Cost-effectiveness analysis of combination statin/ezetimibe therapy for the treatment of elevated low-density lipoprotein cholesterol

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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 monotherapies and combination therapies for the treatment of hyperlipidaemia. The monotherapies assessed were fluvastatin, lovastatin, pravastatin, simvastatin, rosuvastatin and atorvastatin. The combination therapies assessed were lovastatin, pravastatin, simvastatin and atorvastatin, each in combination with ezetimibe. Dosages from 5 to 80 mg were used. Further details of the technologies were not reported.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The details of the study population were not explicitly reported, although the authors stated that they searched for "clinical trials with similar sample size and study methodology". No further details were reported, so it was unclear whether the study population had to have a specific level of elevated LDL-C or other defining characteristics.

Setting
The setting was secondary care. The economic study was carried out in the USA.

Dates to which data relate
The dates when the effectiveness data and cost data were collected were unclear, although the prices were measured in 2004 dollars.

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

Link between effectiveness and cost data
The costing was carried out retrospectively on a different sample of patients to that used in the effectiveness study.

Modelling
The authors used a Monte Carlo simulation to assess the robustness of their conclusions. The model employed triangular distributions using the most likely values, these reduced by 25% and increased to the average wholesale price to define the parameters of the triangular distribution. A total of 5,000 simulations were conducted using Crystal Ball 2002.2 software (Decisioneering Inc., Denver, CO).
Outcomes assessed in the review
The authors search for the "largest average percentage LDL-C reduction" from the comparable clinical trials selected for inclusion in the review. It was unclear whether the review was systematic.

Study designs and other criteria for inclusion in the review
The authors reported only that they searched for "clinical trials with similar sample size and study methodology".

Sources searched to identify primary studies
Published medical literature and 'package inserts' were used to identify appropriate clinical trials. It was unclear exactly what was meant by 'package inserts'.

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
Not reported.

Methods of combining primary studies
The data from the primary studies do not appear to have been combined.

Investigation of differences between primary studies
Not reported.

Results of the review
The largest average percentage LDL-C reductions observed for each health technology of interest, and for each dosage, are reported here:

- atorvastatin, 10 mg = 35%, 20 mg = 40%, 40 mg = 43%, 80 mg = 51%;
- fluvastatin, 20 mg = 22%, 40 mg = 25%, 80 mg = 35%;
- lovastatin, 10 mg = 19%, 20 mg = 26%, 40 mg = 29%;
- pravastatin, 10 mg = 20%, 20 mg = 24%, 40 mg = 29%, 80 mg = 37%;
- rosuvastatin, 5 mg = 40%, 10 mg = 46%, 20 mg = 52%, 40 mg = 55%;
- simvastatin, 10 mg = 27%, 20 mg = 36%, 40 mg = 36%, 80 mg = 44%;
- atorvastatin plus ezetimibe, 10 mg = 50%, 20 mg = 54%, 40 mg = 54%, 80 mg = 60%;
- lovastatin plus ezetimibe, 10 mg = 33%, 20 mg = 39%, 40 mg = 45%;
- pravastatin plus ezetimibe, 10 mg = 34%, 20 mg = 36%, 40 mg = 41%;

NHS Economic Evaluation Database (NHS EED)
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simvastatin plus ezetimibe, 10 mg = 46%, 20 mg = 45%, 40 mg = 65%, 80 mg = 61%.

**Measure of benefits used in the economic analysis**
The maximum percentage reduction in LDL-C, as observed in the effectiveness evidence, was used in the economic analysis.

**Direct costs**
The outpatient clinic acquisition costs at the authors' institution were used as an approximation of the drug costs. These were obtained from the Cardinal Healthcare Website and measured in 2004 prices. The annual costs were estimated at a single point in time and, therefore, discounting was not required in this instance. The quantities were defined by the dosage under consideration.

**Statistical analysis of costs**
The costs were treated deterministically. The authors did not report that any statistical analyses of the costs were carried out.

**Indirect Costs**
The indirect costs were not relevant to the perspective of the study.

**Currency**
US dollars ($).

**Sensitivity analysis**
A Monte Carlo simulation, in which both cost and effect parameters were varied, was carried out. The aim of this analysis was to assess the robustness of the results.

