Statins: where are we now?

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Statin therapy reduces the risk of cardiac events by 30% in both primary and secondary prevention. Although fine-tuning of the evidence will occur as more clinical trials report, the challenge is now to implement the evidence to the benefit of patients.

The link between serum cholesterol levels and risk of coronary heart disease (CHD) is well established. Results of a large number of clinical trials show that lowering cholesterol significantly reduces the rate of major coronary events, regardless of the intervention used. In fact, there is probably more evidence of the benefits of cholesterol lowering than almost any other area of medicine.

Statins have been firmly established as the cornerstone of therapy for patients with hyperlipidaemia, producing dramatic reductions in cholesterol unseen with earlier interventions. Over the past few years, a large number of cholesterol lowering guidelines have been published and target levels have progressively decreased, reflecting the growing body of evidence for the benefits of using statins even in patients with 'normal' cholesterol levels. However, despite this wealth of evidence many people in the UK remain inadequately managed, a situation that has been exacerbated by the budgetary implications of statin therapy.

With the recent publication of the National Service Framework (NSF) for CHD (Department of Health, 2000), it is hoped that this therapeutic nihilism will become a thing of the past. The NSF has highlighted the importance of systematically identifying and appropriately managing risk factors in patients with established cardiovascular disease. Better management of hyperlipidaemia forms a key part of this. The NSF sets targets for lowering cholesterol and health-care professionals are charged with ensuring that these targets are implemented. Achieving these targets efficiently and cost-effectively will be a challenge for us all.

BACKGROUND

Back in the 1950s and 60s small, and often underpowered, trials of dietary intervention showed only modest changes in cholesterol. Even the later dietary trials showed relatively small changes in cholesterol — of the order of 10% (Research Committee, 1965; Burr et al, 1989; Watts et al, 1992). Some, but not all, of these studies showed a reduction in the risk of coronary events and none had the power to show a reduction in total mortality. Early drug studies examined the benefits of lipid-lowering agents, such as fibrates and resins (Rifkind, 1984; Committee of Principal Investigators, 1978). These demonstrated slightly larger reductions in cholesterol, of around 10–15%, and nearly all reported reductions in CHD mortality. But again, total mortality did not always decrease and one trial with clofibrate actually showed an increase in total mortality.

A meta-analysis of these early lipid-lowering trials estimated that an average reduction in total cholesterol of 10% was associated with a decrease in CHD mortality of 13% and total mortality of 10% (Gould et al, 1995).

In the early 1990s, the cholesterol-lowering market was revolutionized by the introduction of the statins. These agents produced dramatic reductions in cholesterol of 20–40% and a number of landmark studies were conducted to investigate the impact of this powerful reduction on cardiovascular and total mortality.

THE EVIDENCE FOR STATINS

Secondary prevention

The first major statin trial to be reported was the Scandinavian Simvastatin Survival Study (4S study). Simvastatin 20–40 mg/day lowered LDL cholesterol by a mean of 35% in patients with established CHD over a 5-year period. This was associated with a 42% reduction in the risk of cardiovascular mortality and a 30% risk reduction in total mortality (Scandinavian Simvastatin

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Survival Study group, 1994). Analysis suggested that the degree of reduction of cardiovascular mortality was determined mainly by the magnitude of change in LDL cholesterol. The investigators estimated that each additional 1% reduction in LDL cholesterol reduced the risk of a major coronary event by 1.7% (Pedersen et al, 1998).

The 4S study was followed by the Cholesterol and Recurrent Events (CARE) trial, in which pravastatin 40 mg/day reduced LDL cholesterol by 32% in patients who had suffered a myocardial infarction and who had average lipid levels (Sacks et al, 1996). This was associated with a statistically significantly 24% reduction in the risk of CHD death or non-fatal reinfarction. The results of these two trials were further endorsed by the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study, in which pravastatin 40 mg/day was again associated with a relative risk reduction of 24% for death from CHD (LIPID study group, 1998) in patients who had a history of recent myocardial infarction or unstable angina.

Primary prevention

With the argument firmly settled on the value of lipid lowering with statins in secondary prevention what is the evidence for the effect of statins in primary prevention, i.e. in patients with no history of cardiovascular disease? Landmark studies such as WOSCOPS (West of Scotland Coronary Prevention Study), using pravastatin, and AFCAPS/TexCAPS, using lovastatin, clearly demonstrated the benefits of effective cholesterol lowering, producing relative risk reductions for cardiac events of 32% and 37% respectively (Shepherd et al, 1995; Downs et al, 1998). The absolute benefit was lower than in secondary prevention, however, because of the lower background risk of cardiovascular events in patients without evidence of vascular disease.

