Cost-effectiveness of rosuvastatin, atorvastatin, simvastatin, pravastatin and fluvastatin for the primary prevention of CHD in the UK

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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 statins for the prevention of cardiovascular disease (CVD) events such as coronary heart disease (CHD) death, myocardial infarction (MI), angina and stroke, in patients with hypercholesterolaemia. The statins examined were rosuvastatin (ROS), atorvastatin (ATO), simvastatin (SIM), pravastatin (PRA) and fluvastatin (FLU). Initial doses were 10 mg for ROS, ATO and SIM, 20 mg for PRA, and 40 mg for FLU. Patients who failed to reach the target cholesterol level with the initial dosage where titrated to the next highest dosage (20 and 40 mg for ROS and PRA, 20, 40 and 80 mg for ATO and SIM, and 40 and 80 mg for FLU).

Type of intervention
Primary prevention.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of 55-year-old men and women, with an initial total cholesterol:high-density lipoprotein cholesterol (TC:HDL) ratio of 5.5. The patients were non-drinkers, non-smokers, did not have diabetes, were not taking antihypertensive medication, and had no evidence of left ventricular hypertrophy by electrocardiography. Women were assumed to be postmenopausal.

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

Dates to which data relate
The effectiveness data were derived from studies published between 1991 and 2004. The resource use data and costs were taken from studies published from 2002 to 2005. The costs were expressed at 2004/05 values.

Source of effectiveness data
The effectiveness evidence was derived from a review of published studies.

Modelling
A long-term quasi-Markov model was used to simulate patient management in a hypothetical cohort of 1,000 patients. The model predicted future CVD events based on Framingham risk equations. The patients were taken through four cycles of statin therapy, each of 12 weeks' duration. At the end of each cycle patients achieving the target TC goal were allocated to remain on that dose, with the corresponding improved TC:HDL ratio, for the remainder of the model. Patients who failed to achieve the target were titrated to the next highest dose of each statin. Those failing to meet the
target by the fourth quarter were assigned to that dose for the remainder of the model. The time horizon of the model was 20 years and the cycle length was 4 years. During the model time horizon, patients could remain CHD free, develop CHD, secondary CHD and CVD (including stroke, congestive heart failure and peripheral vascular disease) or die.

**Outcomes assessed in the review**
The outcomes estimated from the literature were:

- the efficacy rates (change in TL and HDL);
- the primary and secondary total CHD, stroke and other CVD risk;
- all-cause mortality; and
- the utilities for CHD and CVD health states.

**Study designs and other criteria for inclusion in the review**
The authors did not state whether a systematic review of the literature was undertaken. The primary studies appear to have been identified selectively. Drug efficacy in reducing cholesterol levels were mainly taken from two randomised controlled trials. Rates of future events (risk for CVD events) were derived from Framingham risk equations. All-cause mortality was obtained from UK life tables. Utility values were derived from different sources.

