Cost-effectiveness of targeting patients undergoing cardiac surgery for therapy with intravenous amiodarone to prevent atrial fibrillation

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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 prophylactic intravenous (IV) amiodarone therapy for the prevention of atrial fibrillation (AF) in patients undergoing cardiac surgery.

Type of intervention
Secondary prevention.

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

Study population
For the study on AF predictors, three populations were analysed. These were patients undergoing coronary artery bypass grafting (CABG), valve replacement, and combined CABG and valve replacement procedures. Patients with a history of AF were excluded from the study.

For the study on the effect of AF on 5-year survival, the patients underwent coronary or valve surgery.

Setting
The setting was a hospital. The economic study was carried out at the Emory University Hospitals in Atlanta (GA), USA.

Dates to which data relate
The effectiveness and resource use data were gathered from 1994 to 1999 for the cost-effectiveness study and from 1980 to 1995 for the cost-utility analysis. No price year was reported.

Source of effectiveness data
The effectiveness evidence was derived from a single study and from authors' assumptions.

Link between effectiveness and cost data
The costing was performed retrospectively on the same sample of patients as that used in the cost-effectiveness study.

Study sample
Separate studies were conducted to determine the risk factors for AF and to determine the effect of AF on 5-year life expectancy.
For the study on AF predictors, analyses were carried out on three samples corresponding to the three populations specified (see 'Study Population' section). Power calculations, if performed, were not reported. An overall sample of 10,550 patients was enrolled between 1 January 1994 and 30 June 1999. There were 8,709 patients for the CABG sample, 1,217 patients for the valve only sample and 624 patients for the CABG and valve sample. In the CABG group, the mean age was 63 (+/- 13) years for those developing AF and 55 (+/- 15) years for those not developing AF. The proportions of women were 42% (AF) and 46% (no AF), respectively. For the valve only sample, the mean age was 68 (+/- 9) years for those developing AF and 62 (+/- 11) years for those not developing AF. The proportions of women were 27% (AF) and 26% (no AF), respectively. For the CABG and valve sample, the mean age was 71 (+/- 9) years for those developing AF and 67 (+/- 11) years for those not developing AF. The proportions of women were 33% (AF) and 36% (no AF), respectively.

For the study on the effect of AF on 5-year survival, a sample of 25,975 patients from 1980 to 1995 was used. Of these, 21,349 were CABG patients, 3,275 were valve replacement patients and 1,351 were CABG plus valve patients.

**Study design**
For both studies, the analyses seem to have been based on retrospective cohort studies (although it was not clearly expressed), which were collected from the Emory University Hospitals database. The baseline variables were recorded. The outcome data were recorded at one year and every 5 years’ post-procedure, and during all cardiac rehospitalisations. The average length of follow-up was not reported.

**Analysis of effectiveness**
For all analyses, it appears that all of the patients enrolled in the study were taken into account when estimating the effectiveness. The primary study outcomes were mortality rates, occurrence of AF, length of stay in the hospital, and the impact of demographic, clinical, angiographic and surgical characteristics on the probability of developing AF. The development of AF was estimated using a multivariate logistic regression analysis. The c-index values of the discriminatory power of the regression models were reported. Finally, the hazard ratios of death from AF for the three samples were calculated.

**Effectiveness results**
The mortality rate ranged from 2.6% in the CABG group to 11.7% in the CABG plus valve group.

AF occurred in 17.7% of the patients in the CABG group, in 24.6% of those in the valve group, and in 33.8% of those in the CABG plus valve group.

AF was associated with an increase in post-procedural length of stay of 3.4 days in the CABG group, 3.3 days in the valve group, and 6.4 days in the CABG plus valve group.

Multivariate predictors of the recurrence of postoperative AF for the CABG sample were age (odds ratio, OR, 1.84, 95% confidence interval, CI: 1.73 - 1.95), gender (OR 0.85, 95% CI: 0.75 - 0.97), bypass time (OR 1.03, 95% CI: 1.02 - 1.05) and prior myocardial infarction (OR 0.87, 95% CI: 0.77 - 0.98).

