Editorial

Treating low HDL-cholesterol in normocholesterolaemic patients with coronary disease: statins, fibrates or horses for courses?

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This editorial refers to "Effects of pravastatin on coronary events in 2073 patients with low levels of both low-density lipoprotein cholesterol and high-density lipoprotein cholesterol: results from the LIPID study"7 by D. Colquhoun et al. on page 771

A low plasma concentration of high-density lipoprotein (HDL)-cholesterol is a powerful independent risk factor for coronary heart disease (CHD). This notion is supported by consistent evidence from epidemiological, clinical and experimental studies.1 Low plasma HDL-cholesterol is frequently encountered in patients with CHD, either as part of the 'atherogenic-lipid-triad' seen in central obesity or type 2 diabetes,2 or as an isolated lipoprotein abnormality of genetic origin. At present, the expert recommendation is that CHD patients who have appropriately modified their lifestyle and who have an optimal low-density lipoprotein (LDL)-cholesterol (<2.6 mmol/L) and low HDL-cholesterol (<1.05 mmol/L) be treated with HDL modifying pharmacotherapy, such as a fibrate or nicotinic acid.3 In this issue, Colquhoun et al. present a subanalysis from the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study asserting that these patients could equally be treated with a statin,4 a drug usually employed to lower elevated plasma LDL-cholesterol levels.

The LIPID trial is one of the largest secondary prevention trials confirming the cardiovascular benefit of treating CHD patients with a statin, specifically pravastatin 40 mg daily. In the present study, Colquhoun et al. selected a subgroup with plasma lipid entry criteria similar to volunteers in the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT),5 a secondary prevention trial demonstrating the benefits of gemfibrozil (1200 mg/day) on both coronary and cerebrovascular events in CHD patients with normocholesterolaemic dyslipidaemia. Of the original 9014 LIPID subjects, 2073 were accordingly selected with entry LDL-cholesterol <3.6 mmol/L, triglyceride <3.4 mmol/L and HDL <1.0 mmol/L. In this subgroup, the relative risk reduction with pravastatin in the pre-specified primary endpoint (CHD death and non-fatal myocardial infarction) was 27%, with a corresponding absolute risk reduction of 4%. These benefits of pravastatin were associated with a 29% decrease in plasma LDL-cholesterol, a 9% decrease in triglycerides and a 6% increase in HDL-cholesterol. In the VA-HIT, the corresponding relative and absolute risk reductions with gemfibrozil in a similar primary endpoint were 22% and 4.4%, respectively; there was also no change in plasma LDL-cholesterol, but triglycerides fell significantly by 31% and HDL-cholesterol increased by 6%. From these collective data, the authors recommend that pravastatin be considered as first-line therapy in CHD patients with low plasma levels of both HDL and LDL-cholesterol. The study, however, raises several important issues concerning the management of this type of dyslipidaemia in patients with CHD, but first one has to question the validity of the analyses.

The LIPID subgroup analysis component of the study is valid on several grounds.6 Although apparently a post-hoc study, the authors apparently based their analysis on an a priori hypothesis and on a substantial sample size. The magnitude of the treatment effect reported with pravastatin is clinically important, the number needed to treat to prevent a major CHD event over 6 years being 25 patients;4 the results are also biologically plausible and consistent with data from other statin trials. By contrast, the comparison made with
VA-HIT\(^5\) is less justified in that the populations in the two trials are disparate. The LIPID subjects, for example, comprise significantly fewer diabetics, obese subjects and smokers, and their corresponding mean plasma levels of LDL-cholesterol and non-HDL-cholesterol were higher than VA-HIT subjects; also, no women were included in VA-HIT.\(^5\) As discussed later, the differences in the proportion of diabetic and metabolic syndrome subjects between the trials could in particular be of major significance. The higher mean LDL and non-HDL-cholesterol in the LIPID subgroup would also have potentially biased treatment effects in favour of pravastatin. It is noteworthy here that the authors also reported that pravastatin did not decrease CHD events in another subgroup with mean LDL cholesterol more comparable to VA-HIT. To be valid, then, the cardiovascular effects of pravastatin and gemfibrozil in CHD patients with low LDL and HDL-cholesterol should to be compared prospectively within the same population.

