Cost-efficacy analysis of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors based on results of the STELLAR trial: clinical implications for therapeutic selection

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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 study examined the use of rosuvastatin in 10-, 20- and 40-mg doses to achieve reductions in levels of low-density lipoprotein (LDL) cholesterol.

Type of intervention
Primary and secondary prevention of heart disease.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised men and non-pregnant women with an LDL cholesterol level of 160 to 250 mg/dL and a triglyceride level of below 400 mg/dL, stabilised at baseline. More details were reported in the parent study (Jones et al. 2003, see 'Other Publications of Related Interest' below for bibliographic details).

Setting
The study was conducted at 182 "clinical centres" providing (presumably) secondary care. The economic study was carried out in the USA.

Dates to which data relate
The data were collected between April 2001 and March 2002. The drugs were costed at the levels pertaining in May 2004.

Source of effectiveness data
The clinical effectiveness data were derived from a single trial (Jones et al. 2003).

Link between effectiveness and cost data
The costs related to the drug costs incurred by patients in the study were costed at standard wholesale prices.

Study sample
A total of 2,431 patients were eligible for participation after a dietary lead-in. Further details were not provided in this paper, but might be available in the parent study (Jones et al. 2003).

Study design
The study took the form of an unblended, randomised, controlled, multi-centre trial. The patients were randomly assigned to one of the 15 treatment groups. More specifically, 643 patients were assigned to the various rosuvastatin groups, 641 patients to the atorvastatin groups, 655 patients to the simvastatin groups and 492 patients to the pravastatin groups. The patients were followed up for 6 weeks and 2,288 patients (94.1%) completed the trial.

**Analysis of effectiveness**

It was not reported whether the analysis was conducted on an intention to treat basis or otherwise. The primary health outcomes were percentage reductions in LDL and achievement of goals set by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III). Baseline measurements showed that 29% of the patients met the NCEP ATP III LDL goal. The mean LDL levels ranged from 187 mg/dL for patients assigned to rosuvastatin 20 mg, pravastatin 29 mg and simvastatin 40 mg, to 194 mg/dL for the rosuvastatin 40-mg group. "Other" baseline characteristics were reported to be similar among the treatment groups.

**Effectiveness results**

Pair-wise dose-to-dose comparisons of efficacy were presented, as well as the percentage reductions in LDL level and the percentage of patients achieving NCEP ATP III targets after 6 weeks used in the economic evaluation.

Rosuvastatin 10 mg achieved a 45.8% reduction in LDL compared with:
- atorvastatin 10 mg, which achieved a 3.6.8% reduction;
- pravastatin 10 mg, which achieved a 20.1% reduction;
- pravastatin 20 mg, which achieved a 24.4% reduction;
- pravastatin 40 mg, which achieved a 29.7% reduction;
- simvastatin 10 mg, which achieved a 28.3% reduction;
- simvastatin 20 mg, which achieved a 35% reduction; and
- simvastatin 40 mg, which achieved a 38.8% reduction, (p<0.001).

The results for pair-wise comparisons of rosuvastatin 20 mg were also presented in the paper.

Rosuvastatin 40 mg achieved a 55.0% reduction in LDL compared with:
- atorvastatin 40 mg, which achieved a 47.8% reduction;
- pravastatin 40 mg, which achieved a 29.8% reduction;
- simvastatin 40 mg, which achieved a 38.8% reduction; and
- simvastatin 80 mg, which achieved a 45.8% reduction, (p<0.001).

However, the difference between rosuvastatin 40 mg and atorvastatin 80 mg, which showed a reduction of 51.1%, was not significant.

**Clinical conclusions**

Overall, rosuvastatin reduced LDL levels significantly more than simvastatin and pravastatin in all 14 pair-wise comparisons in the STELLAR trial, (p<0.001). Rosuvastatin may also be more efficacious in meeting NCEP ATP III goals than atorvastatin, simvastatin and pravastatin.
Measure of benefits used in the economic analysis
The measures of benefit used in the economic analysis were the percentage reductions in LDL and the percentage of patients achieving NCEP ATP III targets.

Direct costs
The only costs included in the study were the direct costs of the drugs used. The time periods considered were limited to 12 months, obviating the need for discounting. The quantities used were reported as daily doses. The cost per dose was reported separately. The costs were based on “average wholesale prices” using the Drug Topics Red Book. The timeline for costs was May 2004.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
In line with the perspective adopted, the study did not report the indirect costs.

Currency
US dollars ($).

Sensitivity analysis
No sensitivity analysis was reported

Estimated benefits used in the economic analysis
The reductions in LDL level after 6 weeks of treatment were as follows:

36.8% with atorvastatin 10 mg, 42.6% with atorvastatin 20 mg, 47.7% with atorvastatin 40 mg and 51.1% with atorvastatin 80 mg;

20.1% with pravastatin 10 mg, 24.4% with pravastatin 20 mg and 29.7% with pravastatin 40 mg;

45.8% with rosvastatin 10 mg, 52.4% with rosvastatin 20 mg and 55.0% with rosvastatin 40 mg; and

28.3% with simvastatin 10 mg, 35.0% with simvastatin 20 mg, 38.8% with simvastatin 40 mg and 45.8% with simvastatin 80 mg.

