Statins: the key trials

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The second part of this article summarises the key trials that have provided the evidence base for the use of statins.

Part 1 of this article presented an overview of the statins – their mechanism of action, pharmacology, efficacy and safety. Here, the key trials that have provided the evidence base for their use are summarised.

The availability of the statins enabled the cholesterol hypothesis to be tested: does low-density lipoprotein (LDL)-cholesterol-lowering safely and effectively decrease cardiovascular events and overall mortality with no increase in non-cardiovascular disease (CVD) mortality?

SCANDINAVIAN SIMVASTATIN SURVIVAL STUDY

The first definitive trial was the Scandinavian Simvastatin Survival Study (4S), which recruited patients with established coronary heart disease (CHD; n=4444, 827 women) and total cholesterol concentrations between 5.5 and 8.8mmol/l, in spite of dietary measures. Patients were randomised to simvastatin, 20mg/day or matching placebo. The primary endpoint was overall mortality and the study needed to continue until 440 deaths had occurred to meet power calculations. Secondary endpoints were fatal and non-fatal myocardial infarction (MI) and sudden death. In the simvastatin group, the treatment goal was total cholesterol concentration 3.0–5.2mmol/l, and 37 per

Figure 1. Direct imaging of the atheroma plaque by intravascular ultrasound has provided further evidence for the benefits of intensive statin therapy (©Lunagrafix/Science Photo Library)

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cent of patients required uptitration of the statin dose to 40mg/day.

Simvastatin therapy led to a 35 per cent reduction in LDL-cholesterol, an 8 per cent increase in high-density lipoprotein (HDL)-cholesterol and a 10 per cent reduction in triglycerides compared to the placebo group. After a mean follow-up of 5.4 years, there were 182 deaths in the simvastatin group compared to 256 deaths in the placebo group, a 30 per cent reduction in overall mortality (hazard ratio [HR] 0.7; 95 per cent confidence interval [CI] 0.59–0.85; p<0.0003). The secondary endpoint of major coronary events was reduced by 34 per cent. This benefit was observed in women and in older as well as younger patients.

Importantly, there was no excess of non-cardiac mortality and the frequency of adverse events was generally similar between the simvastatin and the placebo group. There was one case of rhabdomyolysis in the statin group, which recovered on drug cessation.

The effects of 4S can be summarised as follows: over six years simvastatin treatment of 100 patients with CHD will save four deaths, seven MIs and six revascularisation procedures. Interestingly, in a further eight-year follow-up of 4S there was continued survival benefit.

Since this landmark study in secondary prevention, there have been other complementary statin trials that have extended the evidence of benefit to post-MI and unstable angina patients with a wide range of baseline cholesterol levels using pravastatin and simvastatin. Benefits are observed irrespective of gender, age, baseline lipid and lipoprotein concentrations, diabetes, metabolic syndrome or hypertension.

WEST OF SCOTLAND CORONARY PREVENTION STUDY
Statins have also been shown to prevent the first manifestation of coronary disease, which is important, as many will die with the first event. The first primary prevention trial to report was the West of Scotland Coronary Prevention Study (WOSCOPS). In this trial, 6595 men, aged 45–64 years, with LDL-cholesterol 4.5–6mmol/l, were randomised to placebo or pravastatin 40mg/day. Although men with previous MI were excluded, those with stable angina were included so long as they had not been hospitalised in the preceding year.

Benefits of statins are observed irrespective of gender, age, baseline lipid and lipoprotein concentrations, diabetes, metabolic syndrome or hypertension.

The primary endpoint was a composite of coronary death and non-fatal MI, and the mean study period was 4.9 years. Over the course of the study, pravastatin therapy was associated with an LDL-cholesterol reduction of 26 per cent, a reduction of triglyceride of 12 per cent and an increase in HDL-cholesterol of 5 per cent. The primary endpoint was reduced by 31 per cent (95 per cent CI 17–43; p<0.001) in the pravastatin group. Similar percentage benefits were observed irrespective of baseline LDL, HDL or triglyceride concentrations, smoking status, age or those with multiple risk factors.

