type 2 diabetes (diabetic dyslipidemia) as well as those with the metabolic syndrome. These metabolic diseases predisposes to atherosclerosis and the development of lipid-rich fragile atherosclerotic plaques vulnerable to rupture. For example, in the Prospective Cardiovascular Münster (PROCAM) study [22], diabetic subjects had a two-to-three-fold increased frequency of this lipid profile compared with non-diabetic subjects (see Fig. 1).

Current international guidelines [6,7] now specifically highlight the increased CHD risk associated with each of these conditions; in particular, the Adult Treatment Panel III [6] in collaboration with the International Task Force for Prevention of Coronary Heart Disease [23], regard the presence of diabetes and the metabolic syndrome as CHD risk equivalents.

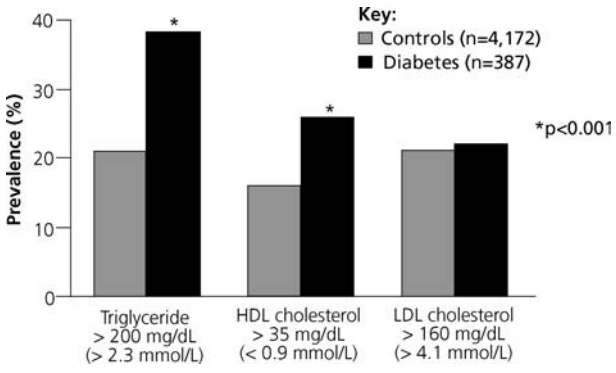

Fig. 1. *Prevalence of lipid abnormalities in diabetic and non-diabetic subjects in the Prospective Cardiovascular Müster (PROCAM) study. Adapted with permission [43].*

Fibrate Therapy as an Alternative Lipid Management Strategy

Taking into account these considerations, fibrate therapy has been advocated as an alternative therapeutic intervention [6,7]. Treatment with a fibrate effectively reduces serum triglycerides by 20–50% and increases HDL-C by 10–15%, as well as reducing LDL-C by 5–20%, and is therefore useful in treating patients with mixed dyslipidemia [24,25]. Angiographic and clinical endpoint studies have shown that fibrate therapy can slow the progression of atherosclerotic disease and reduce CHD morbidity and mortality. In the Lipid Coronary Angiography Trial (LOCAT) [26] in post-coronary bypass men with low HDL-C and LDL-C ≤ 175 mg/dL (4.5 mmol/L), treatment with the fibrate gemfibrozil significantly slowed the rate of change of luminal diameter and resulted in fewer new angiographic lesions compared with placebo. Additionally, the Diabetes Atherosclerosis Intervention Study (DAIS) [27] showed that treatment with fenofibrate 200 mg/day for at least 3 years reduced the angiographic progression of coronary-artery disease in patients with type 2 diabetes, mild lipoprotein abnormalities and at least one visible coronary lesion. Although the trial was not powered to examine clinical endpoints, there were fewer in the fenofibrate group than the placebo group (38 versus 50 events).

The Helsinki Heart Study [12] in 4,081 healthy men with non-HDL-C >200 mg/dL (5.2 mmol/L) showed that treatment with gemfibrozil led to a 11% increase in HDL-C and 43% reduction in triglycerides at 5 years, compared with placebo, and these lipid changes were associated with a 34% reduction in major coronary events, as well as a 26% reduction in coronary mortality. More recently, in the Veterans Affairs HDL Intervention Trial (VA-HIT) [13] in men with CHD, low HDL-C and acceptable levels of LDL-C, treatment with gemfibrozil resulted in 31% reduction in triglycerides and a 6% increase in HDL-C, although LDL-C levels did not change appreciably. These lipid changes were associated with a 22% decrease in the rate of major coronary events. Subsequent multivariate regression analysis showed that the increase in HDL-C was the only treatment effect that predicted clinical benefit [28].