The predictors for the valve sample were age (OR 1.44, 95% CI: 1.30 - 1.60), chronic obstructive pulmonary disease (OR 1.60, 95% CI: 1.07 - 2.41), and smoker condition (former smoker versus never smoked, OR 0.91, 95% CI: 0.68 - 1.24; current smoker versus never smoked, OR 0.59, 95% CI: 0.37 - 0.94).

The predictors for the valve sample were age (OR 1.53, 95% CI: 1.29 - 1.83) and renal insufficiency (OR 1.97, 95% CI: 1.26 - 3.08) in the CABG plus valve group.

The c-index was 0.68 for the CABG model, 0.67 for the valve replacement model, and 0.65 for the CABG plus valve model.

For CABG patients who developed postoperative AF, the hazard ratio for death was 1.19 (95% CI: 1.09 - 1.30). There was no significant hazard of death from postoperative AF for the other two groups.
Clinical conclusions
The effectiveness analysis showed the predictors of post-procedural AF and other outcome data. These were used in the decision model in the cost-effectiveness study.

Modelling
A multivariate logistic regression model was used to examine the effect of several demographic, clinical, angiographic and surgical characteristics on the development of AF. The c-index was also developed to define the ability of the regression model to discriminate among patients with respect to their outcomes. The model was validated internally using a bootstrap analysis (150 bootstrap samples). Finally, a decision analytic model was used to determine the cost-effectiveness of amiodarone in comparison with no amiodarone.

Methods used to derive estimates of effectiveness
The authors made an assumption relating to the efficacy of IV amiodarone, which was derived from a published trial.

Estimates of effectiveness and key assumptions
The efficacy of IV amiodarone was assumed to have been 26%.

The long-term cost-utility model made two other model assumptions for the base-case. First, an event had no effect on utility in the first year. Second, the effect of an event averted on long-term mortality was 100%.

Measure of benefits used in the economic analysis
In the cost-effectiveness study, the proportion of cases averted (based on the AF rate) was used as the benefit measure in the economic analysis. It was derived from modelling, although the details of this were not reported. In the cost-utility analysis, the benefit measure was quality-adjusted life-years (QALYs). Data on survival were derived from the effectiveness study involving 25,975 patients and using the Cox regression proportional hazards model, while the source of utility data was not reported. In the cost-utility analysis, the life-years were discounted at a rate of 3%.

Direct costs
The economic evaluation incorporated hospital and professional costs. The cost/resource boundary adopted in the study was that of the hospital for hospital costs and that of the payer for professional charges. The costs were estimated from the UB-92 formulation of hospital bills for hospital charges and from Current Procedural Terminology codes for professional charges. The longer-term costs were also considered for the long-term cost-utility model. Charges were converted into costs using a departmental cost-to-charge ratio. The costs were discounted at a rate of 3% in the cost-utility analysis only, as a long-term perspective was adopted. The unit costs were not reported separately from the quantities of resources and a breakdown of the costs was not given. No price year was reported.

Statistical analysis of costs
The costs were treated deterministically, but statistical analyses were conducted to determine the influence of clinical and demographic factors on the total costs.

Indirect Costs
The indirect costs were not included.

Currency
US dollars ($).
Sensitivity analysis
Sensitivity analyses were conducted to assess the influence of variations in the cost of therapy, efficacy of therapy and the cut-off probability of AF for initiating therapy on the estimated cost-effectiveness ratios. Two-way sensitivity analyses were conducted. The base-case assumptions on the effect on utility in the first year and the effect of an event averted on long-term mortality were varied.

Estimated benefits used in the economic analysis
The treatment threshold (the predicted risk of AF above which amiodarone therapy would be initiated) was varied from 0 to 100. This resulted in an AF rate ranging from 13.1 to 17.7% in the CABG group, from 18.2 to 24.6% in the valve group, and from 25 to 33.8% in the CABG plus valve group.

In the cost-utility analysis, the mean discounted (3%) life-years over the 5-year follow-up was 4.18 years for patients without AF and 3.92 years for patients with AF.

The number of QALYs gained was not reported.

Cost results
As the treatment threshold varied from 0 to 100, the mean costs of the treatment ranged from $24,443 to $23,296 in the CABG group, from $32,121 to $31,330 in the valve group, and from $40,784 to $40,384 in the CABG plus valve group.

