The cost-effectiveness of a new statin (rosuvastatin) in the UK NHS
Palmer S J, Brady A J, Ratcliffe A E

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 rosuvastatin, compared with other statins, for the treatment of hyperlipidaemia and the prevention of coronary heart disease (CHD).

Type of intervention
Primary and secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The target population comprised all newly diagnosed hypercholesterolaemic patients, who exceeded the UK and European target levels for TC (5 mmol/L) and LDL-C (3 mmol/L).

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

Dates to which data relate
The effectiveness evidence was derived from studies published from 1999 to 2003. The costs were derived from data published in 2002 (monitoring costs) and in 2003 (drug acquisition costs). The price year was 2002.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of completed studies.

Modelling
A model was developed to assist the decision-making process about which statin should be used for to prevent CHD, in the context of the NHS. The structure of the model was a decision tree. The model represented the treatment of newly diagnosed hypercholesterolaemic patients using a policy of dose titration. Each patient was initially assigned treatment with one of the licensed statins, at the lowest licensed dose. Every 3 months, the TC or LDL-C levels were measured (each biochemical parameter was examined in a separate decision tree). If the target level was achieved, then the patient was considered a responder, irrespective of subsequent TC or LDL-C levels, and was maintained on this regimen until the end of the analysis. If the target level was not achieved, the patient was titrated to a higher dose of statin every 12 weeks, until the maximum licensed dose was reached. Those patients not achieving the target levels at the maximum statin dose remained on this dose until the end of the model treatment period. The duration of the model was one year (52 weeks). Events such as non-compliance, discontinuation and failure to titrate in accordance with guidelines were not included in the model structure.
Outcomes assessed in the review
The outcomes assessed in the review were the efficacy of statins and the mean baseline levels of TC and LDL-C. Statin efficacy was expressed as the mean percentage reduction in TC and LDL-C.

Study designs and other criteria for inclusion in the review
The efficacy of statins was derived from a randomised multicentre US clinical trial (randomised controlled trial). The efficacy data for fluvastatin came from a meta-analysis. The baseline TC and LDL-C levels were derived from a UK secondary CHD prevention trial.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
Not stated.

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

Number of primary studies included
Three primary studies were included in the review.

Methods of combining primary studies
The effectiveness data from the primary studies were not combined.

Investigation of differences between primary studies
The authors investigated the differences in the patient populations between the trial that provided most of the efficacy data and the one study that reported corresponding data for fluvastatin, as used in the meta-analysis. They stated that the application of similar inclusion and exclusion criteria and institutional settings in both studies ensured that the populations were broadly comparable. Therefore, no bias was introduced in the results.

Results of the review
The mean reductions in TC levels for each statin and licensed dosage were:

for rosuvastatin, 33% (10 mg), 38% (20 mg) and 40% (40 mg);
for atorvastatin 27% (10 mg), 32% (20 mg), 36% (40 mg) and 39% (80 mg);
for fluvastatin, 13% (20 mg), 19% (40 mg) and 35% (80 mg);
for pravastatin, 15% (10 mg), 17% (20 mg) and 22% (40 mg); and
for simvastatin, 20% (10 mg), 26% (20 mg), 28% (40 mg) and 33% (80 mg).

The mean reductions in LDL-C levels for each statin and licensed dosage were:

for rosuvastatin, 46% (10 mg), 52% (20 mg) and 55% (40 mg);
for atorvastatin, 37% (10 mg), 43% (20 mg), 48% (40 mg) and 51% (80 mg);
for fluvastatin, 17% (20 mg), 23% (40 mg) and 26% (80 mg); for pravastatin, 20% (10 mg), 24% (20 mg) and 30% (40 mg); and for simvastatin, 28% (10 mg), 35% (20 mg), 39% (40 mg) and 46% (80 mg).

The mean baseline levels used in the model were 6.41 mmol/L for TC and 4.37 mmol/L for LDL-C.

Methods used to derive estimates of effectiveness
It was stated that the validity of a key assumption used in the model was confirmed from results presented in other studies.