These new findings from LIPID are supported by a recent meta-analysis from the Prospective Pravastatin Pooling Project,\(^7\) by the Heart Protection Study (HPS) results,\(^8\) and by the angiographic findings in the Lipoprotein and Coronary Atherosclerosis Study (LCAS),\(^9\) as well as by the Air Force/Texas coronary atherosclerosis prevention study (TexCAPS).\(^10\) The data in HPS with simvastatin and in LCAS with fluviastatin in CHD patients with normal LDL and low HDL-cholesterol points to a class effect of statins in this population. In general, both secondary and primary prevention trials have demonstrated that the efficacy of statin treatment is greatest in subjects at high risk of CHD, including those with low HDL-cholesterol. Similar findings also apply to fibrate trials, although the studies carried out with these agents are significantly fewer in number.

Potential mechanisms explaining the benefits of statins in the reference population could involve reduction in both plasma LDL and remnant lipoproteins, elevation in HDL-cholesterol and pleiotropic actions,\(^11\) including anti-inflammatory, anti-thrombotic and antioxidant effects and improvement in endothelial function. Because of these multiple effects of statins, which to some extent are shared with fibrates,\(^12\) it is impossible to resolve in the present analysis whether raising HDL per se decreases the risk of CHD. It is noteworthy, however, that a previous analysis from the parent LIPID population showed that 80% of the benefit on total coronary events could be explained by an effect of pravastatin on plasma LDL-cholesterol, HDL-cholesterol and triglycerides,\(^13\) indicating a lesser contributory role of pleiotropic mechanisms. Whether this also obtains with the present LIPID investigators. The mechanism for this specific effect of gemfibrozil and other fibrates may be due to activation of peroxisome proliferator-activated receptor-alpha (PPAR-\(\alpha\)), with decreased inflammatory signalling, enhanced fibrinolysis and improvement in endothelial function,\(^12\) as well as an increase in the rate of reverse cholesterol transport not reflected by changes in plasma HDL-cholesterol concentrations.\(^17\) By contrast to fibrate trials, no statin trial has hitherto reported statistically significant cardiovascular benefits in subjects with the metabolic syndrome; this includes a subgroup analysis of 38% of the study population with this disorder in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT).\(^18\) HPS did, however, show that simvastatin significantly decreased the pre-specified coronary endpoint in type 2 diabetic patients with and without CHD.\(^19\) Additional subgroup analyses from the LIPID\(^20\) and Cholesterol and Recurrent Events (CARE)\(^21\) studies have suggested a favourable impact of pravastatin on expanded cardiovascular endpoints (including re-vascularizations) in subjects with diabetes or impaired glucose tolerance, but by contrast to VA-HIT no significant effect has been reported on CHD deaths in these patients. In VA-HIT the absolute risk reduction in the primary endpoint (CHD deaths and non-fatal myocardial infarction) was twofold greater than in statin trials in diabetic patients with low-to-normal LDL-cholesterol levels. Collectively, the implication here is that in metabolic syndrome patients with low HDL and LDL-cholesterol a fibrate may be more appropriate first-line therapy than a statin, thereby qualifying a principal assertion of the LIPID investigators.\(^4\)

In aggregate, this new study from LIPID supports using a statin to treat CHD patients with low HDL-cholesterol and normal-to-low LDL-cholesterol levels. However, if low HDL-cholesterol is a constituent of the metabolic syndrome, and LDL and non-HDL cholesterol are not elevated, a better first option may be a fibrate. Using statin or fibrate monotherapy should fundamentally not be considered as mutually exclusive, however. A more consistent with the positive angiographic results with simvastatin plus niacin in the HDL Atherosclerosis Treatment Study (HATS).\(^14\)

