Cost-effectiveness of fluvastatin following successful first 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
Two treatment options for patients with stable or unstable angina, or silent ischaemia, who had already received a successful first percutaneous coronary intervention (PCI) were examined. The two options were diet and lifestyle counselling combined with fluvastatin 80 mg/day, and diet and lifestyle counselling alone. In the second option, fluvastatin 80 mg/day was administered to patients only after a nonfatal major adverse cardiac event (MACE) took place.

Type of intervention
Treatment.

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

Study population
The target population comprised a hypothetical cohort of patients suffering from stable or unstable angina, or from silent ischaemia, who had already received a PCI. All patients were at the age of 60 years when they first received a PCI. No further inclusion or exclusion criteria were reported in the study.

Setting
A setting was not explicitly stated as the study was based on hypothetical patients. The economic analysis was carried out in the USA.

Dates to which data relate
Most of the effectiveness data were gathered from completed studies published between 1996 and 2002. The cost data were derived from sources published between 1991 and 2002. All costs were reported for the fiscal year 2002.

Source of effectiveness data
Most of the effectiveness data were derived from a published study, the Lescol Intervention Prevention Study (LIPS; Serruys et al. 2001, see ‘Other Publications of Related Interest’ below for bibliographic details), and two other studies. Where effectiveness data did not exist in the literature, the authors made assumptions based on their clinical experience.

Modelling
A Markov model was constructed, using Data 3.5 decision analysis software (TreeAge Software, Williamston), to estimate the clinical benefits and costs of the two treatments. Specific health states taking place after a successful PCI and possible transitions between these health states were modelled. Utilities were assigned to each health state. The
cycle length of each health state was 6 months. It appears that the horizon of the model covered the patients’ lifetime.
The health states included were:

fatal or nonfatal myocardial infarction (MI);

reintervention of restenosis (coronary artery bypass graft (CABG) or repeat PCI within 6 months of PCI for treated lesions);

reintervention for reasons other than restenosis;

dead due to a cardiac event (except MI or reintervention); and

noncardiac death from all other causes.

Deaths due to MI or reintervention were assumed to take place within 30 days after the event. All patients could undergo an unlimited number of nonfatal events and all death events in any of the 6-month cycles, and were assumed to take place at the midpoint. In addition, the risks of reintervention due to restenosis, noncardiac death, and death due to MI and reintervention were assumed to be independent of the treatment.

Outcomes assessed in the review
The following input parameters were used in the model:

the probability (per 100 patients) of cardiac death at the age of 60 years and MI after 1 month or more, 2 to 6 months, 7 to 12 months, and more than 12 months (per 6 months) following the first PCI;

the probability of CABG or repeat PCI due to restenosis within 1 to 6 months after the first PCI;

the probability of CABG or repeat PCI due to other reasons than restenosis after 7 to 12 months and more than 12 months (per 6 months) following the first PCI;

the probability of noncardiac death at the age of 60 years;

the probability of death due to MI, PCI or CABG;

the odds ratio (age in years/10) of cardiac and noncardiac death; and

the increased risk of MACE in patients who experience an MI after a PCI.

Study designs and other criteria for inclusion in the review
Most of the model parameters were derived from the LIPS, which was a double-blinded, placebo-controlled randomised trial. However, the authors did not report the study designs or any other criteria for inclusion in the study.

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
Three studies were reported to be sources of effectiveness evidence.

Methods of combining primary studies
The authors estimated event probabilities using repeated-measures logistic regression models. No further methods for combining the primary studies were reported.

Investigation of differences between primary studies
The authors do not seem to have investigated differences between the primary studies.

Results of the review
The results that formed the principal effectiveness parameters used in the model were as follows.

The probability (per 100 patients) of cardiac death at the age of 60 years was 0.74 after 1 to 6 months following the first PCI, 0.43 after 7 to 12 months, and 0.19 after more than 12 months.

The probability (per 100 patients) of MI was 1.78 after 1 to 6 months following the first PCI, 0.63 after 7 to 12 months, and 0.42 after more than 12 months.

The probability of CABG due to restenosis within 1 to 6 months after the first PCI was 1.04.

The probability of repeat PCI due to restenosis within 1 to 6 months after the first PCI was 6.59.

The probability of CABG due to other reasons than restenosis was 0.95 after 7 to 12 months following the first PCI and 0.26 after more than 12 months (per 6 months).

