Lifetime cost effectiveness of simvastatin in a range of risk groups and age groups derived from a randomised trial of 20,536 people


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Simvastatin 40 mg/day was compared with placebo for an average of 5 years. Different age groups with differing risks of vascular disease were evaluated in the primary analysis. The average 5-year risk of vascular events ranged from 12 to 42% (which corresponded to risks of 4 to 12% for non-fatal myocardial infarction or coronary death). The risk groups were subdivided by age at entry to the study (40 - 49, 50 - 59, 60 - 69, and 70 years and older).

Type of intervention
Primary and secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised men and women aged 40 to 80 years with total cholesterol concentrations of at least 3.5 mmol/L (135 mg/dL) and previous coronary, cerebrovascular or other occlusive arterial disease, diabetes mellitus, or, if a man aged 65 or older, treated hypertension.

Setting
The setting was secondary care. The economic study was undertaken in the UK.

Dates to which data relate
The dates of the effectiveness evidence and resource use were not reported in the present paper (see Heart Protection Study Collaborative Group 2002 and 2005). The prices used for different cost components were from 2001 and 2005.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was carried out prospectively on the same sample of patients as that used in the effectiveness analysis.

Study sample
A total of 20,536 patients were included in the parent study. The current study reported no further details (see Heart Protection Study Collaborative Group 2002).
Study design
This was a randomised controlled trial that was conducted in 69 UK Hospitals, with 5-year follow-up (see Heart Protection Study Collaborative Group 2002 for further details).

Analysis of effectiveness
Regression models were applied to HPS individual patient data to derive annual probabilities of the vascular events mentioned in the 'Modelling' section for each of the study arms, adjusting for non-compliance in the simvastatin arm and statin use in the placebo arm. The present paper did not report the effectiveness results of the parent study (Heart Protection Study Collaborative Group 2002).

Effectiveness results
On the basis of full compliance, relative reductions in the risk of death from vascular disease, of a nonfatal major vascular event or vascular death, and of any vascular event were derived from the risk equations. These relative reductions in risk were 25%, 32% and 24%, respectively.

Clinical conclusions
Simvastatin 40 mg was clearly and differentially protective for the different vascular events, even more so when adjusted for compliance. It was not associated with any significant excess of reported muscle symptoms or other adverse event.

Modelling
A Markov state-transition model was developed to predict the annual occurrence of three events (vascular death, major vascular nonfatal event, and other vascular event). The time horizon was the remaining lifetime of the patient sub-groups. The annual probabilities of the occurrence of these events were determined for each sub-group defined by age and risk of major vascular event at the beginning of treatment. The probabilities were estimated by fitting regression models to sampled data from each sub-group in the trial. The probabilities changed for each sub-group each year as the age and the events that occurred during the model were updated.

Measure of benefits used in the economic analysis
The measure of benefits used was the LYs gained. Future LYs were appropriately discounted at an annual rate of 3.5%. In a secondary analysis, predicted life expectancy was adjusted for age-specific and gender-specific health-related quality of life derived from a representative sample of the UK population (Kind et al. 1996 and Dolan et al. 1995, see 'Other Publications of Related Interest' below for bibliographic details).

Direct costs
Two cost categories were included. These were the annual costs of hospital admissions (using 1999 - 2001 resource use and 2001 UK non-reflated prices) and pharmacy reimbursement tariffs for 28 days of 40 mg generic simvastatin therapy (price at April 2005). The quantities and the costs were not reported separately. The quantities and costs were estimated on the basis of actual HPS data. Future costs were discounted at an annual rate of 3.5%, which was relevant given the long-term horizon of the study. A common price year was not specified. The hospital costs were at 2001 prices and the drug costs were at 2005 prices.

Statistical analysis of costs
The costs were treated stochastically. The annual costs of hospital admissions were estimated using linear regression models of data on hospital admission in the HPS on the basis of age, gender, disease history, other baseline characteristics, and vascular events or death within the study. Parameter uncertainty was assessed through non-parametric bootstrapping.
Indirect Costs
No indirect costs were included.

Currency
UK pounds sterling ()

Sensitivity analysis
The uncertainty of LYs gained, costs of hospital stay, and cost per LY was assessed by non-parametric bootstrapping. Each probability estimate was recalculated a thousand times using resamples with replacement.