WOSCOPS can be summarised as follows: pravastatin treatment for five years in 1000 middle-aged men with hypercholesterolaemia will save seven deaths from CVD, two deaths from other causes, 20 non-fatal MIs, eight revascularisations and 14 angigrams.

AIR FORCE/TEXAS CORONARY ATHEROSCLEROSIS PREVENTION STUDY
Some might argue that WOSCOPS was not a true primary prevention trial in that some individuals had symptomatic angina; however, similar findings were described for a healthy population in the USA. In the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TEXCAPS), 6605 subjects, 15 per cent women, aged 55–73 years with no clinical evidence of CVD were recruited on the basis of low HDL-cholesterol (<1.16mmol/l in men and <1.22mmol/l in women) and LDL-cholesterol (3.36–4.91mmol/l). The intervention was lovastatin at 20–40mg/day versus placebo to achieve an LDL-cholesterol <2.9mmol/l.

The primary endpoint was a composite of coronary death, non-fatal MI, sudden cardiac death or the development of unstable angina. Lovastatin was increased to 40mg/day in approximately half of the subjects, but the goal of therapy was achieved in only 42.5 per cent. There was a 25 per cent reduction in LDL-cholesterol, a 15 per cent reduction in triglycerides and a 6 per cent increase in HDL-cholesterol. In the lovastatin group there was a 37 per cent reduction in the primary endpoint (HR 0.63, 95 per cent CI 0.5–0.79, p=0.001) after 5.2 years follow-up. In fact the trial was terminated early on efficacy grounds at the second interim analysis.

Lovastatin therapy was associated with a relative risk reduction of 0.63 (95 per cent CI 0.50–0.79; p<0.001) in the primary endpoint. These effects were observed across subgroups of the population, women, the elderly, those with hypertension and smokers. In addition, benefits were observed independent of baseline tertiles of LDL-cholesterol.

ANGLO-SCandinavian CARDiac OUTcomes TRIAL – LIPID-LOWERING ARM
Primary prevention of CVD events with statins has also been tested in important...
at-risk populations, namely those with hypertension, the elderly and those with type 2 diabetes.

In the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid-lowering Arm (ASCOT-LLA), atorvastatin 10mg/day was compared to placebo in 10,305 hypertensive patients, aged 40–79 years, and random cholesterol ≤5.5mmol/l. The primary endpoint of fatal CHD and non-fatal MI after a median follow-up of 3.3 years (the trial was stopped early on efficacy grounds) was reduced by 36 per cent (HR 0.64, 95 per cent CI 0.50–0.83, p=0.0005). Benefit was observed across all pre-specified subgroups and emerged in the first year of follow-up. An important observation in ASCOT-LLA was the 27 per cent reduction in stroke with the statin in a population well treated for hypertension.10

Trials that have studied intensive statin therapy have demonstrated that the progression of atheroma plaques can be halted and even regressed

**PROSPECTIVE STUDY OF PRAVASTATIN IN THE ELDERLY AT RISK**

Although subgroup analyses of the major statin trials point to benefits in older as well as younger patients, the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) provided welcome efficacy and safety data in a specific elderly population.

**PROSPER**, a randomised controlled trial, enrolled 5804 men and women aged 70–82 years.11 Subjects were recruited on the basis of a history of coronary, cerebral or peripheral vascular disease or an increased CVD risk as a result of cigarette smoking, hypertension or diabetes; baseline cholesterol levels were 4–9mmol/l and triglycerides <6mmol/l. Pravastatin therapy (40mg/day), which reduced LDL-cholesterol by 34 per cent over a mean follow-up period of 3.2 years, reduced the composite primary endpoint (coronary death, non-fatal MI and fatal and non-fatal stroke) by 15 per cent (HR 0.85, 95 per cent CI 0.74–0.97, p=0.014);10 perhaps surprisingly there was no impact on stroke in this study, but the HR for transient ischaemic attack was 0.75 (95 per cent CI 0.55–1.00, p=0.051).11

