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 an implantable cardioverter-defibrillator (ICD) to improve survival among patients at risk of sudden death due to left ventricular systolic dysfunction, but who have not had a life-threatening ventricular arrhythmia.

Type of intervention
Primary prevention.

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

Study population
The study population comprised patients at risk for sudden death due to left ventricular systolic dysfunction, but who have not had a life-threatening ventricular arrhythmia. Patients in different trials had different characteristics in terms of severity of disease.

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

Dates to which data relate
Most of the effectiveness data and resource use estimates were derived from studies published between 1987 and 2005. The price year was 2005.

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

Modelling
A Markov model was constructed to simulate the clinical and economic outcomes associated with ICD and control therapy. The model served also to extrapolate short-term trial-based results to a lifetime horizon. The cycle length was one month. Patients who received an ICD were at risk of death from the implantation procedure. Patients who did not die from the procedure and patients assigned to control therapy entered the Markov tree and were followed until death. A patient could die from arrhythmia, non-arrhythmic cardiac causes, or noncardiac causes. If the patient survived, he or she remained well for the 1-month period. Patients who had an ICD could have a lead infection or failure that could cause them to discontinue treatment.

Outcomes assessed in the review
The outcomes assessed from the literature were:
annual mortality associated with control therapy;

the efficacy of the ICD, which was defined as a reduction in the relative risk of death;

all-cause mortality;

the frequency of ICD generator replacement;

the probability of lead problems requiring surgical intervention; and

the utility values.

**Study designs and other criteria for inclusion in the review**

It was unclear whether a systematic review of the literature was undertaken to identify the primary studies. The efficacy of the ICD over control therapy was estimated from 8 clinical trials. More specifically, these were the Coronary Artery Bypass Graft (CABG) Patch Trial, Defibrillator in Acute Myocardial Infarction Trial (DINAMIT), Multicenter Automatic Defibrillator Implantation Trial (MADIT) I, MADIT II, Multicenter Unsustained Tachycardia Trial (MUSTT), Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial, Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial, and Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). The inclusion criteria for the patients were reported for each trial. Other clinical data were derived from studies that appear to have been identified selectively.

**Sources searched to identify primary studies**

Not stated.

**Criteria used to ensure the validity of primary studies**

The internal validity of the primary studies was high in the case of clinical trials. However, the robustness of the other sources was not discussed.

**Methods used to judge relevance and validity, and for extracting data**

Not stated.

**Number of primary studies included**

Twenty primary studies provided clinical data.

**Methods of combining primary studies**

The primary data derived from the 8 clinical trials were not combined. Other clinical data were entered into the decision model in a narrative way.

**Investigation of differences between primary studies**

Not stated.

**Results of the review**

The annual mortality associated with the control therapy ranged from 7.2% (DINAMIT) to 19.5% (MADIT-I).

The efficacy of the ICD (hazard ratio compared with the control) ranged from 0.45 (MUSTT; range: 0.32 - 0.63) to 1.08 (DINAMIT; range: 0.76 - 1.55).
The frequency of ICD generator replacement was 5 years (range: 2 - 9).

The probability of lead problems requiring surgical intervention was 2.4% (range: 0 - 5).

The utility value associated with control therapy was 0.88 (range: 0.6 - 1).

The all-cause mortality rate was not reported.

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 duration of ICD benefit was assumed to have been lifetime.

The utility value associated with the ICD was 0.88 (range: 0.6 - 1).

The quality of life decrements due to hospitalisation for lead infections were 3.5 days.

Measure of benefits used in the economic analysis
The summary benefit measures used were the life-years (LYs) gained and quality-adjusted life-years (QALYs). These were estimated using the decision model. The source of the utility values, which were combined with expected survival in order to calculate the QALYs, was reported. However, no details of the methods used to elicit patient preferences were given. An annual discount rate of 3% was applied to the benefit measures.

Direct costs
The authors stated that a societal perspective was adopted, but only direct medical costs were included in the analysis. The health services included in the economic evaluation were initial ICD implantation, ongoing therapy for both the control and ICD groups (including visits to physicians, laboratory tests and re-hospitalisations) and the ICD generator or lead replacement. The unit costs were not presented separately from the quantities of resources used for all items. Resource use appears to have been estimated using literature-based data. Most of the costs were estimated from Medicare reimbursement rates and professional fees. Other items were costed using data from the Myocardial Infarction Triage and Intervention patient registry. Discounting was relevant, as the costs were incurred during a long timeframe, and an annual rate of 3% was applied. The price year was 2005. All costs estimated in periods before 2005 were updated to 2005 values using the gross domestic product deflator.

Statistical analysis of costs
The costs were treated deterministically.

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

Currency
US dollars ($).

Sensitivity analysis
A sensitivity analysis was undertaken to assess the robustness of the cost-effectiveness and cost-utility estimates to variations in the clinical and economic inputs. The analysis focused on five parameters. More specifically, the efficacy
of the ICD in reducing mortality, the cost of ICD implantation, the frequency of generator replacement, quality of life and the time horizon. A univariate sensitivity analysis appears to have been used. The ranges of values used were derived from confidence intervals given in the literature and on the basis of the authors' judgement.

**Estimated benefits used in the economic analysis**

In six of the eight populations, implantation of the ICD improved life expectancy relative to control therapy. The discounted increment ranged from 1.40 to 4.14 years (undiscounted range: 2.12 - 6.21) or from 1.01 to 2.99 QALY (undiscounted range: 1.53 - 4.47). In the other two populations (based on the DINAMIT and CABG Patch trials), the life expectancy of patients that received the ICD was lower than that of the control group.

