

The future of lipid-lowering therapy: the big picture

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ABSTRACT

Several lipid-lowering intervention studies published in 2002 shed light on the current status and the future of cardiovascular risk reduction by drug therapy. The Heart Protection Study has demonstrated that simvastatin reduces heart attack, stroke and revascularisation risk by about one-third irrespective of total cholesterol, LDL cholesterol, patient's age or sex, or the nature of pre-existing cardiovascular disease. Coronary heart disease death and myocardial infarction risk reduction in elderly patients by pravastatin in the PROSPER study was similar to the benefit of statins in middle-aged populations in other studies. The ALLHAT-LLT study has failed to demonstrate a benefit of pravastatin on all-cause mortality, CHD death or nonfatal myocardial infarction, illustrating that too modest cholesterol lowering does not result in clinical benefit under all circumstances.

The cholesterol absorption inhibitor ezetimibe has demonstrated significant LDL and total cholesterol lowering, and induced an additional 21% LDL cholesterol lowering when added to ongoing statin therapy. The cholesteryl ester transfer protein inhibitor JYT-705 produced a dose-dependent increase in HDL cholesterol concentrations of up to 34% and improved the total cholesterol/HDL cholesterol ratio in healthy individuals while having very mild side effects. Cholesterol absorption inhibitors and HDL cholesterol enhancers may become useful tools to achieve further improvements in cardiovascular risk reduction in the future.

INTRODUCTION

Over the past decades, the significance of hypercholesterolaemia for the pathogenesis of coronary heart disease (CHD) and the benefits of cholesterol lowering for CHD risk reduction have been convincingly demonstrated in a range of clinical and epidemiological studies. Many well-controlled, randomised clinical trials with lipid-lowering agents, alone or in combination with other risk-reducing interventions, have demonstrated significant CHD risk reduction in various high-risk populations.

Today, no one questions the value of cholesterol-lowering interventions with respect to cardiovascular risk

reduction in high-risk populations, such as those with manifest coronary heart disease or patients with hypercholesterolaemia and other risk factors without clinical evidence of cardiovascular disease. The question arises, however, whether the current achievements represent an end stage or just a point along the line of evolving cardiovascular risk management. In other words, have we achieved most if not all of the benefits of cholesterol lowering, or is the best still to come? Against the background of this question, five original papers, all published in the course of 2002, have been reviewed in search of clues.

HEART PROTECTION STUDY

The Heart Protection Study (HPS), the largest secondary prevention study in cardiovascular medicine conducted to date, has investigated a number of the remaining questions concerning the value of cholesterol lowering by statin therapy, including cardiovascular risk reduction at different baseline LDL concentrations and in specific subgroups such as older patients, women, and patients with various cardiovascular symptomatology at entry.¹ The HPS randomised 20,536 patients, aged 40 to 80 years, with baseline total cholesterol over 3.5 mmol/l and an increased risk of coronary heart disease (CHD) death due to pre-existing disease, notably myocardial infarction or other coronary artery disease, occlusive disease of noncoronary arteries, diabetes mellitus or treated hypertension. Patients were randomised to receive either 40 mg of simvastatin daily or placebo. The use of a statin was not considered specifically indicated or contraindicated by the patients' own general practitioners. Average follow-up was five years and compliance to simvastatin was 85%. In the placebo group 17% of patients were on a statin, as the use of statins other than simvastatin by these patients was not excluded.

At baseline, 52% of HPS participants were at least 65 years of age, and 28% were 70 years or more. Women constituted one quarter of the study population. Baseline total cholesterol concentrations were below 5.0 mmol/l in 20% of participants and between 5.0 and 6.0 mmol/l in 38%. LDL cholesterol concentrations were below 3.0 mmol/l in 33% of participants and between 3.0 and 3.5 mmol/l in another 25%.