**Sources searched to identify primary studies**
Not reported.

**Criteria used to ensure the validity of primary studies**
Not reported.

**Methods used to judge relevance and validity, and for extracting data**
Not reported.

**Number of primary studies included**
Fourteen primary studies provided the clinical data.

**Methods of combining primary studies**
Not reported.

**Investigation of differences between primary studies**
Not reported.

**Results of the review**
The mean changes in TC and HDL levels were, respectively:

- ROS 10 mg, 32.9% (95% confidence interval, CI: 27.4 to 38.5) and 7.7% (95% CI: 2.4 to 17.0);
- ROS 20 mg, 37.6% (95% CI: 31.9 to 43.3) and 9.5% (95% CI: 3.4 to 19.4);
- ROS 40 mg, 40.2% (95% CI: 34.4 to 45.9) and 9.6% (95% CI: 3.4 to 19.6);
ATO 10 mg, 27.1% (95% CI: 22.0 to 32.5) and 5.7% (95% CI: 1.4 to 14.5);
ATO 20 mg, 31.8% (95% CI: 26.4 to 37.3) and 4.8% (95% CI: 1.0 to 13.2);
ATO 40 mg, 35.8% (95% CI: 30.2 to 41.5) and 4.4% (95% CI: 0.9 to 12.7);
ATO 80 mg, 38.9% (95% CI: 33.2 to 44.6) and 2.1% (95% CI: 0.2 to 9.3);
SIM 10 mg, 20.3% (95% CI: 15.8 to 25.2) and 5.3% (95% CI: 1.3 to 13.8);
SIM 20 mg, 25.7% (95% CI: 20.7 to 31.0) and 6% (95% CI: 1.6 to 14.9);
SIM 40 mg, 27.9% (95% CI: 22.7 to 33.3) and 5.2% (95% CI: 1.2 to 13.7);
SIM 80 mg, 32.9% (95% CI: 27.4 to 38.5) and 6.8% (95% CI: 2.0 to 15.8);
PRA 10 mg, 14.7% (95% CI: 10.8 to 19.1) and 3.2% (95% CI: 0.5 to 11.0);
PRA 20 mg, 17.2% (95% CI: 13.0 to 21.9) and 4.4% (95% CI: 0.9 to 12.8);
PRA 40 mg, 21.5% (95% CI: 16.9 to 26.5) and 5.6% (95% CI: 1.4 to 14.3);
FLU 20 mg, 16.4% (95% CI: 12.3 to 21.0) and 4.6% (95% CI: 1.0 to 12.8);
FLU 40 mg, 19.9% (95% CI: 15.4 to 24.8) and 5.2% (95% CI: 1.2 to 13.7);
FLU 80 mg, 21.4% (95% CI: 16.8 to 26.4) and 7.5% (95% CI: 2.3 to 16.8).

The mean relative risk for long-term mortality was:

for angina, 1.72 (95% CI: 1.23 to 2.43);
for MI, 2.37 (95% CI: 1.57 to 3.56);
for stroke, 3.20 (95% CI: 2.80 to 3.70);
for other, 5.50 (95% CI: 4.11 to 7.36).

The following utility values were estimated:

angina, 0.718 (+/- 0.016);
MI (first year), 0.683 (+/- 0.015);
post-MI, 0.718 (+/- 0.016);
stroke mild, 0.740 (+/- 0.026);
stroke moderate, 0.740 (+/- 0.026);
stroke severe, 0.380 (+/- 0.046);
congestive heart failure, 0.683 (+/- 0.020);
peripheral vascular disease, 0.750 (+/- 0.022).

Measure of benefits used in the economic analysis
The summary benefit measure used was the number of quality-adjusted life-years (QALYs). These were estimated by combining utility values and expected survival in the modelling approach. An annual discount rate of 3.5% was used for QALYs gained in the future. The proportions of patients projected to achieve the target cholesterol level were also reported.

**Direct costs**

The analysis of the costs was carried out from the perspective of the NHS. It included the costs of statins and the costs associated with the management of CHD and CVD events (angina, acute coronary syndromes, stroke, transient ischaemic attack, chronic heart failure, peripheral vascular disease and CHD death). The unit costs were not presented separately from the quantities of resources used as most costs were presented as macro-categories. Most of the costs and resource use data were derived from published studies, the majority of which used NHS reference costs. Statin costs were taken from the NHS Drug Tariff. Given the long-term time horizon of the analysis, an annual discount rate of 3.5% was applied to costs incurred after the first year. The costs were expressed as 2004/05 values.

**Statistical analysis of costs**

The costs were assigned a gamma probabilistic distribution.

**Indirect Costs**

The indirect costs were not included in the economic analysis.

**Currency**

UK pounds sterling (£).

**Sensitivity analysis**

A probabilistic sensitivity analysis was carried out to address the issue of uncertainty by assigning stochastic distributions to all model inputs. Cost-effectiveness acceptability curves were generated to show the probability of each statin being cost-effective at different levels of society's willingness to pay for an additional QALY. A univariate sensitivity analysis was also performed to assess the impact on the cost-utility ratios of individual model inputs such as event costs, all-cause mortality, risk of events, proportion of lipid benefit, time horizon, starting age and discounting. Alternative values appear to have been set by the authors or based on the 95% CIs obtained from the literature.

**Estimated benefits used in the economic analysis**

The QALYs were incremental in comparison with no treatment.

In men, the expected QALYs were 0.71 with ROS, 0.60 with ATO, 0.53 with SIM, 0.45 with FLU and 0.42 with PRA. In women, the expected QALYs were 0.51 with ROS, 0.44 with ATO, 0.39 with SIM, 0.33 with FLU and 0.31 with PRA.