**Cost results**

Independent of the patient population, the ICD was more expensive than the control therapy. The increase in the estimated lifetime discounted costs ranged from $55,700 in the CABG Patch Trial to $101,500 in the MUSTT.

**Synthesis of costs and benefits**

Incremental cost-effectiveness ratios (cost per LY saved) and cost-utility ratios (cost per QALY gained) were calculated to combine the costs and benefits of the ICD over control therapy.

In six of the eight populations, the incremental cost-effectiveness ratios ranged from $24,500 (MUSTT) to $50,700 (SCD-HeFT) while the incremental cost-utility ratio ranged from $34,000 (MUSTT) to $70,200 (SCD-HeFT).

In two trials (DINAMIT and CABG Patch), the life expectancy of the patients who received an ICD was less than that of the patients who received control therapy. Thus the ICD was both more expensive and less effective than control therapy, which was the dominant strategy.

The sensitivity analysis showed that the incremental cost-effectiveness of the ICD tended to be more favourable in higher risk patients, given that the efficacy of an ICD is related to the annual mortality rate in the patient population. Similarly, the cost-effectiveness of the ICD improved with reductions in the cost of the device. For example, if the cost of an ICD was reduced to $10,000 ($27,975 in the base-case), the incremental cost per QALY decreased to $27,900 for the MUSTT (minimum) and to $52,400 for the SCD-HeFT. On the other hand, the incremental cost-effectiveness of the ICD was less favourable as the frequency of replacement increased (replacement every 3 years led to an incremental cost per QALY of $41,200 to $88,600).

If the patients' quality of life was decreased by prophylactic ICD implantation, the cost-effectiveness of this approach would have been much less favourable.

In the clinical trials in which prophylactic implantation of an ICD was found to be better than control therapy, a reduction in the patients' utility on the basis of the presence of left ventricular dysfunction resulted in a cost-effectiveness of the ICD of $39,800 to $82,400 per QALY gained.

When keeping a lifelong horizon but assuming that ICD efficacy ceases after the first 3 years, the cost-effectiveness of the ICD was much less favourable in comparison with the control treatment, ranging from $70,200 per QALY gained in the MUSTT to $171,800 per QALY gained in the SCD-HeFT.

The cost-effectiveness became substantially more favourable as the time horizon increased.

**Authors' conclusions**

Compared with control therapy, the implantable cardioverter-defibrillator (ICD) had a cost-effectiveness ratio below $100,000 per quality-adjusted life-year (QALY) gained in populations in which a significant device-related reduction in mortality had been demonstrated. However, the authors stated that the prophylactic implantation of an ICD might not be feasible for health policy-makers, owing to the high cost of the device and the large patient population in which it could be applied.
CRD COMMENTARY - Selection of comparators
The selection of the comparator was appropriate as control therapy was assumed to reflect usual care. However, the control therapy was not described. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The clinical data used as model inputs were estimated from published literature. It was unclear whether a systematic review of the literature was carried out. It appears most likely that the primary studies were identified selectively. These primary studies could be grouped into two categories: the 8 clinical trials used to provide a set of efficacy data (which were used to carry out eight separate cost-effectiveness analyses) and the remaining studies used as complementary information to populate the decision model. The authors pointed out that data from the 8 clinical trials were not pooled because of the heterogeneity in the characteristics of the patients. Indeed, in 2 trials, ICD was less effective than control therapy. This might be explained, as the authors noted, by the specific features of the participating individuals that were undergoing concomitant surgery or who had had an acute myocardial infarction. The clinical characteristics of the patient population of each trial were reported in an appendix. Clearly, the use of clinical trials ensures the validity of the primary sources. Limited information on the second set of data was provided, although some estimates came from a meta-analysis and two observational studies. Finally, some assumptions were made. The issue of uncertainty was extensively addressed in the sensitivity analysis.

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, QALYs and LYs are easily compared with the benefits of other health care interventions. Discounting was applied, as US guidelines recommend. Limited information on the source of the utility weights was provided.

Validity of estimate of costs
The authors stated that a societal perspective was adopted, but the economic analysis was restricted to direct medical costs. This could be on account of the severity of the disease, which does not permit individuals to work regularly. Some unit costs and some data on resource use were reported. The costs were presented as macro-categories. The source of the data was provided and the costs appear to have reflected the payer’s perspective. The costs were treated deterministically but some estimates were varied in the sensitivity analysis. The price year was reported, which aids reflation exercises in other settings. The lifetime costs were estimated in the base-case, although the use of shorter time horizons was investigated in the sensitivity analysis. Discounting was relevant and was appropriately applied.

Other issues
The authors compared their findings with the published economic evaluation of the SCD-HeFT, which estimated a cost per LY saved with the ICD of $33,200. This estimate is lower than the estimates of the current study. The authors noted that the more favourable result was presumably because of the lower cost of the device. The issue of the generalisability of the study results to other settings was not explicitly addressed, but sensitivity analyses were performed. This increases the external validity of the analysis. The authors noted some limitations of their analysis, such as the use of assumptions and summary data from the clinical trials. However, such issues were extensively explored in the sensitivity analysis. In general, the authors underlined the heterogeneity of the patient populations used in the 8 clinical trials.

Implications of the study
The study results suggested that the implantation of a prophylactic ICD might be cost-effective (cost per QALY gained <$100,000) among patients at risk for sudden death due to left ventricular systolic dysfunction who have not had a life-threatening ventricular arrhythmia. The authors highlighted the key issue of the need for appropriate, evidence-based selection of patients.
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