A cost-effectiveness model of alternative statins to achieve target LDL-cholesterol levels

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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 alternative 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) to achieve target low-density lipoprotein cholesterol (LDL-C) levels of 3 mmol/L or less. The statins studied included atorvastatin, cerivastatin, fluvastatin, pravastatin and simvastatin.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with prior coronary heart disease and dyslipidaemia. A starting LDL-C level of greater than 3 mmol/L was considered.

Setting
The setting was primary care. The economic analysis was carried out in the United Kingdom.

Dates to which data relate
The effectiveness evidence was derived from studies published in 1998 to 1999. The resource use data were derived from a set up pathway of care. The cost data related to sources published in 1998 to 2000. No price year was reported.

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

Modelling
A Markov model was developed to estimate the proportion of patients achieving target LDL-C with statin monotherapy, and the total cost of treatment. The model was based on 12-week cycle visits to control the treatment until the target LDL-C level was achieved or until the end of the study (one year). At each visit, if the patient's LDL-C level was still above the target of 3 mmol/L, the statin dose was increased to the next level according to the manufacturers' recommendations (a dose-titration scenario). The patients stayed on the current dose after achieving the target LDL-C level for the rest of the one-year treatment period.

Outcomes assessed in the review
The outcomes assessed in the review were the baseline LDL-C levels in the studied population, assuming a normal distribution defined by its mean and standard deviation. The efficacy of each statin, at each dose, was assessed in terms
of the percentage reduction in LDL-C.

**Study designs and other criteria for inclusion in the review**
The estimates were derived from one meta-analysis supplemented by two additional studies.

**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**
Two primary studies and one meta-analytic study provided evidence for the outcomes of interest.

**Methods of combining primary studies**
The outcomes of interest were combined narratively to populate the Markov model.

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

**Results of the review**
The baseline LDL-cholesterol level was 4.37 mmol/L (standard deviation 0.71).

The mean percentage reductions with different statins and doses were:

36.6 (95% confidence interval, CI: 34.4 - 38.7) with atorvastatin 10 mg/day;
46.3 (95% CI: 44.1 - 48.5) with atorvastatin 20 mg/day;
51.2 (95% CI: 48.7 - 53.7) with atorvastatin 40 mg/day;
54.0 (95% CI: 48.4 - 59.6) with atorvastatin 80 mg/day;
22.5 (95% CI: 21.4 - 23.6) with cerivastatin 0.1 mg/day;
29.5 (95% CI: 28.5 - 30.5) with cerivastatin 0.2 mg/day;
31.2 (95% CI: 30.3 - 32.1) with cerivastatin 0.3 mg/day;
36.2 (95% CI: 35.4 - 37.0) with cerivastatin 0.4 mg/day;
21.7 (95% CI: 19.8 - 23.5) with fluvastatin 20 mg/day;
26.4 (95% CI: 24.9 - 27.9) with fluvastatin 40 mg/day;
29.6 (95% CI: 28.1 - 31.1) with fluvastatin 80 mg/day;
21.3 (95% CI: 18.4 - 24.1) with pravastatin 10 mg/day;
26.1 (95% CI: 24.6 - 27.7) with pravastatin 20 mg/day;
27.8 (95% CI: 23.0 - 32.6) with pravastatin 40 mg/day;
29.1 (95% CI: 27.2 - 30.9) with simvastatin 10 mg/day;
33.5 (95% CI: 30.9 - 36.1) with simvastatin 20 mg/day;
38.8 (95% CI: 35.3 - 42.4) with simvastatin 40 mg/day; and
48.0 (95% CI: 47.1 - 49.7) with simvastatin 10 mg/day

Measure of benefits used in the economic analysis
The measure of benefit was the proportion of patients achieving the target LDL-C level of 3 mmol/L.

Direct costs
Discounting was irrelevant as the costs were incurred over a period of one year. The costs were estimated from the perspective of the health care system. These included the costs of general practitioner (GP) visits, nurse consultations, drug acquisition, blood cholesterol tests and liver function tests. The initiation of statin therapy included one GP consultation, two GP nurse consultations, a total cholesterol test and a lipoprotein test. The costs of adverse events were not included in the analysis. The costs for a monitoring visit included one GP consultation, a total cholesterol test and a lipoprotein test. All patients had an initiation visit and a 12-week monitoring visit. An additional monitoring visit was incurred each time the statin dose was increased. Those patients who achieved the target LDL-C level did not have further monitoring visits during the year.

The overall resource use and the total costs were evaluated using the Markov model. The unit costs and the quantities of resources were reported separately. The costs were mainly estimated from actual data derived from official data. No price year was reported.

Statistical analysis of costs
Statistical analyses of the costs were not carried out.

Indirect Costs
No indirect costs were included in the analysis.

Currency
UK pounds sterling (£).

Sensitivity analysis
Sensitivity analyses were conducted on the following scenarios:

patients remaining on their starting dose therapy for the entire one-year treatment period; and

analysis using the drug acquisition costs only.

Further one-way sensitivity analyses were carried out using the following:
the mean percentage reductions in LDL-C achieved with each dose of statin (ranges: +/-10%, +/- 20%);  
the cost of a physician visit based on the cost of a specialist physician visit (70);  
a 6-week (instead of 12-week) time between the follow-up visits,  
a variation in the baseline population mean LDL-C of +/-2 standard deviations; and  
a 5% drop-out rate after 12 weeks.

A fixed budget analysis was also performed to determine the number of patients who would be treated within a budget of 100,000, on the basis of the calculated cost per patient treated.

