Pharmacoeconomic assessment of HMG-CoA reductase inhibitor therapy: an analysis based on the CURVES study
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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 health technologies examined in the study were 5 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors for the treatment of patients with hypercholesterolaemia.

15 drug regimens were considered:
- once-daily dose of atorvastatin (10, 20, 40, and 80 mg);
- pravastatin (10, 20, and 40 mg);
- simvastatin (10, 20, and 40 mg);
- fluvastatin (20 and 40 mg);
- lovastatin (20 and 40 mg);
- twice/day lovastatin 40 mg (or 80 mg total daily dose).

Type of intervention
Treatement.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with hypercholesterolaemia requiring any cholesterol-lowering therapy.

Setting
The setting was not clearly reported, but it appeared to be primary care. The economic study was carried out in the USA.

Dates to which data relate
The dates during which data on effectiveness and resource use were gathered were not reported. The price year was 1999.

Source of effectiveness data
The effectiveness evidence was derived from a single study, the results of which were mainly published in a different paper.
Link between effectiveness and cost data
Costing was conducted retrospectively on the same patient sample used in the effectiveness analysis.

Study sample
Since the effectiveness evidence analysis was mainly reported in a previous paper, few details were reported in the present study. Power calculations and inclusion criteria were not reported. The overall sample consisted of 534 patients, but only 522 subjects (59% men, 90% white, mean age of 55 years with a range of 20 to 0 years) were included in the analysis.

The number of patients in each group was:

- 73 for atorvastatin 10 mg;
- 14 for pravastatin 10 mg;
- 70 for simvastatin 10 mg;
- 51 for atorvastatin 20 mg;
- 12 for fluvastatin 20 mg;
- 16 for lovastatin 20 mg;
- 41 for pravastatin 20 mg;
- 49 for simvastatin 20 mg;
- 61 for atorvastatin 40 mg;
- 12 for fluvastatin 40 mg;
- 16 for lovastatin 40 mg;
- 25 for pravastatin 40 mg;
- 61 for simvastatin 40 mg;
- 10 for atorvastatin 80 mg;
- and 11 for lovastatin b.i.d.

Study design
The study was a randomised, open-label, parallel-group, 8-week comparison trial carried out in 34 centres. The method of randomisation was not reported. Patients were followed for 8 weeks and clinical examinations were conducted at screening, at randomisation and at the end of the study. Loss to follow-up was not reported.

Analysis of effectiveness
The analysis of the clinical study was based on intention to treat. The primary health outcome was the percentage change from baseline in low-density lipoprotein (LDL) after 8 weeks of treatment. Secondary health outcomes were the changes in total cholesterol, triglycerides and high-density lipoprotein (HDL) levels. The comparability of the groups was not reported.
**Effectiveness results**

The percentage change from baseline in LDL after 8 weeks was:

-38.2 (range: -28.2 to -48.2) for atorvastatin 10 mg,
-18.9 (range: -4.9 to -32.9) for pravastin 10 mg,
-28.2 (range: -16.2 to -40.2) for simvastatin 10 mg,
-46.3 (range: -38.3 to -54.3) for atorvastatin 20 mg,
-16.8 (range: -8.8 to -24.8) for fluvasatin 20 mg,
-16.8 (range: -8.8 to -24.8) for lovasatin 20 mg,
-29.0 (range: -16.0 to -42.0) for lovasatin 20 mg,
-23.9 (range: -14.9 to -32.9) for pravastatin 20 mg,
-35.3 (range: -24.3 to -46.3) for simvastatin 20 mg,
-51.2 (range: -41.2 to -61.2) for atorvastatin 40 mg,
-23.0 (range: -13.0 to -33.0) for fluvastatin 40 mg,
-31.4 (range: -24.4 to -38.4) for lovasatin 40 mg,
-33.8 (range: -24.8 to -42.8) for pravastatin 40 mg,
-41.0 (range: -28.0 to -54.0) for simvastatin 40 mg,
-54.3 (range: -45.3 to -63.3) for atorvastatin 80 mg, and
-47.7 (range: -39.7 to -55.7) for lovasatin b.i.d..

