Potential cost-effectiveness of prophylactic use of the implantable cardioverter defibrillator or amiodarone after myocardial infarction

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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 prophylactic strategies for patients who had myocardial infarction (MI) were examined. The strategies were implantable cardioverter defibrillator (ICD) and amiodarone (AMIO).

Type of intervention
Secondary prevention.

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

Study population
The study population comprised patients who had MI without symptomatic, sustained ventricular arrhythmia. Patients were stratified into three groups according to ventricular EF (≤0.3, 0.31 to 0.4, and >0.4), because EF has consistently been the single most powerful predictor of sudden cardiac death.

Setting
The setting was a hospital and secondary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data and some resource use data were derived from studies published between 1987 and 2001. The price year was 1999.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies and authors' assumptions.

Modelling
A decision model based on a Markov process was used to examine the expected costs and (quality-adjusted) survival in a cohort of patients after MI. The model was based on the modification a published model. The patients received AMIO, ICD, or no anti-arrhythmic therapy. The time horizon of the model was lifetime and the cycle length was one month. Patients who received an ICD (who were at risk for procedural death), and those who received AMIO or no treatment entered the Markov tree. During each period, a patient could die from arrhythmic or non-arrhythmic cardiac causes and could also die of non-cardiac causes. If none of these events occur, the patient remained well. Patients who had an ICD may have a lead infection or failure that causes them to withdraw from treatment (and switch to no anti-arrhythmic therapy). Patients who received AMIO were at risk for AMIO toxicity. A patient could die of toxicity, withdraw from treatment, or have acute toxicity that did not require discontinuation.
Outcomes assessed in the review
The outcomes estimated from the literature were:

- the annual arrhythmic mortality in patients not taking anti-arrhythmic therapy;
- the probability of procedural death with ICD;
- the efficacy of ICD in reducing arrhythmic mortality;
- the frequency of ICD generator replacement;
- the probability of withdrawal from ICD;
- the efficacy of AMIO in reducing total mortality;
- the probability of toxicity;
- the probability of dying given toxicity;
- the probability of withdrawal given toxicity; and
- utility values.

The characteristics of the patient population (e.g. age and clinical characteristics) were also derived from the literature. Mortality rates of the general population were also used.

Study designs and other criteria for inclusion in the review
It was not stated whether a systematic review of the literature had been undertaken to identify primary studies. Much of the data came from the Myocardial Infarction Triage and Intervention (MITI) patient registry (approximately 49,000 patients were admitted between 1988 and 1994). Demographic and clinical characteristics of a sample of patients from this registry were provided. Other data (for AMIO) were obtained from two meta-analyses. Mortality rates were obtained from US statistics.

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
Approximately 24 studies provided evidence.

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
Results of the review
The annual arrhythmic mortality in year 1 in patients not taking anti-arrhythmic therapy was 7.8% (range: 1.95 - 15.6) for EF <= 0.3, 2.5% (range: 0.62 - 5.0) for EF 0.31 - 0.4, and 1.1% (range: 0.27 - 2.2) for EF >0.4.

The annual arrhythmic mortality in year 1 in patients taking anti-arrhythmic therapy was 10.2% (range: 2.55 - 20.4) with EF <=0.3, 6.4% (range: 1.6 - 12.8) with EF 0.31 - 0.4, and 1.5% (range: 0.375 - 3.0) with EF >0.4.

The probability of procedural death with ICD was 0.9% (range: 0 - 3.0). The efficacy of ICD in reducing arrhythmic mortality was 60% (range: 20 - 100).

The frequency of ICD generator replacement was 7 years (range: 2 - 9).

The probability of withdrawal from ICD was 2% (range: 0 - 5) in year 1 and 1% (range: 0 - 5) in subsequent years.

The efficacy of AMIO in reducing arrhythmic mortality was 11% (range: 4 - 20).

The probability of toxicity was 12.5% (range: 10.0 - 15.0) in year 1 and 6.25% (range: 5.0 - 7.5) in subsequent years.

The probability of dying given toxicity was 0.41% (range: 0 - 9.0). The probability of withdrawal given toxicity was 80% (range: 50 - 100).

The utility value associated with current health was 0.88 (range: 0.6 - 1).