Along with central obesity, hypertriglyceridemia, hypertension and insulin resistance, low HDL-cholesterol is a cardinal feature of the metabolic syndrome,\(^2,3\) which was apparently over-represented in VA-HIT and under-represented in LIPID. A recent subgroup analysis from VA-HIT\(^15\) has shown that in insulin resistant subjects, including type 2 diabetics, gemfibrozil decreased the relative and absolute risk of major cardiovascular events by 28% and 8.4%, respectively; these effects were significantly greater than in insulin sensitive subjects and are supported by data from the Helsinki Heart Study.\(^16\) Intriguingly, in the insulin resistant subjects the benefit was also reported to be independent in changes in plasma lipids and lipoproteins, including increase in plasma HDL-cholesterol. Hence, it appears that in VA-HIT most of the benefits with gemfibrozil\(^15\) were seen in the subgroup with the metabolic syndrome, and LDL and non-HDL cholesterol are not elevated, a better first option may be a fibrate. Using statin or fibrate monotherapy should fundamentally not be considered as mutually exclusive, however. A more
important issue arising from this study is whether there is incremental benefit from adding a fibrate to a statin in the low HDL patient with CHD. This can only be resolved in clinical endpoint trials, but no such trials have hitherto been reported; one currently underway is the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, which is testing the efficacy of adding fenofibrate to simvastatin. However, combination statin-fibrate therapy is being commonly employed in clinical practice, with due attention to minimising and monitoring the risk of myositis. Importantly, fenofibrate is less likely to interact adversely with statins than gemfibrozil. Fish oil supplementation in combination with a statin is another potentially effective and safe option. Any therapy in CHD patients directed at elevating low plasma HDL-cholesterol, whether as an isolated abnormality or as part of the metabolic syndrome, needs to be accompanied by behavioural modifications that include weight loss, avoiding high-carbohydrate intake, increasing physical activity, improving glycaemic control, smoking cessation and reviewing potential aggravating medications (e.g. beta-blockers, progestational agents). All CHD patients with low HDL-cholesterol should also evidently receive intensive management of all cardiovascular risk factors beyond dyslipidaemia.

One difficulty with HDL elevating therapy at present is that there is no exact definition of the optimal plasma HDL-cholesterol level, although there is a consensus that <1.05 mmol/L is undesirable in patients with CHD or CHD equivalents. For the metabolic syndrome and type 2 diabetes a therapeutic target of >1.2 mmol/L, or greater, could be recommended, but this requires verification and endorsement by wider expert bodies. Elevating plasma HDL-cholesterol concentration from a low level to a level >1.2 mmol/L can be difficult with conventional approaches. Nicotinic acid is a powerful HDL raising agent, but clinical experience shows that many patients cannot tolerate it owing to flushing and palpitations, and there may be problems with dysglycaemia and hyperuricaemia; no clinical trials have also been reported in low HDL patients with the metabolic syndrome. New HDL elevating agents, such as cholesteryl-ester transfer protein inhibitors, can substantially increase plasma HDL-cholesterol concentration by up to 60%, but the efficacy of these drugs either as monotherapy or in combination with statins and fibrates require further investigation. Other futurisitic HDL-based therapies include use of small molecules that can increase the expression of HDL apoA-I or upregulate ABCAI transporters in macrophages, or the intravenous delivery of recombinant HDL apoA-I, such as apoAI Milano, a particularly promising approach recently shown to regress coronary atherosclerosis in patients with acute coronary syndromes. As with existing treatments, all these new approaches will need to be formally tested in clinical endpoint trials. Finally, an important theraeutic target for future drug discovery is the enhancement of reverse cholesterol transport irrespective of changes in plasma HDL-cholesterol concentrations, but this innovative concept will also need to be vigorously researched and validated.

References

19. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 20 536 high-risk