Pharmacoeconomic evaluation of the effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes

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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 atorvastatin (80 mg/day), initiated 24 to 96 hours after an acute coronary syndrome (ACS), to prevent death and nonfatal ischaemic events in patients with unstable angina or non-Q wave acute myocardial infarction (MI).

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients aged 18 years or older who experienced chest pain or discomfort of at least 15 minutes’ duration that occurred at rest, or with minimal exertion, within the 24 hours preceding hospitalisation and represented a change from their usual anginal patterns. Patients were excluded if the serum total cholesterol level at screening exceeded 270 mg/dL (7 mmol/L) or if coronary revascularisation was planned. Further exclusion criteria were evidence of Q-wave acute MI within the preceding 4 weeks, coronary artery bypass surgery within the preceding 3 months, percutaneous coronary intervention within the preceding 6 months, left bundle-branch block or paced ventricular rhythm, and severe congestive heart failure. Patients having concurrent treatment with other lipid-regulating agents, vitamin E, or drugs associated with rhabdomyolysis in combination with statins, were also excluded. Other exclusions were patients with severe anaemia, renal failure requiring dialysis, hepatic dysfunction or insulin-dependent diabetes, and women who were pregnant or lactating.

Setting
The setting of the study was likely to have been secondary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness and resource use data were gathered from May 1997 to September 1999. The price year was not explicitly reported.

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

Link between effectiveness and cost data
The costing was carried out retrospectively on the same sample of patients as that used in the effectiveness study.
Study sample
Power calculations were performed in the preliminary phase of the study. These suggested that 2,100 patients were required, on the assumption of 20% occurrence of a primary end point event among placebo patients and 14% occurrence among atorvastatin patients, with 95% power and a 5% significance level. However, due to the smaller differences between the groups, a larger sample was required (3,000 patients) to maintain a 95% power to detect a 30% relative treatment effect (or 80% power to detect a 25% relative treatment effect).

The initial study group comprised 3,086 patients, 1,548 received placebo and 1,538 received atorvastatin. The mean age in the placebo group was 65 (+/- 12) years and 34.1% were women. The mean age in the atorvastatin group was 65 (+/- 12) years and 35.5% were women. Details on the method of sample selection were not reported. There was also no information on patients who refused to participate or were excluded for any reason. A group of 161 patients in the placebo group and 175 patients in the atorvastatin group withdrew from study medication, mainly due to a decision made by the physician or participant.

Study design
This was a randomised, double-blind controlled trial, which was carried out in 122 centres in Europe, North America, South Africa and Australasia. The patients were randomly assigned to the two groups with stratification by centre. The length of follow-up was 16 weeks and assessment was carried out at 2, 6 and 16 weeks. Three patients in the placebo group and 8 patients in the atorvastatin group were lost to follow-up. A committee of 6 cardiologists, who were blinded to the treatment assignment, judged all the end points. The patients were unaware of the treatment they received.

Analysis of effectiveness
The analysis of the clinical study was conducted on an intention to treat basis. The primary health outcome was a combined end point of death, nonfatal acute MI, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischaemia with objective evidence requiring emergency re-hospitalisation. This was analysed by time to first event, using a Cox proportional hazards model stratified by country and inclusion event. The secondary health outcomes were:

- the occurrence of each primary end point component as well as nonfatal stroke,
- new or worsening congestive heart failure requiring hospitalisation, but without new objective evidence of ischaemia,
- coronary revascularisation by surgical or percutaneous means,
- time to first occurrence of any primary or secondary end point, and
- percentage changes in blood lipid levels from baseline to study end.

Adverse events were also observed. The study groups were shown to have been comparable at baseline in terms of their demographics and clinical conditions.

Effectiveness results
The combined end point occurred in 17.4% in the placebo group and 14.8% in the atorvastatin group. The relative risk (RR) was 0.84 (95% confidence interval, CI: 0.70 - 1.00).

The occurrence of any secondary outcomes was 22.2% in the placebo group and 22.4% in the atorvastatin group. The RR was 1.01 (95% CI: 0.88-1.15).

Only the occurrence of either fatal or nonfatal stroke (RR 0.50, 95% CI: 0.26 - 0.99) and nonfatal stroke (RR 0.41, 95% CI: 0.20 - 0.87) was significantly lower in the atorvastatin group.

Adverse events were negligible in both groups.
Clinical conclusions
The effectiveness analysis showed that atorvastatin treatment reduced the occurrence of early, recurrent ischaemic events, primarily recurrent symptomatic ischaemia requiring hospitalisation.

Measure of benefits used in the economic analysis
The summary health outcome used in the economic analysis was the number of inpatient events. This was derived from the effectiveness analysis, after adjusting for sample size differences. Side effects were not considered due to the low incidence observed during the trial.

Direct costs
Discounting was irrelevant since the costs were incurred during 16 weeks. The unit costs were reported separately from the quantities of resources used. The cost items considered in the economic evaluation were hospitalisations due to the occurrence of primary or secondary end points. The cost/resource boundary adopted in the study was that of the third-party payer. Resource use was estimated using actual data derived from the clinical trial that provided the effectiveness evidence. The unit costs comprised both inpatient hospital and physician services.