However, even with fibrate therapy there still remains a high level of residual CHD risk. Data from the VA-HIT study showed that the magnitude of the benefit associated with fibrate therapy was similar to that demonstrated for pravastatin therapy in the CARE and LIPID studies. In a population similar to that of the VA-HIT study, 23 patients would need to be treated with gemfibrozil for 5 years to prevent one major coronary event (nonfatal MI or CHD death) [13] (compared

with 28 and 33 patients for the CARE [1] and LIPID studies [2], respectively). As a result, aggressive multidrug therapy has been advocated by current guidelines [6,7] as a means of improving lipid-modifying efficacy and hence patient outcome. Combination therapy with a statin and a fibrate has been shown to be effective, although there are safety concerns, particularly when the fibrate gemfibrozil is used, such as an increased risk of rhabdomyolysis and myopathy, most commonly observed [24]. Moreover, gemfibrozil in association with a statin leads to a significant increase in tissue exposure to the statin, as the pharmacokinetic characteristics of the statin are altered as a result of delayed clearance, with elevation in circulating plasma concentrations and extended half-life [29].

Role of Nicotinic Acid

Alternatively, the addition of nicotinic acid to statin therapy has been suggested [6,7]. Adding nicotinic acid to statin therapy would appear to be a logical choice, given the potential for complementary therapeutic benefit. Nicotinic acid is the most potent agent for increasing HDL-C (by up to 30%) and also has effects on reducing LDL-C [30], as well as attenuating a small LDL phenotype [31]; finally, nicotinic acid markedly reduces triglyceride levels in hypertriglyceridemic phenotypes [30].

Clinical data support the benefit of nicotinic acid therapy for secondary prevention. In the Coronary Drug Project, a long-term study involving 8,341 men with previous MI, treatment with nicotinic acid reduced the incidence of nonfatal MI by 26% and cerebrovascular events by 24% at 6 years compared with placebo [32], and follow-up data at 15 years demonstrated a significant reduction in mortality with nicotinic acid (11% vs. placebo, $p < 0.001$) [33].

The Stockholm Ischemic Heart Disease Secondary Prevention Study [34] investigated combination treatment with nicotinic acid and clofibrate in 555 post-infarct patients. Compared with a control group, combination treatment significantly reduced total and CHD mortality by 26% ($p < 0.05$) and 36% ($p < 0.01$), respectively. Similarly, the Familial Atherosclerosis Treatment Study (FATS) [35] compared combination drug therapy (either nicotinic acid and colestipol, a bile acid sequestrant, or lovastatin or colestipol) plus dietary counseling with conventional therapy (dietary counseling and placebo or use of colestipol) in 120 patients with established CHD and apolipoprotein B levels $\geq$ 125 mg/dL [3.5 mmol/L]. Treatment with nicotinic acid plus colestipol for 2.5 years was associated with a 43% increase in HDL-C and a 32% decrease in LDL-C, compared with only negligible lipid changes in the conventional treatment group, and produced regression in at least 1 of 9 proximal atherosclerotic lesions in a significantly higher proportion of patients compared with conventional treatment (39% vs. 11%, $p < 0.005$). Although the study was not powered to evaluate clinical outcome, a 73% reduction in event rates (death, MI or revascularization for worsening symptoms) was observed.

Combination Lipid-Modifying Therapy

Clinical studies have shown that combining nicotinic acid and a statin is safe and effective. Administration of both nicotinic acid and a statin increased HDL-C by 26% and reduced total cholesterol by 23%, LDL-C by 32%, triglycerides by 30% and lipoprotein (a) by 19% [36], and these improvements in lipid parameters were sustained during long-term treatment [37]. The clinical benefits of combining nicotinic acid and a statin are supported by the results of the HDL Atherosclerosis Treatment Study (HATS) [38]. Patients were treated with both nicotinic acid and simvastatin, either with or without antioxidant vitamins. Treatment with this combination resulted in a 60–90% reduction in the incidence of major coronary events (i.e., death from coronary causes, confirmed MI, stroke or revascularization for worsening symptoms) compared with placebo (see Fig. 2), which compares favorably with reduction in coronary events of 24–37% observed with statin therapy alone [1–5].

Moreover, treatment with both nicotinic acid and simvastatin resulted in significant angiographic regression of stenosis by 0.4% on average, compared with progression of 3.9%, on average, with placebo ($p < 0.001$) (see Fig. 3) [38].

