Prophylactic pacemaker use to allow beta-blocker therapy in patients with chronic heart failure with bradycardia

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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 study compared two treatment strategies for patients with chronic heart failure (CHF). The strategies compared were the conventional strategy and the pacemaker-carvedilol strategy. In the conventional strategy, patients were treated with angiotensin-converting enzyme inhibitors, diuretics and digoxin. In the pacemaker-carvedilol strategy, patients received conventional treatment therapy and had a permanent pacemaker implanted to maintain adequate heart rate after the initiation of beta-blocker therapy with carvedilol. Pacemaker therapy consisted of the implantation of a dual-chamber pacemaker set to an atrial-based rate-response pacing mode (DDDR mode with long atrioventricular (AV) delay).

Type of intervention

Economic study type
Cost-effectiveness analysis.

Study population
As this was a modelling study, the target population comprised a hypothetical cohort of patients with clinically stable CHF (average age 60 years) and a left ventricular ejection fraction of $\leq 35\%$, who were in sinus rhythm with a resting heart rate of $\leq 68$ beats/minutes. No further inclusion or exclusion criteria were reported.

Setting
As this was a modelling study the setting was not explicitly reported at the outset. However, it would appear that the setting was secondary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data were derived from completed studies published between 1994 and 2002. The cost data were derived from sources published from 2001 to 2003. The price year was not explicitly reported.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of completed studies, augmented by authors' assumptions.

Modelling
The authors constructed a Markov model to evaluate the cost-effectiveness of the two treatment options. Their model was based on a published model (Delea et al. 1999, see 'Other Publications of Related Interest' below for bibliographic details). The Markov model included five "alive" ambulatory health states and one "dead" state. Patients were assigned
to each alive health state depending on their number of previous hospitalisations for CHF (none, 1, 2, 3 or >/=4). The time horizon of the model was 20 years and the duration of each cycle was 1 month. During each cycle, patients incurred a risk of death and a risk of hospitalisation. Patients who stayed alive during each cycle moved to the next monthly cycle. Those patients who had not been hospitalised moved to their previous alive state, while those who had been hospitalised moved to the next higher alive state. In the pacemaker-carvedilol strategy, patients incurred risk for chronic pacemaker complications (i.e. pocket erosion, infection and lead complications) with attendant incremental mortality risks. All patients who survived until battery end-of-life had a pacemaker replacement. Several assumptions were used in the model:

all patients would effectively be receiving atrial pacing only;

full carvedilol benefits were assumed for 2 years, with benefits declining for the next 3 years and no additional benefits after 5 years, whereas pacemaker-related adverse events persisted for the entire 20-year follow-up period; and pacemaker-related complications such as pocket erosion and infections would result in device extraction with no replacement.

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

the monthly inpatient and outpatient death rate with conventional and carvedilol treatment;

the probability of monthly hospitalisation in both treatment groups (carvedilol and conventional) when the patient had no prior hospitalisation, or had 1, 2, 3 or >/=4 prior hospitalisations; and

the monthly probability of initial carvedilol adverse events (i.e. mortality rate and rate of discontinuation of the drug during the first 2 months).

The following probabilities were also included for the pacemaker group:

implantation-related complications rates (including pneumothorax requiring active treatment, haematoma requiring reoperation, cardiac perforation, infection requiring reoperation, lead displacement and death); and

annual chronic complication rates (including system infection, mortality risk, pocket erosion, lead replacement, mortality risk, yearly battery life, and risk of development of AV block requiring the use of ventricular lead for pacing).

**Study designs and other criteria for inclusion in the review**
The authors reported that large cohort studies and observational studies were used to assess the outcomes.

**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**
It would appear that no methods were used to assess the validity of the primary studies.

**Number of primary studies included**
The authors used 10 primary studies as sources of effectiveness data.

**Methods of combining primary studies**
The authors did not report any methods used to combine the results of the individual primary studies.

**Investigation of differences between primary studies**
The authors appear to have investigated differences between the primary studies.

**Results of the review**
The monthly inpatient death rate was 20.3 in conventional treatment and 8.0 (range: 8 to 14.2) for carvedilol treatment. The monthly outpatient death rate was 0.7 for conventional treatment and 0.3 (range: 0.3 to 0.5) for carvedilol treatment.

The implantation-related complication rate was:

- 0.9 (range: 0.45 to 1.35) for pneumothorax requiring active treatment,
- 0.8 (range: 0.4 to 1.2) for haematoma requiring reoperation,
- 0.5 (range: 0.25 to 0.75) for cardiac perforation,
- 1.0 (range: 0.5 to 1.5) for infection requiring reoperation,
- 2.1 (range: 1.05 to 3.15) for lead displacement, and
- 0.08 (range: 0.04 to 0.12) for death.

Further outcomes assessed in the review were all reported in terms of their base-case values and ranges, but are too numerous to report here.

**Measure of benefits used in the economic analysis**
The measure of benefit used was the life-years saved. These were derived directly from the model. The health benefits were discounted at an annual rate of 3%.

**Direct costs**
The health service costs included in the analysis were:

- the monthly cost of conventional CHF drugs (lisinopril, furosemide, digoxin);
- the monthly cost of carvedilol;
- the cost of initiation of carvedilol;
- annual outpatient care for CHF;
- the cost per episode for inpatient care for CHF when using conventional treatment and when using carvedilol;
- the cost of outpatient pacemaker initial implantation;
- the cost of an outpatient pacemaker generator change;
- the cost of implantation-related complications (i.e. pneumothorax requiring active treatment, haematoma requiring...
reoperation, cardiac perforation, infection requiring replacement, lead replacement and death);

the cost of chronic complications (i.e. system infections, pocket erosion, lead complications); and

outpatient follow-up of pacemaker.