**HEART PROTECTION STUDY AND THE COLLABORATIVE ATORVASTATIN DIABETES STUDY**

Information on the primary prevention of CVD in diabetes has come from a subgroup of the Heart Protection Study (HPS)12 and the Collaborative Atorvastatin Diabetes Study (CARDs).13

The HPS included 5963 diabetic patients, aged 40–80 years, of whom 2921 were free of clinical vascular disease. In this group, simvastatin 40mg/day was associated with a reduction in first major vascular events of 33 per cent (95 per cent CI 17–46, p=0.0003). After allowing for non-compliance, the authors calculated that statin therapy would prevent about 45 people per 1000 from having at least one major vascular event during the five-year treatment period. These benefits were seen across subcategories including age, type and duration of diabetes, those with hypertension and those with pre-treatment cholesterol levels <5mmol/l.12

The CARDS study was the first to investigate the impact of statin therapy in a specific type 2 diabetic population.13 In this study, 2838 patients aged 40–75 years with no previous history of CVD but with one other CVD risk factor (smoking, hypertension, albuminuria or retinopathy) were randomised to atorvastatin 10mg or placebo. From a mean baseline of approximately 3mmol/l, statin therapy reduced LDL-cholesterol by 40 per cent (1.2mmol/l) and this was associated with a 37 per cent reduction (95 per cent CI –52 to –17, p=0.001) in the composite primary endpoint of first major CVD event. This effect was achieved with a mean duration of therapy of only 3.9 months, as the trial was terminated early after the second interim analysis on grounds of efficacy. The authors calculated that atorvastatin would be expected to prevent at least 37 major vascular events per 1000 patients treated for four years.13

**HOW LOW TO LOWER LDL-CHOLESTEROL?**

In spite of the highly effective reduction in events in both primary and secondary CVD prevention trials with statins, there remains considerable residual risk. As a result, the question arose as to whether more intensive LDL-cholesterol-lowering would result in extra benefit in terms of reduction in CVD events.

This hypothesis has been tested in a number of trials in high-risk patients (either post-acute coronary syndrome, or in chronic stable CVD or very high risk of CVD) by comparing standard statin therapy with more intensive therapy, either with a more effective statin or a higher statin dose. These trials, involving 39,612 subjects and observing 8253 CVD events, have been included in a recent report of the Cholesterol Trials’ Collaboration.14 More intensive statin therapy was associated with a highly statistically significant further reduction in CVD events of 15 per cent [HR 0.85; 95 per cent CI 0.82–0.89, p<0.0001]. Importantly, there was no increase in non-cardiac deaths or incident cancer.

More evidence for intensive statin therapy has come from a very interesting surrogate measure involving intravascular ultrasound, which can image directly the atheroma plaque (Figure 1). Trials that have studied intensive statin therapy have demonstrated that the progression of atheroma plaques can be halted and even regressed.15

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This evidence has led to a tightening of the goals of therapy for LDL-lowering. In the current Joint British Guidelines, an LDL-cholesterol target of <2mmol/l is advocated.16 Guidelines in the USA recommend an additional target LDL-cholesterol of <1.7mmol/l in those at highest risk.17

CONCLUSION
The statins have proved to be highly effective in preventing major cardiovascular events in both primary and secondary prevention trials in a wide range of at-risk patient groups with a wide range of baseline lipid concentrations. Along with this impressive efficacy, they have proved to be generally safe and well tolerated. The comprehensive data available from randomised controlled trials allow the clinician to make informed, evidence-based treatment decisions in many groups of patients.

Declaration of interests
JB has received honoraria for lectures and attendance at advisory boards from all the manufacturers of statin drugs.

REFERENCES

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