The absolute difference in average LDL concentration during follow-up between simvastatin- and placebo-allocated patients was 1.0 mmol/l, without any relationship to pre-existing total cholesterol or LDL cholesterol level. Also age, sex, or prior disease were not determinants of the LDL cholesterol response to simvastatin. Treatment with simvastatin was associated with a significant 17% overall reduction ($p < 0.0001$) in the risk of any vascular mortality. The risk of death due to coronary vascular causes was 5.7% in the simvastatin group and 6.9% in the placebo group. For death due to other vascular causes, these percentages were 1.9 and 2.2 % respectively. Overall mortality risk was reduced by 13% ($p < 0.0003$) by simvastatin compared with placebo. Among nonvascular causes, neoplastic disease was the most prominent cause of death without any relation to treatment (3.5 and 3.4% on simvastatin and placebo, respectively).

Major vascular events, including coronary events (nonfatal myocardial infarction, coronary death), fatal and nonfatal

stroke, and coronary and noncoronary revascularisation occurred less frequently in patients allocated to simvastatin than in patients receiving a placebo (relative risk: -24%; $p < 0.0001$).

Analyses of the outcomes of the HPS in specific categories of patients have yielded a number of interesting conclusions. The proportional risk reduction by simvastatin in terms of the first major event appeared to be relatively independent of a number of factors, including but not limited to:

- Prior disease: myocardial infarction, other CHD or no prior CHD
- Sex
- Age: <65, 65-70, or ≥ 70 years
- Total cholesterol: <5.0, 5.0-6.0, or ≥ 6.0 mmol/l
- LDL cholesterol: <3.0, 3.0-3.5, or ≥ 3.5 mmol/l
- HDL cholesterol: <0.9, 0.9-1.1, or ≥ 1.1 mmol/l
- Triglycerides: <2.0, 2.0-4.0, or ≥ 4.0 mmol/l

The results of these subanalyses for the factors 'age' and 'sex' are shown in *table 1* and for the factors 'LDL cholesterol' and 'total cholesterol' in *table 2*. The results for the other factors were largely comparable with those for the factors shown in these figures, i.e. no notable effect of any factor on the degree of risk reduction by statin therapy.

Table 1
Rate ratio of major vascular events by age and by sex in the Heart Protection Study¹

BASILINE FEATURE	NUMBER	PERCENTAGE
Age (years)	<65	9839 48%
	65-69	4891 24%
	70-74	4543 22%
	>74	1263 6%
Sex	Male	15454 75%
	Female	5082 25%

Table 2
Rate ratio of major vascular events by LDL and total cholesterol in the Heart Protection Study¹

BASILINE LIPIDS	NUMBER	PERCENTAGE
LDL cholesterol (mmol/l)	<3.0 (116 mg/dl)	6793 33%
	≥ 3.0 -<3.5	5063 25%
	≥ 3.5 (135 mg/dl)	8680 42%
Total cholesterol (mmol/l)	<5.0 (193 mg/dl)	4072 20%
	≥ 5.0 -<6.0	7883 38%
	≥ 6.0 (232 mg/dl)	8581 42%

The main conclusion that can be drawn from the HPS is that simvastatin, after allowance for noncompliance, reduces the risk of heart attack, stroke and revascularisation by one-third. Furthermore, this risk reduction occurs irrespective of total cholesterol or LDL cholesterol levels at entry, the patient's age or sex, or the nature of pre-existing cardiovascular disease. There was no evidence of an increased cancer risk, or any other safety concerns in association with simvastatin treatment. Therefore, the HPS has finally resolved a number of issues that were under debate prior to this study, such as the efficacy of statins in patients with average or below-average cholesterol levels, women and elderly patients. The HPS has also confirmed the safety of statins in a large and demographically diverse population.

However, despite these positive outcomes, it should be kept in mind that the majority of deaths on statin therapy (781/1328 deaths) are still attributable to vascular disease, in particular coronary disease. Also, the risk reduction observed in this study is still far below the effect that should be expected from a long-term difference of 1.0 mmol/l in LDL cholesterol on the basis of epidemiological evidence in people without diagnosed vascular disease.