Estimates of effectiveness and key assumptions
The key assumption used in the model was that the percentage reductions in TC and LDL-C were independent of the baseline levels.

Measure of benefits used in the economic analysis
The measure of benefit used was the proportion of patients achieving the target cholesterol levels (TC or LDL-C).

Direct costs
The costs of the health service were included. These covered general practitioner (GP) and practice nurse consultations, lipoprotein and TC tests, and liver function test. The costs of treating adverse effects (including the management of abnormal liver function test results) were not considered in the analysis. The costs and the quantities were reported separately. The quantities and total costs were derived through modelling. The drug acquisition costs were based on the 2003 British National Formulary. The GP and practice nurse unit costs were derived from published literature (2002). Biochemical test costs were estimated from a survey of NHS trusts. Prices relating to 2002 were used. Discounting was not necessary, as the costs were estimated for one year, and was not carried out.

Statistical analysis of costs
The costs were treated deterministically. No statistical analysis of the costs was performed.

Indirect Costs
The indirect costs were not included in the analysis.

Currency
UK pounds sterling (€).

Sensitivity analysis
A probabilistic sensitivity analysis was undertaken using probability distributions of baseline levels, as well as percentage reductions of TC and LDL-C, to reflect the uncertainty in the mean estimates of these inputs to the model. The results were then presented in the form of cost-effectiveness acceptability curves (CEACs). Percentage reductions were assumed to follow a beta-distribution, whereas baseline values were assumed follow a normal distribution. In addition, a series of one-way sensitivity analyses were conducted to explore the impact of alternative assumptions to those applied in the base-case scenario. More specifically, excluding monitoring costs, using the generic acquisition cost for simvastatin, using a higher starting dose for all statins except rosuvastatin, and changing the baseline TC or LDL-C levels (+/- 1 standard deviation). The latter analysis allowed the generalisability of the results to be examined in different patient populations.
Estimated benefits used in the economic analysis
The percentage of patients treated to target TC levels was 99.66% with rosuvastatin, 99.28% with atorvastatin, 68.57% with fluvastatin, 47.90% with pravastatin, and 92.81% with simvastatin.

The percentage of patients treated to target LDL-C levels was 99.94% with rosuvastatin, 99.34% with atorvastatin, 43.92% with fluvastatin, 44.21% with pravastatin, and 94.93% with simvastatin.

These results reflected the efficacy after a year of treatment.

Cost results
The total mean cost per patient achieving the TC target level was 368 with rosuvastatin, 398 with atorvastatin, 342 with fluvastatin, 487 with pravastatin, and 453 with simvastatin.

The total mean cost per patient achieving the LDL-C target level was 365 with rosuvastatin, 404 with atorvastatin, 352 with fluvastatin, 493 with pravastatin, and 457 with simvastatin.

These results represented the costs for one year of treatment and included both the drug acquisition and monitoring costs. The costs of treating adverse effects were not included in the analysis.

Synthesis of costs and benefits
Incremental cost-effectiveness ratios (ICERs) were calculated by combining the estimated costs and benefits of the alternative options assessed. The ICERs were not calculated for dominated strategies (more expensive and less effective than another option), as this was not necessary. In addition, if an ICER for a given strategy was higher than that for the next most effective strategy, then this strategy was ruled out on the basis of extended dominance. After ruling out strategies using principles of dominance and extended dominance, the ICERs were recalculated for the remaining strategies. Atorvastatin, pravastatin and simvastatin were all dominated by rosuvastatin, as they were both more costly and less effective when considering both TC and LDL-C targets. The ICER of rosuvastatin compared with fluvastatin was $83 per additional patient achieving TC level, or 23 per additional patient achieving the LDL-C level. The CEACs demonstrated that the probability that rosuvastatin was cost-effective in comparison with fluvastatin would exceed 0.95 if the maximum willingness to pay were greater than 220 (TC) and 60 (LDL-C) per additional patient achieving the targets for TC and LDL-C, respectively.