The probability of repeat PCI due to other reasons than restenosis was 7.21 after 7 to 12 months following the first PCI and 1.33 after more than 12 months (per 6 months).

The probability of noncardiac death at the age of 60 years was 0.20.

The probability of death due to MI was 8.45 and that due to PCI 0.96.

The odds ratio of cardiac death was 2.00 and that of noncardiac death 2.80.

The increased risk of MACE faced by patients who experience an MI after PCI was 56%.

Methods used to derive estimates of effectiveness
The authors made assumptions to supplement some estimates of effectiveness.

Estimates of effectiveness and key assumptions
The authors reported that the probability (per 100 patients) of cardiac death at the age of 60 years after 1 to 6 months following the first PCI was based on primary data but no further details were provided. Based on their clinical experience, the authors assumed that the risk of MACE was temporarily increased during the months immediately after PCI and MI, while the higher risk was permanent in patients experiencing an MI after PCI. The risk of cardiac and noncardiac death increased with the age of the patient.

Measure of benefits used in the economic analysis
The measures of benefit used were the life-years (LYs) saved and quality-adjusted life-years (QALYs) gained. The utilities assigned to each health state were derived from studies published in the literature. The authors did not report...
any details of the extrapolation of the quality of life values adopted. As the time horizon of the model covered the patients' lifetime, all benefits were appropriately discounted at a rate of 3%.

**Direct costs**
The costs included in the analysis from the health care system perspective were for fluvastatin (mg/day), drug dispensing (90-day prescription), cardiac death (including emergency transportation and hospitalisation in an emergency care department), MI, PCI and CABG (including hospitalisation and inpatient professional services), and annual cardiac and noncardiac care (except MACE) of patients who had received PCI. Only summary unit costs were reported (e.g. the cost of treating MACE). The quantities were derived from the model and all costs were derived from official published sources. In case where only charges were available, the authors adjusted them to costs using a cost-to-charge ratio. All the costs were reported for the price year 2002. As the horizon of the model covered the patients' lifetime, discounting was appropriately carried out.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
No indirect costs were included in the economic analysis.

**Currency**
US dollars ($).

**Sensitivity analysis**
The authors conducted various structural sensitivity analyses to investigate the robustness of the results to variability in the model parameters. The cost-effectiveness of the treatment options was also investigated for specific patient groups. In addition, the authors carried out a probabilistic sensitivity analysis using bootstrapping (n=1,000) to obtain combined empirical distributions of all parameters that were extracted from the LIPS. For every bootstrap sample the authors reran the model using base-case, best-case (favouring fluvastatin treatment) and worst case (favouring diet and lifestyle counselling strategy) estimates for other key model parameters. Cost-effectiveness acceptability curves were also estimated for the resulting distributions of cost-effectiveness ratios.

**Estimated benefits used in the economic analysis**
The authors reported the incremental benefits. The fluvastatin group dominated in terms of overall survival and MACE-free survival after PCI. The projected difference in overall survival between the two treatment groups was 0.9% at 4 years after PCI, reaching a maximum of 2.9% at 22.5 years after PCI.

The difference in MACE-free survival was 6.4% at 4 years after PCI, reaching 11% at 16.5 years after PCI.

The fluvastatin treatment option resulted in an additional 0.78 LYs saved (9.3 months) not discounted and 0.44 LYs discounted, compared with diet and lifestyle counselling alone.

The fluvastatin treatment option resulted in 20.82 discounted (undiscounted 14.32) QALYS, compared with 20.14 discounted (undiscounted 13.94) QALYS for diet and lifestyle counselling alone.

The fluvastatin treatment resulted in 0.68 incremental QALYs not discounted and 0.38 QALYs discounted, compared with diet and lifestyle counselling alone.

**Cost results**
The total lifetime costs (discounted) were $122,028 for the fluvastatin treatment option, compared with $116,149 for diet and lifestyle counselling alone.

The fluvastatin 80 mg/day treatment resulted in an incremental total cost of $5,879 versus the option of diet and lifestyle counselling alone.

**Synthesis of costs and benefits**

Compared diet and lifestyle counselling alone, the option of fluvastatin 80 mg/day following PCI resulted in a cost of $13,505 per LY saved and a cost of $15,454 per QALY gained.

