A systematic review and economic evaluation of statins for the prevention of coronary events

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Executive summary

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Executive summary

Objective

This study evaluated the use of a group of statins, atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin, for the prevention of cardiovascular events.

Epidemiology and background

Cardiovascular disease (CVD) is one of the major causes of premature death in the UK, accounting for 35% of premature deaths in men and 27% in women. It is also a significant cause of morbidity.

The three major manifestations of CVD are:

- coronary heart disease (CHD), including myocardial infarction (MI, heart attack) and angina
- cerebrovascular disease [transient ischaemic attack (TIA) and stroke]
- peripheral arterial disease (obstruction of the arteries carrying blood to the legs or, less commonly, the arms).

Several risk factors for CHD have been identified; these include hyperlipidaemia. Some of these risk factors (e.g. smoking, obesity and hypertension) can be modified, treated or controlled. Others (e.g. age, gender and ethnicity) cannot. CHD risk can be reduced by cholesterol lowering, changes in lifestyle, such as smoking cessation, exercise and the use of cholesterol-lowering diets, along with non-cholesterol drug treatments, including aspirin and antihypertensives. The cost-effectiveness of statins must be seen in the context of these other interventions.

Methods

A review was undertaken to identify all literature relating to the clinical effectiveness of statins for the prevention of coronary events, as well as to identify and evaluate studies exploring the cost-effectiveness of statins in primary and secondary prevention of CHD and CVD in the UK. Electronic literature searches were conducted between November 2003 and April 2004.

A Markov model was developed to explore the costs and health outcomes associated with a lifetime of statin treatment using a UK NHS perspective. Data from UK epidemiological studies were used to inform event rates, and were combined with results from the meta-analysis of RCT evidence on the effectiveness of statins to model the relative risk reductions of event rates for patients on statin therapy. Costs of health states (first-year costs and subsequent year) were based on a review of published evidence to obtain the most recent and appropriate costs. The annual cost of statins is a weighted average cost for statins (weighted by the trial evidence), for different statins at different dosage. Given that statins have a good safety profile, and adverse events are rare, costs of managing adverse events are not modelled. Utility estimates for health states within the model were identified by a literature review. The utility of the general population is assumed to vary by age. Input parameters were assigned probability distributions to reflect their imprecision, and Monte Carlo simulations were performed to reproduce this uncertainty in the results. Results were presented in terms of quality-adjusted life years (QALYs) for both primary and secondary prevention of CHD/CVD events. Costs were at 2004 prices and discount rates of 6% and 1.5% applied to costs and health benefits, respectively.

The basecase analysis considered the cost-effectiveness of statins for a population with CHD or at risk of CHD, taking into account CHD outcomes only. This complied with the scope specifically requested by the Department of Health to consider only coronary heart disease. Two further scenarios were explored to take into account the growing evidence on the impact of statins on reducing stroke events. Scenario 1 was as the basecase but also took into account the potential of statins to reduce stroke events in patients with a history of CHD. Scenario 2 explored the costs and benefits associated with statin treatment in reducing CVD events for patients with or at risk of CVD, with all patients entering the treatment arm of the model assumed to receive benefits associated with statin treatment.

Given that current trials of rosuvastatin report only on the intermediate end-point of cholesterol ▶

lowering and there is currently no direct trial evidence of the effect of rosuvastatin on morbidity and mortality, the ScHARR model was also adapted to calculate the risk of CHD (morbidity and mortality) using a Framingham risk equation. There were, however, several issues concerning the robustness of estimation of cost-effectiveness when using Framingham equations to model the link between cholesterol lowering and CHD risk, which are discussed in detail within the report.

Results

Number and quality of studies, and direction of evidence

Thirty-one randomised studies were identified that compared a statin with placebo or with another statin, and that reported clinical outcomes. Meta-analysis of the available data from the placebo-controlled studies indicates that, in patients with, or at risk of, CVD, statin therapy is associated with a reduced relative risk of all-cause mortality, cardiovascular mortality, CHD mortality and fatal MI, but not of fatal stroke. It is also associated with a reduced relative risk of morbidity (non-fatal stroke, non-fatal MI, TIA, unstable angina) and of coronary revascularisation. It is hardly possible, on the evidence available from the placebo-controlled trials, to differentiate between the clinical efficacy of atorvastatin, fluvastatin, pravastatin and simvastatin. However, there is some evidence from direct comparisons between statins to suggest that atorvastatin may be more effective than pravastatin in patients with symptomatic CHD.