In terms of the one-way sensitivity analyses, excluding the monitoring costs changed only the value of the ICER between rosuvastatin and fluvastatin. This rose to 241 (TC) and 129 (LDL-C) per additional patient achieving the target. With the exception of rosuvastatin, applying a lower acquisition cost for simvastatin, or changing the starting statin dose to a higher level, did not alter substantially the base-case results. Increasing the baseline TC and LDL-C levels by one standard deviation led to a reduction in the ICER of rosuvastatin of 63 (TC) and 20 (LDL-C) compared with fluvastatin. Decreasing the baseline TC and LDL-C levels by one standard deviation increased the ICER of rosuvastatin to 1,198 (TC) and 217 (LDL-C) compared with fluvastatin.

Authors' conclusions
The cost-effectiveness of rosuvastatin in the UK, compared with other licensed statins, appeared extremely favourable in patients with hypercholesterolaemia.

CRD COMMENTARY - Selection of comparators
There was a clear justification for the selection of the comparators. They represented all licensed statins used in the UK for treating hypercholesterolaemia. You should consider whether these options reflect current practice in your own setting.
Validity of estimate of measure of effectiveness
The authors did not state that a systematic review of the literature was undertaken. The effectiveness data were mainly derived from a large multicentre randomised controlled trial. The estimates of effectiveness were not combined. The authors compared the characteristics of patients participating in the two studies that provided the effectiveness data for the analysis. They found it unlikely that there were important differences that would introduce bias into the results.

Validity of estimate of measure of benefit
The estimation of benefits was modelled. The decision tree used for the analysis was appropriate for this purpose. However, the reader must be aware that the model did not consider events such as non-compliance, discontinuation and failure to titrate according to guidelines, which might have affected the results.

Validity of estimate of costs
The study perspective was stated to have been that of the UK NHS. All the relevant categories of costs were included in the analysis. The costs of treating adverse effects were excluded from the analysis. However, the authors stated that this was a conservative assumption, which would only underestimate the magnitude of the cost-effectiveness of rosuvastatin. The costs and the quantities were reported separately. The quantities were derived from modelling. A sensitivity analysis of the costs was conducted, but only for specific assumptions (omitting monitoring costs, and using the generic acquisition cost for simvastatin). Discounting was not carried out, but it was not relevant since the costs were incurred during one year. The date to which the prices referred was reported.

Other issues
The authors made appropriate comparisons of their findings with those from other studies. The issue of the generalisability of the results to other settings was not addressed. The results of the study were reported in full. It was stated that the target population consisted of newly diagnosed hypercholesterolaemic patients. However, baseline data were derived from a UK secondary CHD prevention trial. It is possible that CHD patients have higher TC and LDL-C levels than those found in a newly diagnosed hypercholesterolaemic population without CHD, and this fact was not explicitly reflected in the authors' conclusions.

The authors reported a number of further study limitations. First, the short study period of the randomised controlled trial that provided most of the efficacy data. Second, the efficacy data for fluvastatin were derived from a separate study, although the patient population in this study was comparable with that of the randomised controlled trial. Third, the authors acknowledged that their model was restricted to monotherapy targeted at all individual patients, whereas combinations of statins targeted at specific, appropriate groups of individuals based on their baseline characteristics might be a more cost-effective approach. Finally, the authors questioned whether the focus on achieving TC and LDL-C target levels was the appropriate tactic for the reduction of CHD risk.

Implications of the study
The authors suggested that their results provide a cost-effectiveness message for UK health practitioners in the treatment of hyperlipidaemia, in line with the UK's National Service Framework for CHD. They estimated that, for a notional budget of 1 million, an additional number of 700 patients could be treated achieving TC or LDL-C targets with rosuvastatin, compared with allocating the same amount to treatment with fluvastatin. Finally, the authors suggested that further economic research, based on either actual or projected cardiovascular outcome data, should be carried out to ratify the conclusions of the study and to establish the cost-effectiveness of statins as a preventive measure for CHD in the UK.

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