Estimated benefits used in the economic analysis  
Compared with no treatment, the percentage of treated patients achieving target LDL-C in one year was 99.9% with atorvastatin, 67.1% with cerivastatin, 42.4% with fluvastatin, 36.4% with pravastatin, and 97.5% with simvastatin.

Cost results  
Compared with no treatment, the mean annual cost per patient was 3,721 with atorvastatin, 3,272 with cerivastatin, 3,382 with fluvastatin, 4,296 with pravastatin, and 4,086 with simvastatin.

Synthesis of costs and benefits  
An incremental cost-effectiveness analysis was carried out to combine the costs and the benefits. Compared with no treatment, the incremental cost per extra patient treated to target was 383 with atorvastatin, 501 with cerivastatin, 820 with fluvastatin, 1,213 with pravastatin, and 431 with simvastatin.

Incremental cost-effectiveness ratios compared with the lowest cost treatment (cerivastatin) were 141 per additional patient achieving target LDL-C with atorvastatin and 275 with simvastatin. Fluvastatin and pravastatin were dominated in this analysis.

When considering only the drug acquisition costs, the incremental cost per patient successfully treated to target was lowest for atorvastatin (289), followed by cerivastatin (304), simvastatin (311), fluvastatin (533) and pravastatin (877).  
In the single-dose scenario, atorvastatin represented the most cost-effective treatment (358 per patient treated to target).  
Given a fixed budget, more patients could be treated to target with atorvastatin (261 patients) than with the other four statins (range: 82 - 232 patients).

The results were robust to changes in assumptions about the costs of the therapies, the interval between dose titrations, and the patient drop-out rate of 5%. The cost-effectiveness of therapy varied with the baseline LDL-C. At LDL-C levels only moderately above the target, the lowest costs drugs were also the most effective. At higher LDL-C levels, the efficacy difference between the products was more marked and the more effective drugs demonstrated better cost-effectiveness.

Authors' conclusions  
Under the baseline assumptions of the model, monotherapy with atorvastatin achieved the lowest cost per patient treated to the target low-density lipoprotein cholesterol (LDL-C) level, and therefore, the largest number of patients to be treated to target LDL-C within a fixed drug budget. Atorvastatin monotherapy also enabled the largest proportion of patients to achieve the target LDL-C levels on the starting dose.

CRD COMMENTARY - Selection of comparators  
The choice of alternative statin interventions (all statin licensed in UK at the time the study was conducted) was well justified by the authors, on the grounds of the different costs and relative reduction of cholesterol. No intervention was
used as the basic comparator. You should assess whether a statin is currently used in your own setting.

**Validity of estimate of measure of effectiveness**
The measure of effectiveness was the percentage of the population achieving a target LDL-C level of 3 mmol/L. This relied heavily on the percentage decrease of cholesterol with different statins and doses, derived from the literature. Readers are advised to consider the primary studies used (see Other Publications of Related Interest) given that the authors did not state that a systematic review of the literature had been undertaken. They also did not consider the impact of differences in the primary studies when estimating the effectiveness.

**Validity of estimate of measure of benefit**
The benefit measure used in the analysis was the proportion of patients achieving the target LDL-C level of 3 mmol/L. It was modelled using a Markov model that seems to have been appropriate for the study question. The authors acknowledged that the choice of this specific benefit measure could have failed to detect other aspects of the interventions considered, since it was restricted to target LDL-C achievement. Indeed, these benefits could vary across different statins.

**Validity of estimate of costs**
For the selected cost perspective, the health care system, it appears that the authors have included only the costs of the interventions. The choice of the costs to be analysed seems to have been guided by the choice of the effectiveness measure. Some relevant cost categories, such as the costs of avoided health care events and treatment of possible side effects, were not considered. However, the authors stated that these omissions were not likely to affect the study's results, due to the low occurrence rate of adverse events. The quantities of resource use were based on a pathway of care costing. The costs and the quantities were reported separately. Appropriate sensitivity analyses were performed for some of the costs and the frequency of monitoring. However, no sensitivity analyses were performed on the relative price of different statins that were expected to have significant influence on the results presented. No price year was reported.

**Other issues**
It is unclear how the cost-effectiveness of different statins could have been influenced by the choice of the benefit measure. The authors discussed some of the limitations of the study. First, the lack of comprehensive accounting for the benefits from the actual reduction of LDL-C (i.e. below the 3 mmol/L limit). Second, the fact that the use of a combination of statins to reach the appropriate cholesterol reduction was not considered.

The issue of the generalisability of the study results to other settings was addressed by performing several sensitivity analyses and using a relatively flexible decision model. A population of patients with prior coronary heart disease and dyslipidaemia was considered, and this was reflected in the conclusions of the study.

**Implications of the study**
The authors conclude that monotherapy with atorvastatin achieves the lowest cost per patient treated to the target LDL-C level.

**Source of funding**
None stated.

**Bibliographic details**
Other publications of related interest


Indexing Status
Subject indexing assigned by NLM

MeSH
Atorvastatin Calcium; Cholesterol, LDL /blood; Coronary Disease /blood /economics /prevention & control; Cost-Benefit Analysis; Fatty Acids, Monounsaturated /economics /therapeutic use; Heptanoic Acids /economics /therapeutic use; Humans; Hydroxymethylglutaryl-CoA Reductase Inhibitors /economics /therapeutic use; Indoles /economics /therapeutic use; Models, Economic; Pravastatin /economics /therapeutic use; Pyridines /economics /therapeutic use; Pyrroles /economics /therapeutic use; Simvastatin /economics /therapeutic use

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