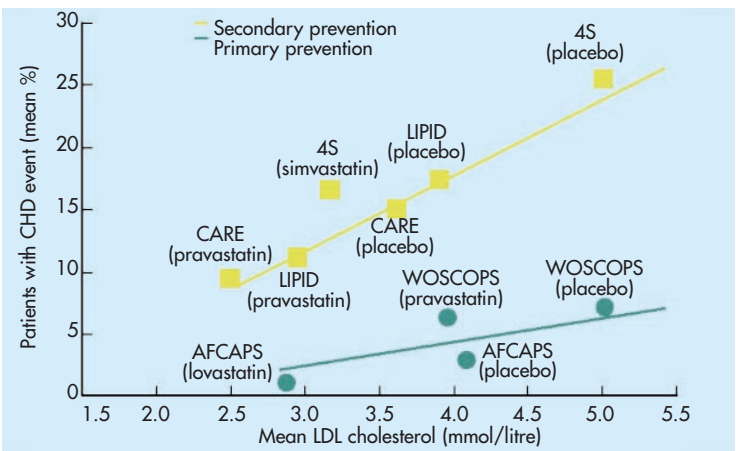

Figure 1. Relationship between low density lipoprotein (LDL) cholesterol and ischaemic events. CHD = coronary heart disease. Adapted from LaRosa (1999).

Mechanism of benefit

Gould et al (1998) published a further analysis of the key large statin studies, which suggested that the relationship between cholesterol reduction and reduction in mortality was constant across the studies. It is likely that statins reduce CHD and total mortality more than other cholesterol-lowering treatment largely because they reduce cholesterol levels more effectively than other therapies.

Figure 1 shows the relationship between the mean LDL cholesterol levels achieved in the major statin studies and the percentage of patients experiencing ischaemic events (LaRosa, 1999). The graph demonstrates an almost linear relationship, suggesting that the further cholesterol is reduced, the fewer ischaemic events may be experienced, just as the observational epidemiological studies have suggested for many years. Statins are effective in reducing clinical events across a wide range of baseline CHD mortality risks, although the absolute benefit is more pronounced in the context of secondary prevention than in patients without pre-existing cardiovascular disease.

DO WE HAVE ENOUGH EVIDENCE?

It is generally accepted that the large statin studies provide very strong evidence that substantial reduction in serum cholesterol with the statins reduces coronary events and total mortality. Epidemiological data and meta-analyses of the early cholesterol reduction studies also suggest that the degree of cholesterol lowering is the critical link in reducing mortality, regardless of intervention used.

The evidence is now so strong that further large studies of statins against placebo in patients with cardiovascular disease are unlikely, if not unethical. Increasingly, percentage reduction in cholesterol is accepted as an appropriate intermediate surrogate marker for reduction in cardiovascular risk. Further trial data are needed, however, to fine-tune the evidence and to address specific issues in cholesterol lowering, such as the timing of therapy after ischaemic events and the optimal levels of cholesterol reduction. Furthermore, randomized trials are underway to support the strong epidemiological evidence for cholesterol lowering in specific patient groups such as those over the age of 75 years, women and patients with diabetes.

TREATING TO TARGETS

Statins, supplementing dietary and other lifestyle advice, have been recommended as first-line treatment in all recent guidelines for cholesterol lowering in patients with CHD. The Joint British Societies recommend treating to a LDL choles-

terol level of <3.0 mmol/litre or a total cholesterol level of <5.0 mmol/litre (Wood et al, 1998). These targets have recently been endorsed by the NSF for CHD (Department of Health, 2000).

Within the next few years, both primary and secondary care will be required to clearly demonstrate with audit data that cholesterol targets are being achieved. Prescribing budgets will still have to be managed effectively and are unlikely to be significantly greater than at present. Treatment of all patients at risk of CHD (primary and secondary prevention) would obviously put an enormous pressure on available resources. Therefore, priority for drug treatment should be determined by a patient's absolute level of risk of developing CHD (*Figure 2*).

Health-care professionals have some way to go before all patients who would benefit from statins are identified and treated, even according to the arguably conservative NSF recommendations (Campbell et al, 1998). The ASPIRE study highlighted the gap that exists between the situation in clinical practice in the mid-1990s and 'optimal' secondary prevention (*Table 1*) (ASPIRE Steering Group, 1996). This under-treatment is not just a result of physician apathy. All clinicians know that patients can be advised to change behaviour and can be informed of the benefits of treatment but may not accept this advice. The simpler the treatment regimen the better when it comes to patient compliance and organization of care.

CHOICE OF STATIN

There are five statins available in the UK (atorvastatin, cerivastatin, fluvastatin, pravastatin and simvastatin). Factors affecting choice of agent in a patient include:

- Evidence of efficacy
- Degree of cholesterol lowering required to reach target levels
- Cost effectiveness
- Safety profile
- Practical considerations, e.g. titration steps, need for nocturnal dosing.

With the publication of the NSF for CHD, a major factor in the selection of a statin will be the ability of that agent to achieve the defined cholesterol targets in as many patients as possible. A treatment that lowers cholesterol effectively, with minimum need for dose titration, is likely to be the agent that will be the most straightforward to use in routine practice and the most efficient at ensuring that as high a proportion of patients as possible reach the NSF target levels.