There is no evidence from randomised controlled trials (RCTs) for the effectiveness of the 10-mg over-the-counter dose of simvastatin in preventing clinical events.

No relevant studies of rosuvastatin were identified that reported clinical outcomes. Thus, although there is RCT evidence to suggest that rosuvastatin is more effective than atorvastatin, pravastatin and simvastatin in reducing both total and low-density lipoprotein cholesterol, it is not possible to prove that these reductions translate into comparable reductions in clinical events.

There is limited evidence for the effectiveness of statins in different subgroups. There is no evidence that statins differ in their effectiveness, measured in terms of relative risk reduction, in primary compared with secondary prevention, in women compared with men at a similar level of cardiovascular risk, in people with diabetes compared with those without, or in people aged 65 and over compared with those younger than 65. In renal transplant patients, statin therapy is associated with a reduced risk of CHD death or non-fatal MI. However, no benefit has been demonstrated in cardiac transplant patients. For ethical reasons, no placebo-controlled trials have been carried out in patients with familial hypercholesterolaemia. The only randomised trial in this group compared two statins, and found no significant difference between them. People from the Indian subcontinent are known to be at increased risk of CVD. However, no placebo-controlled studies were found that studied the clinical effectiveness of statins in this population.

Safety

Although concerns have been raised about rosuvastatin, statins are generally considered to be well tolerated and to have a good safety profile. This view is generally supported both by the evidence of the trials included in this review and by postmarketing surveillance data. Although increases in creatine kinase and myopathy have been reported, rhabdomyolysis and hepatotoxicity are rare. However, some patients may receive lipid-lowering therapy for as long as 50 years, and long-term safety over such a timespan remains unproven.

Summary of cost-effectiveness evidence

Review of existing cost-effectiveness literature

The literature searches identified 206 potentially relevant publications. Of these only five UK studies satisfied all inclusion and exclusion criteria and formed the basis of the review. These studies were assessed for quality using components of the BMJ and Eddy checklists. All scored well on modelling methodologies and presentation of results.

All five UK studies reported on cost per life-year gained (LYG), rather than cost per QALY. Four of the five studies had results below £30,000 in primary prevention treatment, varying between £8000 and £30,000 depending on baseline risk. One study estimated cost-effectiveness at £136,000, which appears anomalous compared with the other studies. Cost-effectiveness in secondary treatment was estimated in two studies and ranged from £6000 to £40,000.

As part of their industry submissions to the National Institute for Health and Clinical Excellence, Pfizer, Novartis, Bristol-Myers Squibb and AstraZeneca presented cost-effectiveness ▶

models. These were critiqued using the combined BMJ and Eddy framework. Of the four models submitted, two (Pfizer and AstraZeneca) used the surrogate end-point of cholesterol lowering for predicting reductions in clinical end-points and two (Novartis and Bristol-Myers Squibb) used trial evidence on reductions in clinical end-points. The time-horizon in the four models varied between 5 years and lifetime. Overall, taking into account the differences in techniques and objectives, the results from all four models could be considered to be of a similar order of magnitude. The estimated cost per QALY for both secondary and primary prevention is typically below £10,000. The most significant difference between the model results is the secondary prevention results from the AstraZeneca model, which are markedly higher than the other evaluations. In this model, treatment is reported to be less cost-effective in secondary prevention than in primary prevention. The within-trial economic analysis of simvastatin by Merck Sharp & Dohme produced results in secondary prevention of a similar magnitude to the Novartis and Pfizer evaluations.

Base-case analysis

The cost-effectiveness of statins depends on the CHD risk in the population treated and the age and gender of the population under consideration. Cost-effectiveness results were presented for men and women aged 45–85 years in 10-year age bands.

In secondary prevention the cost per QALY was estimated to vary between around £10,000 and £17,000 between the ages of 45 and 85, with incremental cost-effectiveness ratios (ICERs) increasing with age, but with little difference between genders. These results are sensitive to the modelling time-frame and to the discount rates. The results of probabilistic sensitivity analysis showed that, using a threshold of £20,000 per QALY, statin therapy was cost-effective for all patients with a history of CHD.