Methods used to derive estimates of effectiveness
The authors made some assumptions that were used in the decision model.

Estimates of effectiveness and key assumptions
The utility values associated with ICD and AMIO therapy were 0.88, which was the same as the utility for current health. The disutility due to perfect health lost because of acute drug toxicity was 1 day (range: 0 - 30).

Measure of benefits used in the economic analysis
The summary benefit measures used were life-years (LYs) and quality-adjusted life-years (QALYs). These were obtained from the decision model. An annual discount rate of 3% was applied. The utility values were obtained from published studies and from authors’ assumptions, but the method used to elicit preferences were not described. The number-needed-to-treat to prevent one arrhythmic death was also reported.

Direct costs
Discounting was relevant, as the costs were incurred during a long timeframe, and a 3% discount rate was applied. The unit costs were not presented separately from the quantities of resources used. The health services included in the economic evaluation were initial hospitalisation, ongoing therapy, and the replacement of ICD generator or leads. Ongoing therapy included physician visits, laboratory tests, drugs, and re-hospitalisation for IDC-related complications or AMIO toxicity. The cost/resource boundary of the study was unclear. Both costs and resource use were estimated using data derived from the MITI registry, as well as published studies. The costs were updated to 1999 values using the Consumer Price Index.

Statistical analysis of costs
The costs were treated deterministically.
Indirect Costs
The authors stated that indirect costs, such as patient travel and inconvenience, were considered. It would appear that these costs should have been included in the categories of non-medical direct costs and intangible costs. Productivity costs do not appear to have been included in the analysis.

Currency
US dollars ($).

Sensitivity analysis
Univariate sensitivity analyses were carried out on all model inputs to examine the robustness of the cost-effectiveness results to variations in base-case assumptions. A selective two-way sensitivity analysis and a probabilistic sensitivity analysis were also performed. The ranges of values used were either derived from the literature or based on authors' assumptions. Further, the results were reported using different scenarios, that is, for three EF groups and three levels of efficacy of AMIO and ICD.

Estimated benefits used in the economic analysis
The expected outcomes varied substantially according to EF and assumptions on the efficacy of the interventions. In general, the use of an ICD consistently led to the longest (quality-adjusted) life expectancy, while AMIO led to intermediate (quality-adjusted) life expectancy, and no therapy resulted in the worst outcomes. However, there were some exceptions. Life expectancy was slightly better with no treatment than with AMIO if the efficacy of AMIO was low and the EF exceeded 0.3. Conversely, if the efficacy of AMIO was high, AMIO resulted in better outcomes than ICD in patients with EFs exceeding 0.4.

The prevention of one death (over 5 years) would require implantation of an ICD in 9.6 to 207.5 patients, or administration of AMIO therapy in 14.4 to 2,127.6 patients, depending on EF.

The results in terms of QALYs depended on the efficacies of these prophylactic treatments. For example, the estimated QALYs for a patient with EF 0.31 to 0.4, assuming moderate efficacy, were 7.87 with ICD, 7.69 with AMIO and 7.42 with no therapy.

Cost results
In general, the use of an ICD consistently led to the highest costs, while AMIO led to intermediate costs, and no therapy resulted in the lowest costs. For example, the lifetime costs of a patient with EF 0.31 to 0.4, assuming moderate efficacy, was $131,400 with ICD, $96,800 with AMIO and $78,300 with no therapy.

Synthesis of costs and benefits
Incremental cost-effectiveness ratios and cost-utility ratios were calculated to combine the costs and benefits of the alternative strategies.

In general, prophylactic therapy was more cost-effective at lower EFs. At any EF, therapy was more cost-effective as efficacy increased (although there were some exceptions). For example, the projected cost per QALY with ICD compared with AMIO for a patient with EF 0.31 to 0.4 was $128,100 with low efficacy, $195,700 with moderate efficacy, and $517,100 with high efficacy. The projected cost per QALY with ICD compared with no treatment for a patient with EF 0.31 to 0.4 was $186,300 with low efficacy, $116,800 with moderate efficacy, and $85,900 with high efficacy.