Although all the statins are effective at reducing cholesterol, there are significant differences in the scale of that reduction across the dosage range. *Table 2* summarizes the efficacy of each of the five statins at their starting doses (and the most commonly prescribed doses in clinical practice) in lowering cholesterol. Comparative data on the number of patients who could be expected to achieve the NSFs target LDL cholesterol level of below 3.0 mmol/litre with each of the statins have yet to be demonstrated. However, a study by Smith et al (1999) examined the efficacy of the starting doses of atorvastatin, fluvastatin, pravastatin and simvastatin in enabling patients to reach a modified European Atherosclerosis Society target LDL cholesterol of 2.8 mmol/litre (*Table 2*).

COST CONSIDERATIONS

Even with prioritization, broader use of statins will have considerable budgetary implications. Although drug pricing is a key issue, it is important not to lose sight of the clinical effect of a drug: the most cost-effective drug may not be the one sold at the lowest price. There is a strong argument that within a defined budget the statin that enables the highest proportion of patients to reach NSF target cholesterol level should be preferred over its competitors. The cost of arranging repeat cholesterol tests and making decisions regarding need for dose titration should also be considered.

THE FUTURE

Now that the relationship between cholesterol lowering and reduction in cardiovascular events has been accepted, and the government has defined which patients should receive the drugs as a priority, the future use of statins is likely to be shaped by fine-tuning of the evidence and any changes in

Step 1: In people with diagnosed CHD or other occlusive arterial disease

and

Step 2: In people without diagnosed CHD or other occlusive arterial disease with a CHD risk greater than 30% over 10 years:

Statins and dietary advice to lower serum cholesterol concentrations either to less than 5.0 mmol/litre (low density lipoprotein cholesterol to below 3.0 mmol/litre) or by 30% (whichever is greater)

Figure 2. National Service Framework for Coronary Heart Disease (CHD) — patient priorities and statin recommendations. From Department of Health (2000).

TABLE 1.
Under-treatment of cholesterol in the ASPIRE study (1996)

72% of men and 83% of women had a total cholesterol > 5.2 mmol/litre at least 6 months after experiencing an acute ischaemic event or having a revascularization procedure
Only a minority of patients appropriate for secondary prevention with lipid-lowering therapy were receiving it
Over 50% of patients who were receiving cholesterol-lowering therapy still had a total cholesterol of >5.5 mmol/litre
The recording of hypercholesterolaemia history in patients' notes was absent in 40% of cases, making it the least frequently recorded measurement

fiscal policy on health-care funding in the UK. Over the next few years, a number of studies will be completed, answering key questions, such as:

- Will reducing cholesterol to very low levels produce additional benefits?
- Is there an age at which drug treatment should be stopped?
- Should patients with diabetes be treated particularly aggressively?
- How soon after an event should treatment be initiated? Is it important to start treating immediately, or to wait for 3–6 months, as many of the trials have done?
- Do statins have beneficial effects in addition to lowering lipid levels?
- Should statins also be used in people at risk of stroke and peripheral vascular disease?
- Which statin should we be using to obtain optimum benefit?
- Which patients should be treated with a fibrate in preference to, or in addition to, a statin?

CONCLUSION

There is a wealth of evidence to support cholesterol reduction with statins as a key component of a national strategy for reducing the burden of CHD in our patients. The challenge now is to ensure that the current guidelines are implemented, starting with the high risk group of patients with pre-existing CHD. Clinicians caring for patients with such disease should think carefully about how they are to ensure systematic and effective cholesterol lowering within the constraints of NHS drug budgets. HM

Conflict of interest: Pfizer and other pharmaceutical companies marketing statins have funded Dr Cowie's attendance at scientific meetings and provided independent research grants to his department.

TABLE 2.
Efficacy of statins at their starting doses

	Mean reduction in LDL cholesterol from baseline	Mean reduction in total cholesterol from baseline	No. of patients achieving a target LDL cholesterol of <2.8 mmol/litre
Atorvastatin 10 mg	38%*	28%*	55%†
Cerivastatin 100 μg	22.5%‡	16.4%‡	–
Fluvastatin 20 mg	17%*	13%*	17%†
Pravastatin 10 mg	19%*	13%*	25%†
Simvastatin 10 mg	28%*	21%*	35%†

*Jones et al (1998); † Smith et al (1999); ‡ Stein et al (1999). LDL = low density lipoprotein

KEY POINTS

- There is strong evidence for the value of statins in both the primary and secondary prevention of coronary events, although the absolute benefit is greater in secondary prevention.
- Both the Joint British Recommendations and the National Service Framework for Coronary Heart Disease recommend the use of statins to meet target cholesterol levels in secondary prevention and high-risk primary prevention.
- Statins and dietary advice should be given to lower cholesterol concentration either to <5 mmol/litre (low density lipoprotein cholesterol <3.0 mmol/litre) or by 30%, whichever is greater.
- The immediate challenge for physicians is to ensure the effective implementation of current guidelines.

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