PROSPER

There have been many debates about the value of cholesterol lowering by statins in truly elderly patients. The HPS has already demonstrated that the benefits of statin therapy extend to patients aged 70 years or more. The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) has specifically investigated the potential benefits and safety of statin therapy in even older patients.^{2,3} The double-blind PROSPER study, conducted in Scotland, Ireland and the Netherlands, enrolled 5804 patients, men and women aged 70 to 82 years (mean: 75 years) with a history of, or risk factors for, vascular disease. Total cholesterol at entry was between 4.0 and 9.0 mmol/l. Patients were randomised to treatment with either pravastatin 40 mg a day or placebo. Average follow-up was 3.2 years. Major cardiovascular events were recorded, as well as general safety, cognitive function and disability.

Pravastatin lowered LDL cholesterol levels by 34% to an average of about 2.5 mmol/l, and total cholesterol levels by 23%. The risk of CHD death, nonfatal myocardial infarction, or fatal or nonfatal stroke (primary endpoint) was reduced by 15% ($p=0.014$) in patients receiving pravastatin. The risk of CHD death or nonfatal myocardial infarction (one of the secondary endpoints) was also significantly reduced by pravastatin (-19%; $p=0.006$), but the risk of fatal or non-fatal stroke was not significantly altered (+3%; $p=0.81$).

CHD mortality was reduced by 24% ($p=0.043$). There were no significant treatment effects on heart failure requiring hospitalisation, revascularisation procedures, cognitive function, disability or all-cause mortality. Pravastatin was safe and well tolerated.

The relative risk reduction of the primary endpoint in the PROSPER study was slightly less than that seen in other statin trials in middle-aged patient populations. It may therefore be concluded that older age is no longer a reason to withhold statin therapy from patients at increased risk of major cardiovascular events. However, the degree of risk reduction on a number of endpoints, including the primary endpoint, was relatively limited just as in the HPS study.

ALLHAT-LLT

The third recently published trial shedding new light on the usefulness of cholesterol lowering by statins is the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT-LLT) in 10,355 patients.^{4,5} This trial was part of the large-scale ALLHAT study in high-risk hypertensive patients in the primary care setting. Eligibility for ALLHAT-LLT was based on LDL cholesterol levels in patients aged over 55 years already enrolled in the main ALLHAT study. ALLHAT-LLT participants were older (average age 66 years), hypertensive, moderately hypercholesterolaemic patients with at least one additional CHD risk factor. Eligible patients were randomised to either pravastatin (40 mg a day) or usual care consisting of measures, at the discretion of the primary care physician, aimed at reducing LDL cholesterol. These measures could include statins or other lipid-lowering drugs. Patients were followed up for an average of 4.8 years.

In the course of the study, the percentage of patients in the pravastatin group who were on a statin decreased from 88% at two years to 83% at six years, while the percentage of statin users in the usual care group increased from 8% at two years to 26% at six years. Total cholesterol and LDL cholesterol levels dropped in both groups in the course of the study. Although the largest drop in cholesterol levels occurred in the pravastatin group, differences between the pravastatin and the usual care group were modest. LDL cholesterol levels in the pravastatin group were reduced by 28% from baseline, whereas the reduction in the usual care group was 11%. Accordingly, differences in cardiovascular endpoints were small and failed to reach statistical significance. The relative risk of all-cause mortality was 0.99 (95% CI: 0.89-1.11). The relative risk of CHD death and nonfatal myocardial infarction was 0.91 (95% CI: 0.79-1.04). Also all-cause mortality risk was not significantly

reduced in any of the subgroups of patients analysed, such as younger patients, older patients, men, women, diabetics, nondiabetics or patients with or without CHD at baseline.

Thus, the ALLHAT-LLT study has failed to demonstrate a benefit on the primary endpoint of all-cause mortality or the key secondary endpoint of CHD death or nonfatal myocardial infarction. Several explanations have been proposed for the lack of benefit from statin treatment, such as the relatively low adherence to pravastatin in the statin group and cross-over to statin therapy in the usual care group. The ALLHAT-LLT study has demonstrated that cholesterol lowering by statins does not result in clinical benefit when LDL cholesterol reduction is too modest. Taken in conjunction with the outcomes of the HSP and PROSPER studies discussed above, the ALLHAT-LLT results make it clear that there is still room for considerable improvement. Several strategies to improve cardiovascular risk reduction by lipid-altering strategies are being pursued and important emerging results will be reviewed briefly below.