The percentage of patients achieving NCEP ATP III targets after 6 weeks of treatment were as follows:

69.0% with atorvastatin 10 mg, 74.7% with atorvastatin 20 mg, 85.3% with atorvastatin 40 mg and 82.4% with atorvastatin 80 mg;

31.3% with pravastatin 10 mg, 43.9% with pravastatin 20 mg and 54.7% with pravastatin 40 mg;

82.1% with rosvastatin 10 mg, 88.8% with rosvastatin 20 mg and 89.2% with rosvastatin 40 mg; and

50.9% with simvastatin 10 mg, 63.0% with simvastatin 20 mg, 66.5% with simvastatin 40 mg and 82.2% with simvastatin 80 mg.

The side effects were not reported with these results.
Cost results
The estimated daily costs for the various drug regimens were as follows:

- Atorvastatin 10 mg $2.58, atorvastatin 20 mg $3.75, atorvastatin 40 mg $3.75 and atorvastatin 80 mg $3.75;
- Pravastatin 10 mg $3.24, pravastatin 20 mg $3.30 and pravastatin 40 mg $4.84;
- Rosuvastatin 10 mg $2.63, rosuvastatin 20 mg $2.63 and rosuvastatin 40 mg $2.63; and
- Simvastatin 10 mg $2.74, simvastatin 20 mg $4.79, simvastatin 40 mg $4.79 and simvastatin 80 mg $4.79.

No confidence intervals or other statistical tests were reported for the costs which used average US wholesale prices.

Synthesis of costs and benefits
The costs and benefits were combined in cost-effectiveness ratios in which the incremental costs of all regimens were reported in comparison with the baseline measurements.

Rosuvastatin 40 mg dominated all other treatment options with the exception of atorvastatin 10 mg.

An incremental analysis with respect to dominated treatments would be superfluous. It might have been performed with respect to the slightly cheaper atorvastatin 10 mg, but was not.

The annual drug cost per percentage reduction in LDL was reported to be $25.63 for atorvastatin 10 mg and, respectively, $20.92, $18.28 and $17.42 for the 10-, 20- and 40-mg formulations of rosuvastatin.

The findings were confirmed when the outcomes were measured as achievement of NCEP ATP III recommendations. Rosuvastatin was the most effective, with 82.2% of patients achieving the recommendations. This was substantially higher than the slightly cheaper atorvastatin, where 69% of the patients achieved the recommendations.

Neither a sensitivity analysis nor statistical tests were performed on the cost-effectiveness ratios.

Authors’ conclusions
Rosuvastatin was the most cost-effective treatment in terms of the percentage reduction in low-density lipoprotein (LDL) when compared with other statins, with the 40-mg formulation being the most cost-effective.

CRD COMMENTARY - Selection of comparators
The study compared 14 treatment regimens involving differing strengths of four drugs. Rosuvastatin was reported as being a recently approved potent statin. The other three drugs were justified as drugs that were "available". The effect of each treatment option was compared with a "baseline" in which patients were reported to be receiving both primary and secondary prevention, according to NCEP ATP III guidelines and with or without coronary heart disease and coronary heart disease risk equivalents". Thus, the treatments were compared both with pre-existing treatments and with each other in terms of improvements over pre-existing treatments. In such a large multi-centre national trial, it might be reasonable to suppose that the pre-existing treatments were representative of practice within the country (the USA). You are advised to consider whether the same practice applies in your own setting.

Validity of estimate of measure of effectiveness
The study was based on a multi-centre randomised design, which was appropriate to the study question and for which the study sample appears to have been representative. There was a small difference between groups in their LDL level at baseline, with patients receiving rosuvastatin 40 mg having a mean score of 194 mg/dL compared with 187 mg/dL (the lowest LDL) for patients receiving rosuvastatin 20 mg, pravastatin 20 mg and simvastatin 40 mg. If the percentage reductions in LDL were to differ with different initial levels of LDL, then this might have introduced a small bias into the results. No attempt appears to have been made to control for such an eventuality. Other patient characteristics were
reported to be similar between the groups. Given the level of reporting on the methodology of the clinical study, it was difficult to fully evaluate the internal validity of the effectiveness outcomes obtain

**Validity of estimate of measure of benefit**
The measure of benefit was derived directly from the effectiveness results. The reader is referred to the comments in the 'Validity of estimate of measure of effectiveness' field (above).

**Validity of estimate of costs**
The perspective of the study was restricted to that of the health care funding authority, and it included only the direct drug costs. The authors specifically excluded the costs of monitoring and the treatment of adverse events, which might potentially have been important. The unit costs and the quantities were reported separately. Resource use was determined by the treatment protocol established at randomisation. The prices were obtained from a published US source and were not subjected to any form of statistical or sensitivity analysis. The restricted perspective adopted by the authors might have limited the results obtained.

**Other issues**
The authors made appropriate comparisons of their findings with those from other studies. They do not appear to have presented their results selectively, and they discussed the possibility that there might have been adverse effects from the use of the various statins that were not incorporated in the analysis. The claim was made that low dosage formulations might be more cost-effective in the treatment of patients requiring small reductions in LDL (presumably patients with low baseline LDL concentrations), but no sub-group analysis was reported to provide evidence that reductions in LDL were equally achievable across groups with different baseline levels. The authors also implied the need for additional evidence concerning claims made by the manufacturers that adverse events occur with similar frequency with each of the statins reported in this study.

**Implications of the study**
The authors concluded that rosuvastatin should be used for patients similar to those in the STELLAR trial, as was more cost-effective than the other statins with which it was compared. They await long-term efficacy and safety data.

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None stated.

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**Other publications of related interest**

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