The percentage of patients achieving the target cholesterol level with the initial dose was 88% with ROS, 70.3% with ATO, 44% with SIM, 34.5% with PRA and 43.1% with FLU.

**Cost results**

The costs were incremental in comparison with no treatment.

In men, the expected costs were 2,608 with ROS, 2,871 with ATO, 871 with SIM, 2,002 with FLU and 125 with PRA.

In women, the expected costs were 2,982 with ROS, 3,233 with ATO, 1,076 with SIM, 2,265 with FLU and 243 with PRA.
Synthesis of costs and benefits

Incremental cost-utility ratios were calculated to combine the costs and benefits of the alternative strategies.

In men, the incremental cost per QALY was 9,735 with ROS over SIM, 6,883 with SIM over PRA, and 296 with PRA over no treatment. ATO and FLU were dominated (less effective and more expensive).

In women, the incremental cost per QALY was 15,184 with ROS over SIM, 10,790 with SIM over PRA, and 779 with PRA over no treatment. ATO and FLU were dominated (less effective and more expensive).

The incremental cost-utility ratio of ROS, the most effective therapy, in no case exceeded the threshold of 30,000 per QALY.

The probabilistic sensitivity analysis showed that, at a willingness to pay of 30,000 per QALY, the probability that ROS is cost-effective was approximately 80% in men and 70% in women. PRA was the most cost-effective strategy at thresholds lower than 10,000 per QALY.

The univariate sensitivity analysis showed that the model inputs with the greatest impact on cost-utility ratios were the baseline risk, time horizon and treatment efficacy. However, the ranking among the alternative statins did not change.

Authors’ conclusions

All statins represented cost-effective treatments in the primary prevention of coronary heart disease (CHD) in comparison with no treatment, but ROS was the most cost-effective from the perspective of the National Health Service (NHS). The probabilistic sensitivity analysis confirmed that there was a high probability of rosuvastatin (ROS) being cost-effective under conditions of uncertainty.

CRD COMMENTARY - Selection of comparators

The rationale for the choice of the comparators was clear as all available statins were considered. Initial dosages were clearly stated and the issue of subsequent dose adjustment was discussed. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness

The effectiveness evidence might have been derived from selectively identified studies since details on the method and conduct of a systematic review of the literature were not reported. Limited information on the studies used to estimate clinical inputs was provided. It was therefore difficult to determine the validity of the primary sources, with the exception of the clinical trial used to derive short-term data on the efficacy of treatment. However, the Framingham risk equations are frequently used for estimating the long-term CVD risk. The authors did not report the method used to combine the primary estimates and did not investigate homogeneity among the different studies. However, the issue of variability in the data was addressed in the probabilistic sensitivity analysis.

Validity of estimate of measure of benefit

QALYs were the most appropriate benefit measure because they capture the impact of the interventions on both quality of life and survival, which are the most relevant dimensions of health for patients at risk of CVD events. Some information on the instrument used to derive utility was reported. The use of QALYs permits comparisons to be made with the benefits of other health care interventions. Discounting was appropriately applied.

Validity of estimate of costs

The analysis of the costs was consistent with the perspective of the study. Typical NHS sources were used to derive the costs. However, details of the unit costs and quantities of resources used were not presented. In effect, a detailed breakdown of the cost items was not given. In addition, some costs were presented as macro-categories, which will
hinder the replication of the analysis in other settings. The cost estimates were specific to the study setting but variations in the cost categories were explored in the sensitivity analysis. Statistical analyses of the costs were carried out and probabilistic distributions were assigned. This represents a strong feature of the cost analysis. The price year was reported, which will facilitate reflation exercises in other time periods. Discounting was appropriately performed and the impact of changing discount rates was investigated in the sensitivity analysis.

Other issues
The authors did not compare their findings with those from other studies. They did not explicitly address the issue of the generalisability of the study results to other settings, although the sensitivity analysis considered the impact of individual parameters, as well as in a simultaneous approach. The authors pointed out that the model did not address the issue of compliance, but non-compliant patients should not differ among treatments. The study referred to patients with hypercholesterolaemia and this was reflected in the authors' conclusions.

Implications of the study
The study results support the use of ROS for the treatment of patients requiring cholesterol-lowering therapy to prevent CVD events.

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Supported by AstraZeneca.

Bibliographic details

Other publications of related interest


Indexing Status
Subject indexing assigned by NLM

MeSH
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