EMERGING LIPID-ALTERING STRATEGIES

From the lipid-lowering trials and epidemiological studies conducted thus far, it can be concluded that cardiovascular risk is reduced more as LDL cholesterol levels are reduced further. One possible strategy to achieve further reductions in cardiovascular morbidity and mortality is therefore to apply more aggressive lipid lowering. Another possible strategy, which is reviving, is to increase the concentration of the 'protective' HDL cholesterol.

Several ongoing trials are investigating aggressive lipid lowering using currently approved statins. These trials are anticipated to provide valuable insights into the usefulness of aggressive lipid lowering in the next few years.

The development of more potent statins is exemplified by the recent approval and introduction of rosuvastatin, which is reported to reduce LDL cholesterol levels by 52 to 63% in the approved dose range of 10 to 40 mg daily.⁶ Rosuvastatin has not yet been investigated in long-term clinical endpoint studies, but this will most likely occur in the years to come.

Novel drugs affecting lipid levels by mechanisms other than HMG-CoA reductase inhibition are cholesterol absorption inhibitors, such as ezetimibe, and cholesteryl ester transfer protein (CETP) inhibitors, such as the experimental agent JJT-705. Human data on ezetimibe

and JJT-705 supporting their potential for cardiovascular risk reduction have recently been reported.

Ezetimibe

Ezetimibe is an orally active 2-azetidinone derivative which is rapidly absorbed and extensively conjugated to form a glucuronide.⁷ Ezetimibe-glucuronide acts at the brush border of the small intestine and inhibits the uptake of dietary and biliary cholesterol into enterocytes, but not the absorption of triglycerides or lipid-soluble vitamins. In animals, ezetimibe inhibited intestinal cholesterol absorption by up to 96%. It has a long terminal half-life allowing once-daily dosing.

The effect of ezetimibe on cholesterol absorption and plasma lipids has recently been investigated in a randomised, double-blind, placebo-controlled cross-over study in 18 male patients with mild to moderate hypercholesterolaemia. During ezetimibe treatment for two weeks, cholesterol absorption was significantly reduced by 54% compared with placebo treatment ($p < 0.001$). Endogenous cholesterol synthesis increased, but the overall effects of ezetimibe on plasma lipids were favourable (figure 1), showing significant reductions in total and LDL cholesterol concentrations. The addition of ezetimibe to ongoing statin therapy significantly reduced LDL cholesterol (-21%; $p < 0.001$) and triglyceride levels (-11%; $p < 0.01$) compared with placebo.⁸ The incremental lowering of LDL cholesterol concentrations when statins and ezetimibe are combined may be due to the ability of statins to reduce the compensatory increase in hepatic cholesterol synthesis induced by ezetimibe.

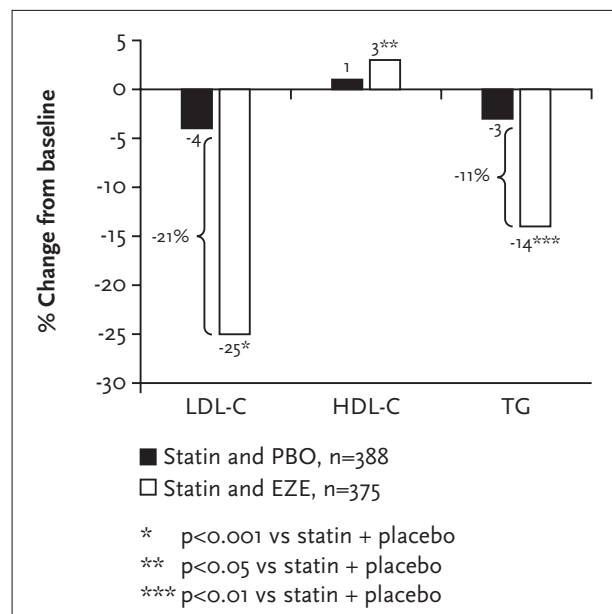


Figure 1
Changes in plasma lipids (baseline versus endpoint) induced by ezetimibe or placebo in male patients with mild to moderate hypercholesterolaemia⁷