The sensitivity analysis showed the following results:

the cost-effectiveness of prophylactic therapies compared with no anti-arrhythmic therapy became more favourable as the efficacy of treatments increased;
ICD was cost-effective compared with AMIO only in the group with the lowest EF; if the underlying cardiac mortality rate of the population was reduced by 25% or more, the cost-effectiveness of both the ICD and AMIO compared with no treatment would be far less favourable; conversely, if the population risk were 25% or higher, both AMIO and use of an ICD would be more economically attractive; if the cost of ICDs decreased substantially, ICDs would seem cost-effective in a larger number of patients; if AMIO reduced the quality of life compared with an ICD, then use of an ICD becomes much more favourable.

The multivariate sensitivity analysis revealed that for patients with an EF of 0.3 or less, AMIO dominated ICD in 2.6% of the simulations. The ICD was more effective, yet more costly, in the remaining 97.4% of simulations (median incremental cost-effectiveness ratio $83,200/QALY). In 0.02% of simulations, ICD was dominated by no treatment. In the remaining 99.98%, it had a median cost-effectiveness ratio of $67 700/QALY compared with no treatment. AMIO was dominated by no anti-arrhythmic therapy in 0.07% of the simulations and had a median cost-effectiveness ratio of $47,000/QALY in the remaining 99.93%. Similar results were observed in the other EF groups (although the incremental cost-effective ratios increased at higher EFs).

Authors’ conclusions
The use of implantable cardioverter defibrillators (ICDs) or amiodarone (AMIO) as prophylactic strategies after myocardial infarction (MI) could be cost-effective, compared with no anti-arrhythmic therapy, in patients with severely depressed left ventricular function (i.e. left ventricular ejection fraction <=0.3), as long as the ICD reduced sudden cardiac death by at least 50% and AMIO reduced total mortality by at least 7%. In patients with well-preserved ventricular function (i.e. ejection fraction >0.4), neither AMIO nor ICD were cost-effective.

CRD COMMENTARY - Selection of comparators
The selection of the comparators was appropriate as the possible preventive strategies for patients who had MI were considered. However, the two interventions investigated in the study were not accurately described. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from published studies. It was not stated whether a systematic review of the literature had been undertaken, but the primary studies appear to have been identified selectively. Much of the data were derived from a patient registry and it would appear that few randomised controlled trials were available. The methods used to extract and combine the data were not described. Clinical inputs were varied in the sensitivity analysis, which addressed the issue of uncertainty in some estimates.

Validity of estimate of measure of benefit
Several benefit measures were used. The use of QALYs as a summary benefit measure was appropriate as it incorporated the impact of the interventions on survival and quality of life. Limited information on the utility values was given. The utility values were mainly based on assumptions but were varied in sensitivity analyses, showing a strong impact on final ICERs. Discounting was applied, as recommended in US guidelines. QALYs and LYS are comparable with the benefits of other health care interventions.

Validity of estimate of costs
The authors stated that a societal perspective was adopted in the study, but it seems that productivity costs had not been included in the analysis. A detailed breakdown of the items was not provided, and the unit costs were not reported separately from the quantities of resources used. These factors limit the possibility of replicating the analysis in other settings.
settings. The source of the data was unclear. No statistical analysis of the costs was performed, but it would appear that all economic inputs were varied in the sensitivity analysis, although only the results of some key estimates were given. The price year was reported, which aids reflation exercises.

Other issues
The authors stated that their findings differed from published studies because of the different patient populations considered in the analysis. The issue of the generalisability of the study results to other settings was not explicitly addressed, although sensitivity analyses were carried out and the results of the analysis were extensively reported. The authors noted some limitations of their study. For example, the use of data derived from an observational study (the MITI registry) and the lack of further patient stratification into more precise risk categories. However, the use of the MITI registry included a broad range of patients from a variety of hospitals and it is likely to represent the study population.

Implications of the study
The study results supported the use of ICD and AMIO in patients with reduced left ventricular function (EF <=0.3). However, the authors stressed that, since their findings strongly depended on some assumptions on treatment efficacy, it would be crucial to know whether the results of two ongoing trials (MADIT II and the Sudden Cardiac Death Heart Failure Trial) will confirm the estimates used in the current model.

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Other publications of related interest


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