In primary prevention the estimated ICERs varied according to risk level and age. This rose from around £20,000 to £28,000 for men between 3 and 0.5% CHD risk, and between £21,000 and £57,000 for women. There was significant variation with age within risk levels. At an annual CHD risk of 3%, the estimated cost per QALY ranged from £10,000 to £37,000 for men and from £14,000 to £48,000 for women between the ages of 45 and 85. At the age of 85 years the estimated cost per QALY rose from £37,000 and £48,000 for men and women, respectively, at 3% CHD risk, to around £105,000 and £111,000 for men and women at 0.5% CHD risk.

Alternative scenarios

Alternative scenarios also considered the cost-effectiveness in statins in the wider context of CVD risk and outcomes. For scenario 1 (CHD analysis with CVD outcomes) the ICERs were similar to the base-case results (CHD analysis). For scenario 2 (CVD analysis) the ICERs were substantially lower than the base-case results owing to the additional impact of statin treatment on reducing stroke and TIA events for all patients.

Conclusions

The cost-effectiveness modelling presented here has shown that statin therapy in secondary prevention is likely to be considered cost-effective when compared with other current standard treatments available to the NHS. In primary prevention, the cost-effectiveness ratios are dependent on the level of CHD risk and age, but the results, for the CVD analysis in particular, offer support for the more aggressive treatment recommendation issued by recent guidelines in UK.

Limitations of cost–utility estimates

One of the major limitations of the analyses is the requirement to extrapolate well beyond the time-frame of the trial period. This period of extrapolation will be longer for younger patients and therefore the results for the lower age bands are subject to greater uncertainty. In addition, the analyses for primary prevention extrapolated effectiveness results from higher risk primary prevention populations to the treatment of populations at much lower risk, and have to be viewed with caution.

The analyses are sensitive to the cost of statin, and the future cost of statins is a key unknown. Therefore, the cost-effectiveness results will need to be reviewed in the light of any significant changes in the price of statins.

These analyses do not take into account the costs of identifying and screening the relevant population. In primary prevention, as the risk threshold becomes lower the size of the population eligible for treatment increases. The number of patients who will require regular monitoring will expand, placing additional demands on staff and resources at GP surgeries.

Evidence on clinical end-points for rosuvastatin is awaited. Modelling clinical outcome on cholesterol lowering inherently favours drugs that are more potent at lowering cholesterol. In the absence of strong and conclusive evidence on the exact relationship between cholesterol lowering and clinical end-points, cost-effectiveness results for rosuvastatin are subject to additional uncertainty.

The role of statins must be seen in the context of other interventions to reduce CHD risk, including smoking cessation, exercise and the use of diet, as well a range of drug treatments, such as antihypertensives, β-blockers and aspirin. Use of other interventions prior to statin prescribing to reduce CHD risk potentially has the effect of reducing an individual's risk to levels below which they would become eligible for statin treatment. A comparison of statins with alternative interventions to reduce CHD risk has not been addressed here.

Generalisability of the findings

The generalisability of the findings is limited by the exclusion, in some studies, of patients who were hypersensitive to or intolerant of statins, who were known to be unresponsive to statins, or who were not adequately compliant with study medication during a placebo run-in phase. A considerable proportion of patients with or at risk of CHD may have been excluded in this way. Consequently, the treatment effect may be reduced when statins are used in an unselected population.

There is a major question regarding the generalisability of the results of RCT evidence to routine clinical practice and the effectiveness of statins here could well be lower than suggested by the trials, particularly because of issues such as compliance and continuance. However, sensitivity analysis on compliance and continuance assumptions shows that the impact on cost-effectiveness results is not likely to be significant.

Recommendations for further research

Additional high-quality evidence on quality of life and compliance and continuance for patients on statins is required.

Large outcome studies at lower CHD/CVD risk thresholds would be useful to determine whether the relative risk reduction figures remain valid at lower risk levels and to determine the extent to which potential disutility due to statins may become an issue as treatment is extended to a vast proportion of the 'well' population.

Future service implementation research is important, particularly on effective policies for targeting low-risk populations. Research on the attitudes of low-risk patients and relatively healthy 45-year-olds to taking lifetime medication is required, along with research into the optimal methods of explaining risks and benefits of treatment to patients so that they can make informed choices.

Publication

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NIHR Health Technology Assessment Programme

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health.

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