Synthesis of costs and benefits
An incremental analysis was conducted to combine both the benefits (QALYs and the proportion of AF cases averted) and costs.

In the cost-effectiveness analysis, as the treatment threshold was varied from 0 to 100, the incremental cost per AF event averted for a strategy of treating patients at one cut-off level versus the next highest cut-off level ranged from $55,854 to $10,938 in the CABG group, from $43,011 to $4,219 in the valve group, and from $39,698 to $69 in the CABG plus valve group.

In the cost-utility analysis for CABG patients, in the base-case, the cost per QALY gained ranged from $824,786 at the 0 - 10% treatment threshold to $174,089 at the 45 - 50% treatment threshold.

The sensitivity analysis for the cost-utility analysis of CABG patients showed that, if the utility of a patient for the first year was reduced by 20% due to an AF event, the cost per QALY gained would be significantly reduced with amiodarone use at all treatment thresholds. The cost per QALY gained fell below $50,000 at the 45 - 50% treatment threshold.

The effect of an event averted on long-term mortality had little effect on the cost per QALY gained in comparison with the effect on utility. Still, assuming a 20% drop in utility from an AF event, if the effect on long-term mortality from an event averted were reduced from 100 to 0%, the cost per QALY gained would only increase from $47,553 to $65,423 at the 45 - 50% treatment threshold.

Authors' conclusions
The short-term cost-effectiveness analysis and longer-term cost-utility analysis suggest that the administration of intravenous (IV) amiodarone to coronary artery bypass graft (CABG) patients is not cost-effective. Assuming that the maximum willingness to pay per quality-adjusted life-year (QALY) gained was $50,000 from the societal point of view, the authors stated that only a small fraction of patients at high level of risk should be treated. If a threshold of $5,000 per AF episode averted were used, then the therapy would be recommended only for 5% of valve replacement patients and about two thirds of CABG plus valve patients.
CRD COMMENTARY - Selection of comparators
The study focused on sub-group analyses for three patient groups (CABG, valve, and CABG plus valve) and the treatment threshold given. The authors stated that earlier studies had compared IV amiodarone with oral amiodarone, so one can assume that oral amiodarone had been the comparator. You should decide whether it is a useful comparator in your own setting.

Validity of estimate of measure of effectiveness
Both AF predictors and the effect of AF on 5-year survival were determined for three populations. The samples were different for these two analyses. In both cases it seems that retrospective cohort studies have been undertaken. Few details were given against which to judge the internal validity of the studies. The quality of the reporting was poor. Assumptions were also made for the cost-utility analysis, and only a couple of these were investigated in sensitivity analyses.

Validity of estimate of measure of benefit
Two benefit measures were used in the economic analysis. However, as in the effectiveness analysis, only a few details of the methodology and source of data were reported. The utility values used to calculate the QALYs were not given and the survival data were incomplete. The information was fragmented.

Validity of estimate of costs
The perspective adopted in the study was not reported explicitly. It was therefore not possible to assess whether all the relevant categories of costs were included in the analysis. Overall, only a few details of the cost analysis were reported. For example, the source of the cost data and the use of a cost-to-charge ratio to derive the true costs of the services, which were based on charges. Neither the unit costs nor the quantities of resources used were reported, and no price year was given. This makes inflation exercises in other settings difficult. The costs and the quantities were treated deterministically and statistical analyses were conducted to determine the influence of specific factors on the total costs. Few sensitivity analyses were conducted on the costs.

Other issues
The authors stated that their study was the first to examine the cost-effectiveness of targeting patients undergoing cardiac surgery for IV amiodarone treatment according to their predicted risk level, using data from a single study. However, the issue of the generalisability of the study results to other settings was not addressed, thus limiting the external validity of the study. The authors acknowledged that the model was limited by the assumptions made and the moderate ability of the logistic regression model to predict the occurrence of postoperative AF.

Implications of the study
The authors suggested that IV prophylactic amiodarone was not cost-effective in low-risk patients, while it was cost-effective in patients at higher risk, especially old patients undergoing valve surgery or CABG plus valve surgery. However, caution is required when interpreting these results due to the highlighted limitations of the study.

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