The sensitivity analysis demonstrated that if the relative risk of reduction for MACE excluding restenosis was varied over its 95% confidence interval (16 to 46%), the fluvastatin treatment resulted in a cost of $8,649 to $31,773 per LY saved ($9,890 to $36,389 per QALY). The cost-effectiveness ratio was most sensitive to the probability and cost of reintervention due to other causes than restenosis, and to the probability of cardiac death.

In terms of specific patient groups, the cost-effectiveness ratios were reported to be lower for older patients, patients with diabetes and patients with multi-vessel disease. The cost per LY saved and per QALY gained were the highest for patients with baseline low-density lipoprotein cholesterol levels of less than 130 mg/dL, with a cost of $22,896 per LY saved ($26,121 per QALY gained).

The probabilistic sensitivity analysis demonstrated that with the base-case assumptions for other parameters (reference-case assumptions) there was a greater than 90% probability that the fluvastatin treatment resulted in a cost of less than $26,000 per LY saved ($30,000 per QALY gained). If parameters were concurrently set to favour the diet and lifestyle counselling alone option, there was a greater than 90% probability that the cost-effectiveness of fluvastatin was less than $36,000 per LY saved ($42,000 per QALY gained), while it was $17,000 per LY saved ($19,000 per QALY gained) if these parameters were concurrently set to favour the fluvastatin treatment.

Overall, the probability that the cost-effectiveness of fluvastatin was less than $50,000 per QALY gained was 97% in the base-case scenario and 95% and 98% in the best- and worst-case scenarios, respectively.

**Authors' conclusions**

Fluvastatin treatment, administered after a first successful percutaneous coronary intervention (PCI), resulted in a cost per quality-adjusted life-year (QALY) gained of less than $50,000 (a commonly used threshold). This makes it a cost-effective treatment option for patients with near or above optimal to borderline high low-density lipoprotein cholesterol levels.

**CRD COMMENTARY - Selection of comparators**

The authors compared the immediate use of fluvastatin combined with diet and lifestyle counselling versus diet and lifestyle counselling alone, with conditional use of fluvastatin only in case of a future MACE. They did not discuss the existence of alternative medical therapies. You should decide if this represents a widely used technology in your own setting.

**Validity of estimate of measure of effectiveness**

The authors extracted most of the effectiveness data from one published study (LIPS) and no systematic review of the literature was undertaken. Although this is common practice with models, it does not always ensure that the best data available are used in the model. It is also possible that effectiveness data from the available studies were used selectively. The authors did not note any differences between the efficacy estimates from the primary studies. However, the authors carried out several sensitivity analyses relating to the efficacy estimates. These analyses improve both the internal validity and the generalisability of the study by demonstrating the robustness of the results to changes in the base-case estimates. Some key assumptions of the authors were based on the primary data available, but these were not analysed further. Further assumptions were based on the authors' clinical expertise, but no details on the method used to
estimate effectiveness were reported.

Validity of estimate of measure of benefit
The measures of benefit were the LYs saved and QALYs gained. The utility values were derived from published studies but no further details of the extrapolation of the quality of life values (e.g. specific tools used to measure the utility values) were reported.

Validity of estimate of costs
The cost analysis was performed from the perspective of the health care system. Whilst the relevant cost categories were included in the analysis, the use of summary costs makes it impossible to know precisely what aspects of costs were included within these categories. This fact may limit extrapolation exercises to other settings. All the costs were derived from official published sources and were appropriately adjusted to the year 2002. Where only charges were available, they were appropriately converted to costs using a cost-to-charge ratio. Discounting was appropriately carried out as the study horizon was longer than 2 years. An extensive sensitivity analysis was performed to assess the robustness of the estimates used. The authors reported the price year, which will enhance any future inflation exercises.

Other issues
The authors reported that their analysis supported existing guidelines issued by the Adult Treatment Panel III. In terms of the generalisability of the results, the authors acknowledged that the adoption of a US health care system perspective in the economic analysis may mean that the results are not applicable to non-US settings. The study enrolled patients with stable or unstable angina, or silent ischaemia, who have already had a successful PCI and this was reflected in the authors' conclusions. The authors reported a number of limitations to their study. For example, they assumed that the patients would fully comply with fluvastatin therapy and that they would experience a 33% reduction in the risk of MACE. This might have resulted in an underestimation of the cost-effectiveness results. The authors also acknowledged the limitations of the method employed to derive costs from billed charges.

Implications of the study
The authors did not make explicit recommendations for changes in policy or practice, or the need for further research. However, the discussion highlighted some areas where more information is required.

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