Cost-effectiveness of simvastatin in people at different levels of vascular disease risk: economic analysis of a randomised trial in 20536 individuals
Heart Protection Study Collaborative Group

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
The use of simvastatin (40 mg/day) for the reduction of cardiovascular events was examined.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised adult patients aged about 40 to 80 years with a non-fasting blood total cholesterol concentration of at least 3.5 mmol/L (135 mg/dL). Patients were eligible if they had a medical history of coronary disease, cerebrovascular disease, other occlusive arterial disease, diabetes mellitus, or treated hypertension (if also male and aged at least 65 years). People were ineligible if their doctor considered statin therapy to be clearly indicated or contraindicated. Other factors for ineligibility were:

- recent stroke, myocardial infarction, or angina hospitalisation;
- chronic liver disease or abnormal liver function;
- severe renal disease or substantially impaired renal function;
- inflammatory muscle disease or other muscle problems;
- concurrent treatment with contraindicated drugs;
- child-bearing potential;
- severe heart failure;
- a life-threatening condition other than vascular disease or diabetes; or
- conditions that might limit compliance.

Setting
The setting was primary and secondary care. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness and resource use data were derived from a study published in 2004. The price year was 2001.
**Source of effectiveness data**
The effectiveness evidence was derived from a published study (Heart Protection Study Collaborative Group 2004, see 'Other Publications of Related Interest' below for bibliographic details).

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

**Study sample**
The method used to select the sample was unclear. After the initial screening visit, a sample of 20,536 eligible patients entered an 8- to 10-week run-in treatment phase. There were 10,269 patients in the simvastatin group and 10,267 patients in the placebo group. The patients' characteristics were reported for the entire sample and not for the two groups separately. In total, there were 15,454 men and 5,082 women, and 13,386 had coronary heart disease. In terms of age, 9,839 patients were younger than 65 years, 4,891 were aged between 65 and 70 years, and 5,806 were older than 70 years.

**Study design**
This was a prospective randomised clinical trial. The number of centres where it was carried out was not stated. The method of randomisation was not described. The length of follow-up was 5 years. The patients were followed at 4, 8 and 12 months, and then 6-monthly. Clinical staff blind to treatment allocation reviewed information pertaining to clinical data. No information on the loss to follow-up was reported.

**Analysis of effectiveness**
The analysis of the clinical study appears to have been conducted on an intention to treat basis. The primary outcome measures used were:

- the 5-year rates of first event (i.e. major vascular event (MVE), major coronary event (MCE) and vascular death) in the overall group, as well as in a sub-group of patients stratified by prior disease, gender, age, LDL cholesterol level, or risk group; and

- the rates in the simvastatin and placebo groups of MVEs, other vascular events, non-vascular events, vascular death and non-vascular death.

The baseline comparability of the study groups was not discussed. A multivariate risk score was derived to define quintiles of patients ranked by their risk of vascular events.

**Effectiveness results**
The 5-year rate of first MVE in the overall group was 25%.

The 5-year rate of first MCE was 11%.

The 5-year rate of first vascular death was 9%.

The sub-group analysis revealed that such rates were consistently higher in patients with more risk factors, in male patients, in older patients, and in groups with higher cholesterol levels. Lower rates were observed in patients with diabetes.

The number of MVEs was 2,773 in the simvastatin group and 3,689 in the placebo group (ratio 0.75, 95% confidence interval, CI: 0.71 - 0.80; 89 +/- 10 events avoided per 1,000 with simvastatin; p<0.0001).

The number of other vascular events was 4,355 in the simvastatin group and 4,905 in the placebo group (ratio 0.89,
95% CI: 0.83 - 0.94; 54 +/- 14 events avoided per 1,000 with simvastatin; p=0.0002).

The number of non-vascular events was 12,432 in the simvastatin group and 12,718 in the placebo group (ratio 0.98, 95% CI: 0.94 - 1.02; 28 +/- 25 events avoided per 1,000 with simvastatin; p=0.3).

The number of vascular deaths was 781 in the simvastatin group and 937 in the placebo group (ratio 0.83, 95% CI: 0.76 - 0.91; 15 +/- 4 events avoided per 1,000 with simvastatin; p<0.0001).

The number of non-vascular deaths was 547 in the simvastatin group and 570 in the placebo group (ratio 0.96, 95% CI: 0.86 - 1.08; 2 +/- 3 events avoided per 1,000 with simvastatin; p=0.5).

**Clinical conclusions**  
The effectiveness analysis showed that the use of simvastatin significantly reduced the rates of vascular events and deaths in comparison with placebo.

**Measure of benefits used in the economic analysis**  
The summary benefit measures used were the rate of MVEs and the rate of vascular deaths. Both measures were derived from the clinical study. A 3.5% discount rate was applied to future benefits (in the cost-effectiveness analysis).

**Direct costs**  
A 3.5% annual discount rate was applied to the costs, although discounted results were given only in a cost-effectiveness ratio. The unit costs were not presented separately from the quantities of resources used for all items. The economic evaluation included the costs of hospitalisation for vascular events and statin therapy. The cost/resource boundary of the NHS was adopted in the study. The costs of hospitalisation for non-vascular events or concomitant medications were not included because they were not significantly different between groups. Also, the costs of monitoring and drug dispensing were excluded because of their small impact on the total costs. The costs were estimated from typical NHS sources, such as the British National Formulary and UK Trust Financial Returns. Resource consumption came from the sample of patients included in the effectiveness study. Missing information about length of stay was imputed for a small proportion of events (8%). Patients taking less than 10% of statin therapy, or those having stopped therapy, were attributed no cost for study statin during that follow-up period. The price year was 2001.