Estimated benefits used in the economic analysis
The undiscounted LYs gained with full compliance with 40 mg generic simvastatin ranged from 0.64 (95% confidence interval, CI: 0.31 to 0.98) for people aged over 70 with a 12% 5-year risk of a major vascular event, to 2.49 (95% CI: 1.55 to 3.36) for those aged 40 to 49 with a 42% 5-year risk.

The corresponding discounted figures in the selected sub-groups were 0.38 LYs for people aged 70 and over with a 12% 5-year risk of a major vascular event, and 1.24 years for those aged 40 to 49 with a 42% 5-year risk.

Cost results
Discounted costs for the same age and risk categories are presented here by way of example.

The lifetime drug costs due to simvastatin were 670 for people aged over 70 with a 12% 5-year risk of a major vascular event and 880 for those aged 40 to 49 with a 42% 5-year risk.

The hospital admissions savings due to simvastatin were -640 for people aged over 70 with a 12% 5-year risk of a major vascular event, and -2,100 for those aged 40 to 49 with a 42% 5-year risk.

Synthesis of costs and benefits
Generic simvastatin 40 mg daily was cost-saving for most of the risk and age categories in the HPS and more effective than no statin use (i.e. it was dominant).

The reduced admission costs due to fewer vascular events outweighed the increased costs of statin treatment in all but one category (80 per LY gained for people aged 70 years or older at the start with a 12% 5-year risk).

The upper limits of the 95% CIs for all risk and age groups were below 1,000 per LY gained.

Gains in life expectancy and cost-savings decreased with increasing age and with decreasing risk of vascular disease.

Adjusted and unadjusted quality of life estimates were similar.

The estimated costs per LY gained with only 5 years' use of generic simvastatin 40 mg daily were also similar to those for lifetime treatment, with both costs and benefits reduced proportionally.

Cost-effectiveness estimates were favourable even with proprietary 40 mg simvastatin, even though they were no longer cost-saving. The cost per LY ranged from 2,610 to 9,260.

Statins remained cost-saving or cost less than 2,500 per LY gained in people as young as 35 years, or as old as 85 years, with 5-year risks of a major vascular event as low as 5% at the start of treatment.

Authors' conclusions
At current UK prices for generic simvastatin, 40 mg simvastatin daily is cost-saving and costs less than 2,500 per life-year (LY) gained for people with an annual risk of major vascular events of 1% or more, independent of their age at the start of treatment.

CRD COMMENTARY - Selection of comparators
The choice of the comparator (no statin therapy) was based on the parent trial design, which used a placebo for one arm.

Validity of estimate of measure of effectiveness
The parent study design was appropriate for the study question and the patient sample appears to have been representative of the study population. Few details of the parent trial were given, but the reader was referred to the HPS 2002 or 2005 for further detail. Although the parent trial was a randomised controlled study and there was significant crossover between arms, the study evaluated the effectiveness of simvastatin, deriving the benefits of full compliance in the study group, and no active treatment in the placebo group.

Validity of estimate of measure of benefit
The measure of benefit used was directly derived from the trial-based model in the primary analysis (LYs gained). In a secondary analysis, when adjusting for quality of life, adequate UK data sources were used. In addition, the authors estimated benefits based on the model and extrapolation beyond the study population.

Validity of estimate of costs
The perspective of the analysis was not explicitly stated, but the categories of costs were clear. It was unclear whether all the costs were valued at a common price year. The quantities and the costs were not reported separately, but further detail might have been reported in the related published paper. As the authors stated, although hospital outpatient costs and primary care costs were not measured, their inclusion would not have altered the main conclusions given their comparatively low level. A statistical analysis of the costs was performed, and data from the trial were used to extrapolate cost data to a lifetime horizon.

Other issues
The authors did not make appropriate comparisons of their finding with those from other studies. However, the issue of generalisability to other settings was partially addressed by evaluating drug prices relevant to other settings. The authors did not present their results selectively and their conclusions clearly reflected the scope of the analysis. Other issues the authors acknowledged were the exclusions of muscle symptoms and their rare significance.

Implications of the study
Statin therapy should be considered routinely for people across a wider age range and at lower risk of vascular disease than is currently recommended by the UK and other international guidelines. Lifetime treatment with generic simvastatin is cost-saving, or very cost-effective, for people aged 35 to 85 with risks of major vascular events as low as 1% per annum (about half the risk threshold proposed by the National Institute for Health and Clinical Excellence). This strategy was cost-effective even at the much higher UK proprietary price, which may be relevant to countries where simvastatin is more expensive.

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**Other publications of related interest**
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**MeSH**
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