Cholesteryl ester transfer protein inhibition

A low HDL cholesterol level has been identified as a risk factor for CHD. A potential strategy to improve the CHD risk profile would be to increase plasma HDL cholesterol concentration. Cholesteryl ester transfer protein (CETP) represents a possible drug target by which this may be achieved. In human lipoprotein metabolism, CETP mediates the transfer of cholesteryl esters from HDL to apolipoprotein-B containing particles in exchange for triglycerides. CETP inhibition may thus be expected to lead to higher HDL concentrations.

JJT-705 is an experimental agent, which has been shown to inhibit CETP, to increase HDL cholesterol and to inhibit the progression of atherosclerosis in cholesterol-fed rabbits. JJT-705 has now been investigated in healthy individuals to assess its effects on HDL and LDL cholesterol levels and its safety.⁹ This study was a multicentre, randomised, placebo-controlled, dose-response study in 198 healthy individuals, aged 18 to 65 years, with mildly elevated LDL cholesterol levels (mean 3.9 mmol/l), HDL cholesterol ≤ 1.6 mmol/l and triglycerides ≤ 4.5 mmol/l. After a four-week run-in period, subjects were treated with JJT-705 at dose levels of 300, 600 or 900 mg a day, or placebo for four weeks.

At the end of the four-week treatment period, HDL cholesterol levels showed a dose-dependent increase of up to 34% at the highest dose (table 3). This was accompanied by a slight but significant 7% decrease in LDL cholesterol concentration at the highest dose. The ratio total cholesterol/HDL cholesterol was dose-dependently decreased, indicating reduced atherogenicity of the lipid profile under treatment with JJT-705. Measurements of CETP activity and CETP mass were altered in the direction expected for a drug known to inhibit CETP.

The side effect profile of JJT-705 was remarkably clean and the drug was well tolerated. There were no signs of

toxicity according to physical examination and routine laboratory tests during and after treatments (there was a four-week post-treatment observation period). JJT-705 may have mild gastrointestinal side effects: diarrhoea, flatulence and nausea tended to be associated more frequently with JJT-705 treatment than with placebo, although this association failed to reach statistical significance for any of the doses of JJT-705 tested.

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Table 3

Absolute changes in CETP activity, CTP mass and plasma lipids and lipoproteins in healthy individuals treated with JJT-705 for four weeks⁹

	PLACEBO	JJT-705		
	(n=50)	300 mg (n=48)	600 mg (n=47)	900 mg (n=52)
CETP activity (% control)	0.9 ± 13.2	-15.4 ± 11.9 [§]	-29.6 ± 19.5 [§]	-37.2 ± 17.6 [§]
CETP mass (µg/ml)	0.0 ± 0.3	0.9 ± 0.6 [§]	1.3 ± 0.5 [§]	1.6 ± 0.8 [§]
TC (mmol/l)	0.0 ± 0.5	-0.1 ± 0.5	0.0 ± 0.6	0.0 ± 0.6
HDL (mmol/l)	0.04 ± 0.15	0.18 ± 0.15 [#]	0.32 ± 0.22 [§]	0.40 ± 0.29 [§]
LDL (mmol/l)	-0.1 ± 0.5	-0.2 ± 0.5	-0.2 ± 0.6	-0.3 ± 0.6 [†]
Triglycerides (mmol/l)	0.0 ± 0.4	0.0 ± 0.6	-0.1 ± 0.5	-0.2 ± 0.6
TC/HDL (ratio)	-0.2 ± 0.6	0.7 ± 0.8 [#]	0.9 ± 0.8 [§]	-1.2 ± 0.7 [§]

Values are means ± SD. TC = total cholesterol, * p \leq 0.01, # p \leq 0.001, § p \leq 0.0001 (versus placebo).