**Statistical analysis of costs**  
An intention to treat comparison was carried out to examine the costs. Statistical analyses were carried out to test the significance of the observed difference in costs between the groups.

**Indirect Costs**  
The indirect costs were not included in the economic evaluation.

**Currency**  
UK pounds sterling (€).

**Sensitivity analysis**  
A sensitivity analysis was performed to examine the impact of reductions in the cost of simvastatin (given that the UK patent expired in May, 2003).

**Estimated benefits used in the economic analysis**  
See the 'Effectiveness Results' section.
Cost results
Over a 5-year follow-up period, undiscounted hospitalisation costs due to vascular events were 1,800 with simvastatin and 2,301 with placebo (difference -501 +/- 78; p<0.0001). Non-vascular related hospitalisation costs were not statistically significantly different between groups. Undiscounted statin costs were 1,712 with simvastatin and 215 with placebo (difference 1,497 +/- 8; p<0.0001).

The discounted incremental cost of statin allocation ranged from 630 (+/-126) in the highest risk quintile to 1,164 (+/-45) in the lowest.

Synthesis of costs and benefits
An incremental cost-effectiveness ratio was calculated to combine the costs and benefits of simvastatin over placebo.

The discounted incremental cost per MVE avoided with simvastatin was 11,600 (95% CI: 8,500 - 16,300). A substantial variation between the risk sub-groups was observed. For example, among individuals with a 42% 5-year risk of an MVE (highest risk quintile), the estimated cost per MVE avoided was 4,500 (95% CI: 2,300 - 7,400). By contrast, among those with a 12% 5-year risk (lowest risk quintile), it was estimated to be 31,100 (95% CI: 22,900 - 42,500).

The incremental cost per vascular death avoided ranged from 21,400 (95% CI: 10,700 - 46,100) in the highest risk quintile to 296,300 (95% CI: 178,000 - 612,000) in the lowest. The sensitivity analysis showed that if the price of simvastatin fell to 25% of the 2001 price then 40 mg/day simvastatin would generate cost-savings during the treatment period for individuals with a 5-year risk of MVEs greater than 18% (or, equivalently, of MCEs greater than 7%) and could be approximately cost-neutral for individuals with somewhat lower 5-year risks.

Authors’ conclusions
The cost-effectiveness of statin therapy among a wide range of individuals with vascular disease or diabetes depended strongly on their underlying risk of vascular events and the costs of statins. The results of the analysis suggest that simvastatin at a lower price could also be cost-effective in patients at lower risk for coronary and other vascular events.

CRD COMMENTARY - Selection of comparators
The selection of the comparator (placebo) was appropriate as it represented the standard care for most patients, especially those with a low risk level. You should decide whether this is a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from a clinical trial, which was appropriate for the study question. Limited information on the design and patients; characteristics were reported because the trial had been published already. Thus, it was difficult to examine the validity of the study. However, the robustness of the clinical evidence was ensured by the randomised design, the large group of patients recruited and the intention to treat approach. Further, the results were presented for sub-groups of patients and appropriate statistical analyses were performed.

Validity of estimate of measure of benefit
The summary benefit measures were specific to the disease considered in the study. However, the authors stated that the rate of MVEs was more readily interpreted by clinicians and their patients, whereas the rate of vascular deaths facilitated comparisons with other lifesaving interventions. It was also noted that the use of life-years gained would have seriously underestimated the gains during the 5-year follow-up period. Strong assumptions should have been made to extend the time horizon of the analysis.

Validity of estimate of costs
The authors stated explicitly which perspective was adopted in the study. As such, it appears that all the relevant
categories of costs have been included in the economic evaluation. Information on the unit costs and the quantities of resources was not provided separately for all items. The source of the cost data was given. Statistical analyses of the costs were conducted and the cost of simvastatin was varied in the sensitivity analysis. The price year was reported, which aids reflation exercises in other settings. Reasons for the exclusion of some categories of costs were provided and these appear to have been appropriate. In particular, the authors stated that the exclusion of cost categories that were not significantly different between groups did not alter the results of the cost-effectiveness analysis but improved the precision of the cost estimates. Prescribing costs were not included, but their impact on cost estimates was negligible.

Other issues
The authors made some comparisons of their findings with those from other studies. With respect to the issue of transferability of the study results to other settings, the authors stated that their estimates of cost-effectiveness at different levels of risk were likely to be generalisable to a wide range of different settings using appropriate local data to estimate the risks for particular individuals. However, only limited sensitivity analyses were carried out, which reduces the external validity of the study.

Implications of the study
The study results suggested that it would be appropriate to consider reducing the estimated level of vascular event risk at which statin therapy is recommended. The analysis highlighted the importance of distinguishing patients at different levels of vascular risk.

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Bibliographic details

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Other publications of related interest
Heart Protection Study Collaborative Group. MRC/Protection Study of cholesterol lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high risk conditions. Lancet 2004;363:757-67.


Indexing Status
Subject indexing assigned by NLM
MeSH
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