Changes in total cholesterol, triglycerides and HDL levels were:

-28.0, -12.5, and 5.5 for atorvastatin 10 mg,
-13.1, 2.9, and 9.9 for pravastatin 10 mg,
-20.9, -11.5, and 6.8 for simvastatin 10 mg,
-34.8, -20.1, and 5.1 for atorvastatin 20 mg,
-13.0, -5.0, and 0.9 for fluvastatin 20 mg,
-20.8, -11.8, and 7.3 for lovasatin 20 mg,
-18.4, -15.4, and 3.0 for pravastatin 20 mg,
-26.4, -16.7, and 5.2 for simvastatin 20 mg,
-39.7, -32.2, and 4.8 for atorvastatin 40 mg,
-18.8, -12.9, and -3.0 for fluvastatin 40 mg,
-22.5, -2.3, and 4.6 for lovasatin 40 mg,
-24.3, -9.5, and -6.2 for pravastatin 40 mg.
-30.2, -14.5, and 9.6 for simvastatin 40 mg,

-41.8, -24.6, and -0.1 for atorvastatin 80 mg, and

-35.9, -12.5, and 8.0 for lovastatin b.i.d..

Adverse events were quite infrequent and similar across the treatments.

**Clinical conclusions**
The analysis of the effectiveness of the drug regimens indicated that atorvastatin (10, 20, and 40 mg) was statistically more effective than the milligram-equivalent dosages of fluvastatin, lovastatin, pravastatin, and simvastatin. At 80 mg/day, atorvastatin reduced LDL by 54.3% and only lovastatin 40 mg twice/day (47.7%) was not statistically different.

**Measure of benefits used in the economic analysis**
The benefit measure used in the economic analysis was the monthly decrease in levels of LDL, as derived from the effectiveness analysis.

**Direct costs**
Discounting was not relevant because costs occurred over a period of 8 weeks. Unit costs and the quantities of resources used were not reported. The cost/resource boundary was not reported. Only the acquisition costs of the drugs were included in the analysis and were based on actual data, derived from average wholesale prices in 1999. The dates of the resource data gathering were not reported in the study.

**Statistical analysis of costs**
No statistical analysis of costs was conducted.

**Indirect Costs**
No indirect costs were included.

**Currency**
US dollars ($).

**Sensitivity analysis**
To assess the possible variability in data, univariate sensitivity analysis was conducted on values of LDL reductions (by the range reported). Cost estimates were also varied to find out threshold values at which results of the analysis would change.

**Estimated benefits used in the economic analysis**
Please refer to the effectiveness results reported earlier.

**Cost results**
The monthly and yearly costs were:

$56.40 and $686 for atorvastatin 10 mg,

$57.60 and $701 for pravastatin 10 mg,
$65.40 and $796 for simvastatin 10 mg,
$87.00 and $1,058 for atorvastatin 20 mg,
$37.50 and $456 for fluvastatin 20 mg,
$72.60 and $883 for lovastatin 20 mg,
$61.80 and $752 for pravastatin 20 mg,
$114 and $1,387 for simvastatin 20 mg,
$105 and $1,278 for atorvastatin 40 mg,
$37.50 and $456 for fluvastatin 40 mg,
$130.50 and $1,588 for lovastatin 40 mg,
$112.20 and $1,365 for pravastatin 40 mg,
$210 and $2,555 for atorvastatin 80 mg, and
$261 and $3,176 for lovastatin b.i.d..

**Synthesis of costs and benefits**

Costs and benefits were combined performing an average cost-effectiveness analysis. An incremental analysis was not conducted. The monthly cost per LDL decrease and the yearly cost per LDL decrease (and the range for the latter) were:

$1.48 and $17.96 (range: $14.23 - $24.33) for atorvastatin 10 mg,
$3.05 and $37.09 (range: $21.31 - $143.06) for pravastatin 10 mg,
$2.32 and $28.23 (range: $19.80 - $49.14) for simvastatin 10 mg,
$1.88 and $22.85 (range: $19.48 - $27.62) for atorvastatin 20 mg,
$2.23 and $27.14 (range: $18.39 - $51.82) for fluvastatin 20 mg,
$2.50 and $30.45 (range: $21.02 - $55.19) for lovastatin 20 mg,
$2.59 and $31.46 (range: $22.88 - $50.47) for pravastatin 20 mg,
$3.23 and $39.29 (range: $29.96 - $57.08) for simvastatin 20 mg,
$2.05 and $24.96 (range: $20.88 - $31.02) for atorvastatin 40 mg,
$1.63 and $19.83 (range: $13.82 - $35) for fluvastatin 40 mg,
$4.16 and $50.57 (range: $37.10 - $65.08) for lovastatin 40 mg,
$3.33 and $40.50 (range: $31.89 - $55.04) for pravastatin 40 mg,
$2.78 and $33.83 (range: $25.68 - $49.54) for simvastatin 40 mg,
$3.87 and $47.05 (range: $40.36 - $56.40) for atorvastatin 80 mg, and
$5.47 and $66.58 (range: $57.02 - $80) for lovastatin b.i.d..

When the drugs’ LDL-reducing effect was set at the minimum value of the range reported, fluvastatin 20 and 40 mg were slightly more cost-effective than atorvastatin. When the maximum value of the range of efficacy was used, atorvastatin remained the most cost-effective drug. Finally, for the other drugs to be as cost-effective as atorvastatin, the reductions in acquisition costs would have to be 16% for fluvastatin ($73), 25% for lovastatin ($221), 27% for pravastatin ($203), and 47% for simvastatin ($652).

Authors’ conclusions
Atorvastatin was the most cost-effective strategy for lowering LDL levels in patients with hypercholesterolaemia. The only other drug dose with an annual cost per LDL reduction less than $20 was fluvastatin 40 mg, but it only reduced LDL by 23%.

CRD COMMENTARY - Selection of comparators
The drug therapies were chosen because they represented five commercially available HMG-CoA reductase inhibitors, as reported in the primary study from which the effectiveness evidence was derived. However, the authors highlighted that recently introduced drug regimens, based on higher dosages of fluvastatin and simvastatin and on cerivastatin, were not included in the study. You, as a user of this database, should consider whether they represent widely used drug therapies in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness was likely to be valid given the use of randomisation. Many details, such as comparability across study groups and the dates during which data on effectiveness were gathered, were not reported because the results of the trial were mainly published elsewhere. However, for some patient groups the sample size was quite small and power calculations were not reported, thus weakening the validity of the effectiveness results.

Validity of estimate of measure of benefit
The benefit measure was derived directly from the effectiveness analysis. The authors noted that LDL reduction was used as a surrogate marker for mortality reduction, which represented the main objective of the drug therapies. However, LDL reduction was widely used as a short-term treatment goal and also recommended by the National Cholesterol Education Program expert panel in the USA.

Validity of estimate of costs
The perspective of the study was not clearly reported and only drug acquisition costs were included in the analysis and, as pointed out by the authors, these prices may not reflect true costs to individuals or to institutions. Costs for the treatment of adverse events were not considered relevant, since the rate of adverse events did not differ between the agents studied. Estimates of cost and quantities of resources used were treated deterministically and no statistical analyses were conducted. The dates during which the resource use data were collected were not reported.

Other issues
The authors did not make any comparison of their findings with those from other studies. The generalisability of the study results to other settings was quite limited because few sensitivity analyses were conducted and both cost and effectiveness estimates appear to have been quite specific to the US setting.

Implications of the study
The study results suggest that atorvastatin at low dosages (10 mg) is the most cost-effective strategy for the treatment of
patients with hypercholesterolaemia. However, long-term effects were not analysed in the study.

**Source of funding**
None given.

**Bibliographic details**

**PubMedID**
10907971

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adult; Aged; Aged, 80 and over; Anticholesteremic Agents /adverse effects /economics /therapeutic use; Cholesterol, LDL /blood; Cost-Benefit Analysis; Female; Humans; Hydroxymethylglutaryl-CoA Reductase Inhibitors /adverse effects /economics /therapeutic use; Hypercholesterolemia /drug therapy /economics; Lipids /blood; Male; Middle Aged

**AccessionNumber**
2200001163

**Date bibliographic record published**
31/10/2002

**Date abstract record published**
31/10/2002