**Estimated benefits used in the economic analysis**
See the 'Effectiveness Results' section.

**Cost results**
The annual costs observed for each health technology of interest, and for each dosage, were as follows:

- atorvastatin, 10 mg = $510, 20 mg = $798, 40 mg = $798, 80 mg = $798;
- fluvastatin, 20 mg = $171, 40 mg = $218, 80 mg = $216;
- lovastatin, 10 mg = $46, 20 mg = $79, 40 mg = $155;
- pravastatin, 10 mg = $407, 20 mg = $435%, 40 mg = $452, 80 mg = $634;
- rosuvastatin, 5 mg = $625, 10 mg = $624, 20 mg = $621, 40 mg = $626;
- simvastatin, 10 mg = $412, 20 mg = $763, 40 mg = $919, 80 mg = $596;
- atorvastatin plus ezetimibe, 10 mg = $1,088, 20 mg = $1,376, 40 mg = $1,376, 80 mg = $1,376;
- lovastatin plus ezetimibe, 10 mg = $624, 20 mg = $657, 40 mg = $733;
pravastatin plus ezetimibe, 10 mg = $985, 20 mg = $1,013, 40 mg = $1,030;

simvastatin plus ezetimibe, 10 mg = $854, 20 mg = $854, 40 mg = $854, 80 mg = $854.

**Synthesis of costs and benefits**
The authors did not report specific cost-effectiveness ratios. Instead they presented their results graphically. They stated that lovastatin 10, 20, or 40 mg, and fluvastatin 80 mg, are appropriate choices for patients requiring a less than 40% reduction from baseline LDL-C. In addition, simvastatin 40 mg was the most cost-effective choice for reductions in LDL-C greater than 40%.

**Authors' conclusions**
The authors reported that their "conclusions (referring to their results) were not found to be robust to variations in drug cost or LDL-C (low-density lipoprotein cholesterol) reduction". They concluded this because the 95% confidence intervals surrounding the point estimates overlapped (i.e. there were no statistically significant results).

**CRD COMMENTARY - Selection of comparators**
The authors compared a broad range of monotherapies and combination therapies for the treatment of elevated LDL-C. These technologies represented all those that were approved by the Food and Drug Administration at the time of the study. You should decide if these represent valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The authors did not state that a systematic review of the literature had been carried out. They presented very few details of the literature searched or used in the review (e.g. type of study), or the methodology used to compare studies or combine the data. They also did not report bibliographic details indicating the source of their data. This leaves the reader unable to assess the quality of the data included in the review and, therefore, sheds doubts on any results and conclusions drawn using these data.

**Validity of estimate of measure of benefit**
The authors used the percentage reduction in LDL-C as their summary measure of health benefit. This measure was taken directly from the effectiveness analysis. The authors used the largest percentage reduction, and it was unclear why they used the largest instead of the average (or any other measure) percentage reduction. The use of the largest percentage reduction potentially introduces a bias in the results, which favours all LDL-C treatments since it suggests better cost-effectiveness than is actually the case in practice. The authors acknowledged that the use of a surrogate end point, such as the one used here, is one of the limitations of the study. In particular, this end point prevents the results and conclusions being broadly compared with other health technologies. For example, in an attempt to discover the best use of a limited available budget.

**Validity of estimate of costs**
The costs reported were appropriate to the perspective of the study. However, the narrow perspective (the hospital) severely limits the generalisability of the study. Although the authors reported that the costs were taken from their own hospital acquisition costs, it was not entirely clear what these costs represented. For instance, did the cost include any element of overhead costs facing the hospital as these would be relevant to the perspective of the study?

**Other issues**
The authors reported that, to their knowledge, this was the first study to evaluate the cost-effectiveness of ezetimibe-statin dual therapy. This means that they were unable to make comparisons of their results. The authors did not address the issue of generalisability although, as already stated, it is limited by the use of a surrogate end point and institution-specific cost data. The exclusion of other potential therapies was cited as a further limitation. The authors presented
their results in graphical form, which enables the reader to gain an overall picture of cost-effectiveness. Specific ratios, particularly for those treatments judged to be most cost-effective, would have provided useful data for the reader. The authors correctly highlighted the degree of uncertainty in their results and conclusions.

**Implications of the study**
The authors did not make any specific recommendations further to their study, although they suggested that the use of cost-effectiveness ratios may not be "appropriate when clinical practice guidelines are taken into consideration". Further work, in the form of conducting similar evaluations on a periodic basis to provide up-to-date, accurate and clinically relevant results, was suggested.

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None stated.

**Bibliographic details**

**Indexing Status**
Subject indexing assigned by CRD

**MeSH**
Cholesterol, LDL; Cost-Benefit Analysis; Drug Synergism; Hydroxymethylglutaryl-CoA Reductase Inhibitors /therapeutic use /administration & dosage /pharmacology /economics; Hyperlipidemias /prevention & control /drug therapy; Lovastatin /therapeutic use /administration & dosage /pharmacology /economics; Monte Carlo Method; Pravastatin /therapeutic use /administration & dosage /pharmacology /economics; Sensitivity and Specificity; Simvastatin /therapeutic use /administration & dosage /pharmacology /economics

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