A cost-effectiveness analysis of fluvastatin in patients with diabetes after successful percutaneous coronary intervention

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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 fluvastatin (40 mg twice daily) added to dietary and lifestyle counselling for patients with diabetes after successful percutaneous coronary intervention (PCI).

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised patients with diabetes who had undergone a successful PCI.

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

Dates to which data relate
The effectiveness data were derived from a study published in 2002. No dates were explicitly reported for resource use that was mainly based on assumptions. The price year was 2002.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was not performed on the same sample of patients as that used in the effectiveness study.

Study sample
The sample of patients included in the current study was a sub-group of those enrolled in the whole trial (that included 1,677 patients). There was limited information on the method used to select the sample since most of the details of the study had been published elsewhere. The sample comprised 120 patients (80% male) in the fluvastatin arm and 82 patients (80.5% male) in the control arm. The mean age was 63.1 (+/- 8.2) years in the fluvastatin group and 62.0 (+/- 8.9) years in the control group. Power calculations (that referred to the primary trial) showed that the study sample would have provided the study with 90% power for a 2-sided alpha-level of 0.05, assuming a 25% rate of MACE at 3 years in the placebo group and an 18.75% rate of MACE in the fluvastatin group.
Study design
This was a prospective, multi-centre, randomised controlled trial that was carried out in 77 centres in Europe, Canada and Brazil. No details of the randomisation procedure were reported. The patients were followed up for 4 years. The investigators were blinded to the lipid values but it was unclear whether they were aware of treatment allocation.

Analysis of effectiveness
The analysis of the clinical study was conducted on an intention to treat basis. The outcome measures used in the effectiveness study were:

- the rates of AMI, PCI, CABG, cardiac and noncardiac death;
- the uptake rate of other lipid-lowering drugs;
- fluvastatin withdrawal; and
- the probabilities of outcomes associated with AMI, PCI and CABG.

The study groups were comparable at baseline in demographic and some clinical characteristics. However, the authors noted that more patients with diabetes were randomly assigned to the fluvastatin group, while more insulin-dependent patients and a smaller proportion of patients with multi-vessel coronary disease were observed in the control group.

Effectiveness results
The annual rates for the fluvastatin group versus the control group were as follows:

- for AMI before month 28, 0.023 for both groups (assumed equal for both groups because no statistically significant difference was found in the trial);
- for AMI after month 28, 0.006 (+/- 0.001) versus 0.025 (+/- 0.008), (p<0.001);
- for PCI, 0.043 (+/- 0.011) versus 0.078 (+/- 0.016), (p<0.001);
- for CABG at or before month 18, 0.044 for both groups (assumed equal for both groups because no statistically significant difference was found in the trial);
- for CABG after month 18, 0.000 (+/- 0.000) versus 0.016 (+/- 0.007), (p<0.001);
- for cardiac death at or before month 11, 0.016 for both groups (assumed equal for both groups because no statistically significant difference was found in the trial);
- for cardiac death after month 11, 0.003 (+/- 0.001) versus 0.013 (+/- 0.005), (p<0.001); and
- for noncardiac death, 0.021 for both groups (assumed equal for both groups because no statistically significant difference was found in the trial).

The uptake rate of other lipid-lowering drugs was 0.048 in the fluvastatin group versus 0.081 in the control group.

The fluvastatin withdrawal rate was 0.037.

The probabilities of outcomes associated with AMI were remain healthy 0.000, CABG 0.750, subsequent PCI 0.250 and cardiac death 0.000.

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Clinical conclusions
The clinical data derived from the trial were used as model inputs.

Modelling
A Markov model was constructed to assess the economic impact of fluvastatin, compared with standard care, in a cohort of patients with diabetes after a successful PCI. The health states considered were healthy, post-acute myocardial infarction (AMI), post-PCI2, post-coronary artery bypass graft (CABG), cardiac death and "other" death. "Healthy" referred to patients with diabetes and coronary artery disease who survived their index PCI. "Post-PCI2" referred to patients who survived a second or subsequent PCI after the index PCI. The model was populated mainly with data derived from the LIPS. The time horizon of the model was 10 years and monthly cycles were considered.

Measure of benefits used in the economic analysis
The summary benefit measures used were the life-years (LYs) and quality-adjusted life-years (QALYs). Both were estimated using the decision model. The utility values used to calculate the QALYs were derived from published data where patient preferences were elicited using the time trade-off technique (Euro-Qol). The utility weights were 0.86 for remain healthy, 0.78 (standard deviation, SD=0.15) for post-AMI, and 0.86 for post-PCI2 and post-CABG. Disutility weights were also assigned to specific conditions, such as subsequent AMI (SD=-0.083), PCI (SD=-0.042), or CABG (SD=0.059). An annual discount rate of 3.5% was applied.

Direct costs
The cost analysis was performed from the perspective of the NHS. The health services included in the economic evaluation were inpatient costs (for AMI, PCI and CABG), outpatient visit costs for follow-up (after cardiothoracic surgery, cardiology and endocrinology), fluvastatin, other lipid-lowering drugs, general practitioner (GP) consultation, GP home visit, paramedic or ambulance, and cardiac death. The unit costs were presented separately from the quantities of resources used for most items. The costs of inpatient and outpatient visits were estimated using health-related group costs, weighted by emergency and elective procedures. Inpatient costs were also weighted according to the proportion of patients with and without complications. The cost of cardiac death came from a US estimate. Resource use was estimated on the basis of authors' assumptions. Discounting was relevant, owing to the long timeframe of the model, and an annual rate of 3.5% was applied. The price year was 2002.