For each type of end point considered in the MIRACL study, the corresponding diagnosis-related group (DRG) was identified. The costs were estimated from the Nationwide Inpatient Sample (NIS) database. To estimate the true costs, the DRG-specific cost-to-charge ratio was used. Physician costs, which were estimated from the 2001 Physician Fee and Coding Guide, were then added to the cost of a DRG to estimate the total costs of each event. The authors stated that deaths unrelated to the study were not considered ($0). Drug costs were estimated from average wholesale prices. The costs of monitoring were also considered. The price year was unclear.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not considered, which was in line with the perspective adopted.

Currency
US dollars ($).

Sensitivity analysis
Uni- and multi-variate sensitivity analyses were carried out on all inputs. The area of uncertainty investigated was the robustness of the results to variations in the base-case values used in the analysis. All the inputs were varied in the Monte Carlo simulation (10,000 iterations), where the number of event combinations was varied randomly within the 95% CIs following a normal distribution. The cost data were varied within a range of +/- 20%. The ranges of variations used for the costs were those observed in the literature. The following scenarios were also considered:

the exclusion of hospitalisation for worsening angina;
the removal of assumed costs of monitoring for adverse effects and for hospitalisations for hepatitis among the atorvastatin population;
the inclusion of an estimated cost for patients lost to follow-up; and
the inclusion of an assumed cost of death for those deaths which were not classifiable.
Estimated benefits used in the economic analysis
The number of inpatient events was 626 in the placebo group and 563 in the atorvastatin group.

Cost results
The total costs were $7,225,191 in the placebo group and $7,419,398 in the atorvastatin group ($6,778,740 for inpatient events and $640,658 for atorvastatin).

The mean total cost per patient was $4,667 in the placebo group and $4,824 in the atorvastatin group. Thus, the use of atorvastatin led to an additional cost of $157 per patient.

Synthesis of costs and benefits
An incremental cost-effectiveness ratio (ICER) was calculated to combine the costs and benefit. The ICER of atorvastatin relative to placebo was $4,086 per event avoided.

The sensitivity analysis showed that if angina hospitalisation were excluded, the ICER would rise to $26,236.

When additional monitoring costs and hospitalisations for hepatitis were excluded, the ICER fell to $583.

The inclusion of patients lost to follow-up increased the cost per patient to $205, while the inclusion of unclassifiable deaths led to an incremental cost of $172.

The sensitivity analysis showed that the cost of coronary artery bypass grafting was a relevant cost driver, but the difference in costs between the treatment options did not change. The Monte Carlo simulation suggested that in more than 98% of the simulations, atorvastatin led to better outcomes. The one-way analysis showed that variations in the rates of MI, percutaneous transluminal coronary angioplasty, fatal MI and coronary artery bypass graft within their 95% CIs would result in a break-even cost for both treatment options.

Authors' conclusions
The short-term analysis showed that the use of high dosages of atorvastatin was cost-effective, as it reduced the occurrence of early ischaemic events and death in patients who had experienced an acute coronary syndrome (ACS) at reasonable costs from the perspective of the third-party payer.

CRD COMMENTARY - Selection of comparators
The authors compared the study drug with placebo. Placebo was clearly selected as the basic comparator in order to estimate the true effect of atorvastatin after ACS. Other statins were clearly available, but were not considered to be relevant comparators. You should consider whether placebo represents a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness used a double-blind, randomised placebo-controlled trial, which was appropriate for the study question and ensured a high internal validity. The study was powered to detect statistically significant differences in the main composite end point. However, inferences on the significance of differences in secondary outcomes should be made with caution. The basis of the analysis was intention to treat and the randomisation process was stratified. This further increases the validity of the analysis. The patients were recruited from many centres, reflecting different disease patterns, which ensures that the effectiveness measure is even more reliable. The loss to follow-up was minimal. Assumptions about the treatment of these patients were made and then varied in the sensitivity analysis. Overall, the analysis was carried out credibly and the internal validity was high.

Validity of estimate of measure of benefit
The summary benefit measure was derived directly from the effectiveness study. Since it represented a disease-specific
intermediate outcome, it is difficult to compare it with the benefits of other health care interventions. Quality of life issues were not considered. This may be due to the fact that the study drug had the greatest impact on survival and only a short-term horizon was considered. However, the impact of severe impairment would have been better captured by measures such as quality-adjusted life-years.

Validity of estimate of costs
The authors stated explicitly the perspective adopted in the study and only relevant costs were included in the analysis. Accordingly, the indirect costs were not considered. However, the authors stated that the use of atorvastatin could reduce long-term indirect costs due to fewer hospitalisation episodes. Hospitalisation costs were estimated from DRG charges, which were then converted into true costs using a specific cost-to-charge ratio. Other expenses were derived from actual costs. Resource use was estimated from actual data collected alongside the MIRACL trial. The price year was not explicitly stated and this could limit the possibility of reflating the estimated costs in other settings. The authors conducted a sensitivity analysis to analyse the robustness of their results. Different scenarios for the costs were considered.

Other issues
The authors did not compare their findings with those from other studies. The issue of the generalisability of the study conclusions was partially addressed when the authors stated that their results might not be generalisable to other scenarios in the USA due to the variety of insurance and health care plans. However, several sensitivity analyses were carried out and the results were reported satisfactorily. This enhanced the transferability of the study results to other settings since wide ranges of values were considered, which may reflect alternative treatment or reimbursement patterns. The study conclusions appear to have been consistent with the scope of the analysis.

Implications of the study
The study results suggested that atorvastatin represents a safe, effective and efficient option for the prevention of fatal and nonfatal ischaemic events among patients who have experienced an ACS. No recommendations for future research were proposed.

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Other publications of related interest

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