The costs and the quantities were not reported separately. The authors only reported summary costs for the resources used. The costs were derived from published sources but the price year was not explicitly reported. Resource use was derived using the model. As the time-horizon of the model was 20 years, the costs were appropriately discounted.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not included in the analysis.

Currency
US dollars ($).

Sensitivity analysis
The authors appear to have conducted various sensitivity analyses on all input parameters of the model to investigate robustness of the results to variability in the data. Most of the ranges used were derived from the literature. When there were no data in the literature, the authors used higher and lower bounds of the estimates (+/- 50%). The authors also conducted a second analysis in which theoretical risks of atrial pacing were included in the model. This analysis was conducted by increasing the risk of death and hospitalisation, depending on hospitalisation. Additional sensitivity analyses were carried out by applying the rates of death (61%) and heart failure hospitalisation (54%) (taken from a published trial) to hypothetical patients in the carvedilol-pacemaker arm who required AV pacing (rather than atrial pacing alone).

Estimated benefits used in the economic analysis
The base-case analysis demonstrated that the pacemaker-carvedilol strategy resulted in 99 months of life versus 80 months for the conventional strategy. The pacemaker-carvedilol strategy resulted in 1.6 undiscounted life-years gained in comparison with the conventional treatment strategy. When the benefits were discounted, the pacemaker-carvedilol strategy resulted in 1.3 incremental life-years gained in comparison with the conventional treatment strategy.

Cost results
The total costs were reported per patient. The total discounted costs were $29,402 in the conventional treatment group and $37,208 in the pacemaker-carvedilol group. The difference resulted in an incremental cost of $7,800.

Synthesis of costs and benefits
An incremental cost-effectiveness analysis was carried out where both the costs and benefits were discounted. The analysis demonstrated that the pacemaker-carvedilol strategy resulted in an incremental cost of $6,100 per additional life-year saved.

The sensitivity analyses showed that the results were most sensitive to the cost of hospitalisation when on pacemaker-carvedilol therapy, the cost of hospitalisation when on conventional therapy, a reduction in carvedilol benefit (50% for mortality and 43% for hospitalisation), the rate of AV block, hospitalisation due to atrial pacing, and the cost of pacemaker insertion. It was reported that when the cost of hospitalisation when on conventional therapy was increased
by 50%, the conventional therapy was dominated by the pacemaker-carvedilol strategy.

When using a 1.7% annual rate of AV block and related increases in hospitalisations and mortality, the cost-effectiveness of the pacemaker-carvedilol strategy was reduced to $19,300 per life-year saved.

All the results from the sensitivity analyses were reported in full.

Authors' conclusions
The insertion of a prophylactic pacemaker to facilitate beta-blocker treatment in patients with chronic heart failure (CHF), with low resting heart rates, has the potential to produce clinical benefits in a highly cost-effective manner.

CRD COMMENTARY - Selection of comparators
A justification was provided for the comparators used. Pacemaker therapy allows beta-blocker treatment in bradycardic patient with heart failure. You should decide if this represents a valid health technology in your own setting.

Validity of estimate of measure of effectiveness
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. The authors appear to have used data from the available studies selectively. In addition, the impact of differences between the identified studies was not taken into account when estimating effectiveness. Some estimates of effectiveness were based on authors' assumptions. However, the authors did not provide any justification for their choice of assumptions. Sensitivity analyses were conducted to improve both the internal validity of the study and the generalisability of the results.

Validity of estimate of measure of benefit
The authors used life-years gained as the measure of benefits. These were derived directly from the model.

Validity of estimate of costs
The authors reported that the study had been conducted from a societal perspective. However, the indirect costs were not included. The costs and the quantities were not reported separately and, as the authors reported summary costs, it was difficult to know which aspects of the costs were included in the analysis. This would not enable the analysis to be easily reworked for other settings. Although the costs were treated deterministically, extensive sensitivity analyses were conducted. These 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. Discounting was relevant, as the costs were incurred over a long period (more than 2 years), and was appropriately conducted and reported. The price year was not reported, which hampers any future reflation exercises.

Other issues
The authors did not compare their findings with those from other studies, so it is not known how far their results agree with other published results. The issue of generalisability of the results to other settings was not directly addressed. The authors do not appear to have presented their results selectively. The study enrolled patients with clinically stable CHF and this was reflected in the authors' conclusions. The authors reported several limitations to their study which were concerned with the clinical assumptions used in the model. They used various conservative assumptions and, in effect, the cost-effectiveness of the pacemaker-carvedilol strategy was underestimated.

Implications of the study
The authors suggested that pacemakers can be used to extend the benefit of beta-blockers to a large and previously excluded group of patients with systolic heart failure. They did not make explicit recommendations about the need for
further research.

**Source of funding**
Supported by GlaxoSmithKline.

**Bibliographic details**

**PubMedID**
16569541

**DOI**
10.1016/j.ahj.2005.06.007

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adrenergic beta-Antagonists /therapeutic use; Bradycardia /epidemiology; Carbazoles /therapeutic use; Comorbidity; Cost-Benefit Analysis; Decision Support Techniques; Decision Trees; Heart Failure /drug therapy /economics /epidemiology /therapy; Hospitalization /statistics & numerical data; Humans; Markov Chains; Middle Aged; Pacemaker, Artificial; Propanolamines /therapeutic use; Risk Assessment; Sensitivity and Specificity

**AccessionNumber**
22006000687

**Date bibliographic record published**
31/12/2006

**Date abstract record published**
31/12/2006