Although HATS did not make a direct comparison of the effects of both treatments with statin monotherapy, the authors concluded that the clinical and angiographic benefits observed with nicotinic acid and statin therapy were greater than those expected from statin therapy alone [38], as demonstrated by the Lipoprotein and Coronary Atherosclerosis Study (LCAS) [39]. In this study, patients treated with fluvastatin alone (20 mg twice daily, with or without cholestyramine), had angiographic evidence of slowed progression of stenosis rather than regression of stenosis, even in patients with low HDL-C [40]. Moreover, data from

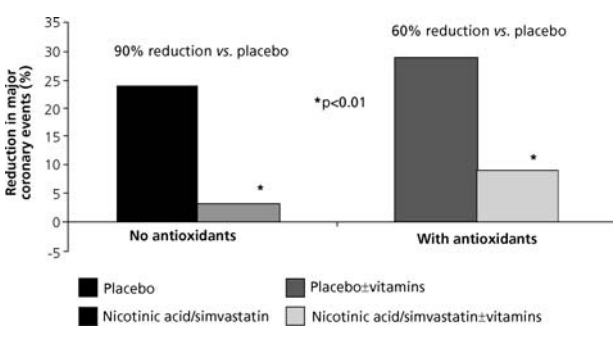

Fig. 2. *Treatment with simvastatin and nicotinic acid reduced the frequency of major coronary events by 60–90%. Data from the HDL Atherosclerosis Treatment Study (HATS) [38].*

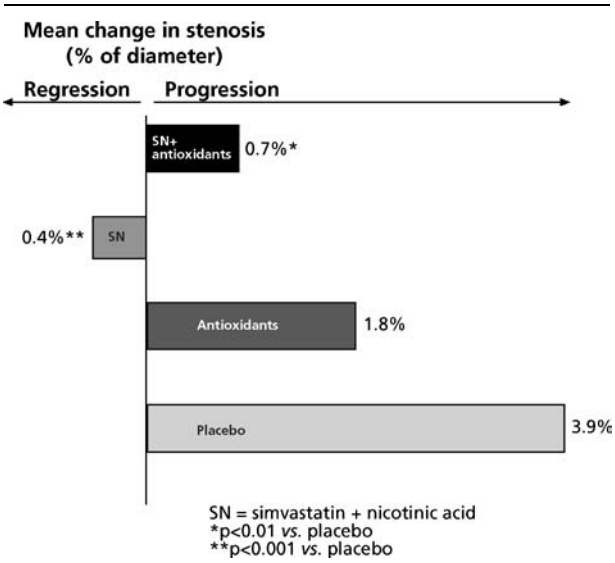

Fig. 3. *Treatment with simvastatin and nicotinic acid resulted in significant angiographic regression of stenosis compared with progression on placebo. Data from the HDL Atherosclerosis Treatment Study (HATS) [38].*

another study [41], showed that although treatment with high-dose lovastatin (40 mg twice daily) was associated with significant reduction in LDL-C levels (by 42%), there was no significant difference between lovastatin-treated and placebo patients with respect to the extent of angiographically-determined stenosis 6 months following coronary angioplasty.

Finally, the results of the recently published Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER 2) study [42] demonstrate the beneficial atheroprotective effect of combination therapy with prolonged-release nicotinic acid and a statin compared with statin therapy alone. After one year of treatment with a moderate dose (1 g/day) of prolonged release nicotinic acid, which raised HDL-C by 21%, progression of atherosclerosis as defined by a change in carotid intima media thickness (CIMT) was significantly reduced and statistically stopped in the group receiving the nicotinic acid combination. Although outcome data are awaited, these preliminary data provide justification for this approach.

Conclusion

Given the relatively high prevalence of mixed dyslipidemia including low HDL-C amongst patients with CHD, multi-drug lipid-modifying therapy may offer a more effective strategy for CHD management. Of the various potential strategies, adding nicotinic acid to primary statin therapy may represent a logical approach to achieving lipid targets set by current international guidelines [6,7], in particular in patients with diabetes and the metabolic syndrome, who are considered at increased CHD risk. This combination offers the advantages of additional clinical benefits via complementary mechanisms of action as well as potential cost-effectiveness. The results of future intervention studies with such a combination in dyslipidemic patients at high risk of premature cardiovascular disease are eagerly awaited.

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