Statistical analysis of costs
The costs were treated deterministically in the base-case.

Indirect Costs
The indirect costs were not considered in the economic analysis.

Currency
UK pounds sterling (£). The costs were then converted into US dollars ($) using purchasing power parity.

Sensitivity analysis
A probabilistic sensitivity analysis was performed running 10,000 Monte Carlo simulations. Probabilistic distributions were assigned to all model inputs. A univariate sensitivity analysis was also carried out by varying key model inputs, such as the cost of fluvastatin, cost of cardiac death, discount rates and the time horizon. Further, the uptake of lipid-lowering drugs in the control group, withdrawals from fluvastatin, and crossovers from fluvastatin to other lipid-lowering drugs were assessed by increasing and decreasing these parameters by 50%.
Estimated benefits used in the economic analysis
Over the 10-year time horizon, the expected LYs were 7.908 (+/- 0.031) with fluvastatin and 7.717 (+/- 0.094) with standard therapy. The expected QALYs were 6.776 (+/- 1.034) with fluvastatin and 6.580 (+/- 0.948) with standard therapy. The differences in both LYs and QALYs were statistically significant, (p<0.001).

Cost results
Over the 10-year time horizon, the expected costs were 6,327 +/- 421 ($9,734 +/- 648) with fluvastatin and 6,317 +/- 443 ($9,718 +/- 682) with standard therapy. The difference in costs did not reach statistical significance.

Synthesis of costs and benefits
Incremental cost-effectiveness ratios and cost-utility ratios were calculated to combine the costs and benefits of fluvastatin treatment in comparison with standard care.

The incremental cost per LY saved was 52 ($80). The incremental cost per QALY gained was 51 ($78).

The sensitivity analysis showed that with fluvastatin more QALYs were obtained in 92.5% of the simulations and higher costs were incurred in 51.6% of the simulations.

The probability of higher costs and worse outcomes with fluvastatin was 3.3%, while the chance that fluvastatin had better outcomes and lower costs (dominant strategy) was 44.2%. In 48.3% of the simulations, greater costs and better outcomes were generated.

The univariate sensitivity analysis indicated that the probability of a CABG in the fluvastatin group had a large effect. However, even under the most unfavourable scenario, the incremental cost per QALY was 2,845.

The time horizon also had an effect on the final cost per QALY. Fluvastatin remained dominant for a time horizon longer than 10 years and 3 months, while the incremental cost-effectiveness ratio was raised to 5,561 with a 4-year time horizon.

Fluvastatin was dominant at a monthly cost less than or equal to 17.25.

Authors' conclusions
The use of fluvastatin after percutaneous coronary intervention (PCI) in patients with diabetes significantly increased health benefits for a small increase in costs over 10 years in the UK. This conclusion was robust to variations in the model inputs. The sensitivity analysis showed a high probability that fluvastatin was dominant.

CRD COMMENTARY - Selection of comparators
The selection of the comparators was appropriate as the new proposed statin (i.e. fluvastatin) was compared with standard therapy. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from a published clinical trial, which was appropriate for the study question. The use of a multi-centre and randomised design, together with the intention to treat approach, ensures a high internal validity. However, limited information on the primary study was reported since the trial had been published. Further, the current study was based on a small sub-group of patients that had been included in the primary trial. The authors stated that more insulin-dependent patients were included in the control group, and the impact of this condition on the current pharmacoeconomic study was unclear. On the other hand, the authors used a conservative approach, assuming equal effectiveness values for both groups when no statistically significant difference was found in the trial.
Validity of estimate of measure of benefit
The benefit measures used in the analysis were appropriate as they captured the impact of the interventions on the most relevant dimensions of care (i.e. survival and quality of life). Further, the use of QALYs and LYS enables comparisons with the benefits of other health care interventions. Some information on the source used to derive the utility weights was provided. Discounting was applied, as recommended by UK guidelines for economic evaluations.

Validity of estimate of costs
The authors stated explicitly which perspective was adopted. As such, all the relevant categories of costs were included in the analysis. The unit costs and resource use data were provided for most items, which enhances the possibility of replicating the analysis in other settings. Further, the price year was stated, which aids reflation exercises in other time periods. The source of the data was consistent with the perspective chosen for the analysis. However, some costs came from US sources and resource use data were mainly based on authors’ assumptions. Extensive sensitivity analyses were performed to deal with uncertainty around some of the cost estimates.

Other issues
The authors compared their findings with those from a published study that had assessed the cost-effectiveness of simvastatin. Differences in the patient populations were highlighted. The issue of the generalisability of the study results to other settings was implicitly addressed in the sensitivity analysis, where all model inputs were varied. This increases the external validity of the analysis. The authors noted that the validity of the current study relied on the robustness of the primary estimates used in the model. It was also noted that, owing to the availability of drug-eluting stents, the estimated costs for the control group could decrease more than those for the fluvastatin group.

Implications of the study
The study results support the use of fluvastatin in the treatment of patients with diabetes after a PCI. In particular, the authors suggested “all patients with ischemic heart disease should be using statins unless they have a contraindication, intolerance, or insufficient response”.

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