Dual-chamber pacemakers for treating symptomatic bradycardia due to sick sinus syndrome without atrioventricular block: a systematic review and economic evaluation

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Scientific summary

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Scientific summary

Background

Bradycardia is defined as a resting heart rate below 60 beats per minute (b.p.m.). A slow heart rate is common and is not necessarily associated with a physical illness. However, conditions affecting the electrical conduction system of the heart lead to pathological bradycardia. People suffering from symptomatic bradycardia may present with dizziness, confusion, palpitations, breathlessness, exercise intolerance and syncope (blackout or fainting).

Pathological bradycardia has many causes, including sick sinus syndrome (SSS), which might or might not be associated with comorbid atrioventricular (AV) block; AV block can occur independently from SSS. SSS is caused by dysfunction of the sinus node, the heart's natural pacemaker. SSS encompasses a spectrum of arrhythmias with different underlying mechanisms. The only effective treatment for patients suffering from symptoms is implantation of a permanent pacemaker. Pacemaker implantation does not cure or affect the prognosis of SSS; thus, pacemakers are implanted with the aim of alleviating symptoms and improving the patient's quality of life (QoL).

During 2012–13 in England, more than 20,000 people had a single- or a dual-chamber pacemaker implanted. SSS was the fourth most prevalent primary diagnosis (9.5%) necessitating implantation of a single- or a dual-chamber pacemaker. Reoperation after implantation may be required because of a complication, such as lead displacement or infection, but it can also be because of a need for pacemaker upgrade (single to dual) or the end of battery life. The complication rate associated with a reoperation is substantially higher than that associated with initial implantation.

Current guidance is that people with SSS in whom, after full evaluation, there is no evidence of impaired AV block receive a single-chamber atrial pacemaker. However, it is unclear if there is any difference between single-chamber atrial pacing and dual-chamber pacing in outcomes for people with SSS and no AV block.

Objectives

The aim of this review was to appraise the clinical effectiveness and cost-effectiveness of dual-chamber pacemakers compared with single-chamber atrial pacemakers for treating symptomatic bradycardia in people with SSS in whom there is no evidence of impaired AV conduction. This report is a partial update of the National Institute for Health and Care Excellence (NICE)'s technology appraisal (TA) number 88 in relation to this indication [National Institute for Health and Care Excellence (NICE). *Dual-Chamber Pacemakers for Symptomatic Bradycardia due to Sick Sinus Syndrome and/or Atrioventricular Block*. London: NICE; 2005. URL: www.nice.org.uk/Guidance/TA88/Documents (accessed June 2014).]

Methods

Clinical effectiveness review methods

Evidence for the clinical effectiveness of dual-chamber and single-chamber atrial pacemakers was identified by searching multiple electronic bibliographic databases from inception to January 2014, and an updated search was run in May 2014. The databases searched were MEDLINE (via Ovid), EMBASE (via Ovid), Health Technology Assessment (HTA) database and NHS Economic Evaluations Database (NHS EED). Search terms included medical subject headings and text terms for pacemakers. Search terms for the condition (i.e. bradycardia and SSS) were not included. Only randomised controlled trials (RCTs) were considered for inclusion in the review.

Potentially relevant full publications were assessed independently by two reviewers for inclusion or exclusion against pre-specified criteria. The quality of the clinical effectiveness data was assessed independently by two reviewers in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and was recorded using the Cochrane Risk of Bias Tool.

Randomised controlled trials evaluating permanent implantable dual-chamber pacemakers programmed to dual-chamber pacing against permanent implantable pacemakers (single or dual) programmed to atrial pacing in people with symptomatic bradycardia due to SSS without AV block were eligible for inclusion in the review. Outcome measures of interest were all-cause mortality, heart failure (HF), atrial fibrillation (AF), stroke, exercise capacity, cognitive function, requirement for further surgery, adverse effects of pacemaker implantation, and health-related quality of life (HRQoL).

Review methods

Extracted data and quality assessments for each study were presented in structured tables and as a narrative summary. Where sufficient comparable data were available for each outcome measure, pairwise meta-analysis was performed.

Methods of analysis/synthesis

Treatment effects were analysed as odds ratios (ORs) for dichotomous data and as the mean difference for continuous outcomes.

Cost-effectiveness systematic review

Multiple electronic databases were searched: MEDLINE (via Ovid), EMBASE (via Ovid), HTA database and NHS EED. In addition, experts in the field were contacted with a request for details of relevant published and unpublished studies of which they might have knowledge. The website of NICE was searched for recently published TAs in pacing that had not already been identified via database searches. Reference lists of key identified studies were reviewed for additional potentially relevant studies.

Search strategies for MEDLINE and EMBASE included terms for population (pacing) and interventions (dual-chamber pacemakers) of interest and relevant terms to capture economic evaluations/costing studies. The search strategy for HTA and NHS EED combined terms for the target condition (AV block and SSS) with terms for the intervention (pacemaker). All databases were searched from inception.

The searches were carried out in December 2013 and updated in June 2014. No restrictions on language or setting were applied. The titles and abstracts of papers identified through the searches were independently assessed for inclusion by two health economists. Results were described narratively, and quality assessed against the NICE reference case, and Philips *et al.*'s checklist [Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, *et al.* Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technol Assess* 2004;**8**(36)].

A Markov cohort model was developed. The model structure was derived from that used in a previous HTA that evaluated the cost-effectiveness of dual-chamber pacemakers versus single-chamber atrial pacemakers in people with SSS and no AV block (NICE TA88). The model uses a monthly cycle length with a time horizon of 10 years. Analyses were undertaken from the perspective of the NHS and Personal Social Services, with costs and benefits discounted at 3.5% per annum. Model outputs are reported as incremental cost-effectiveness ratios (ICERs).

Results

Clinical effectiveness results

The systematic review of clinical effectiveness identified six RCTs of relevance to this review. Three studies were of a parallel-group design and three were crossover trials. The parallel RCTs all compared device against device, whereas the crossover trials evaluated variation in pacing mode programme.

The quality of the trials was generally good, with appropriate trial design and methodology. The crossover trials included in this review involved a small number of people (12–21 people) and were of short duration (up to 3 months), which limited the outcomes that could be captured and the power to detect any differences between the pacing modes. The parallel-group RCTs were larger (50–1415 patients) and had longer follow-up (from 1 to 5.4 years mean follow-up) than the crossover trials.

There was limited opportunity to combine the results using meta-analysis from the six RCTs identified from the published literature. When this was possible, the results tended to follow the largest trial (DANPACE).

Mortality

Meta-analysis of two parallel RCTs identified no statistically significant difference between dual-chamber and single-chamber atrial pacing in all-cause mortality [OR 0.97, 95% confidence interval (CI) 0.67 to 1.41]. However, the meta-analysis of mortality is unlikely to have sufficient power to identify a statistically significant difference.

Heart failure

There was variation across the three parallel RCTs in the measures used to capture the incidence of HF. All three RCTs found no statistically significant difference between dual-chamber pacing and single-chamber atrial pacing in risk of HF. Subgroup analysis of data from the largest trial (DANPACE) showed that younger patients ($\leq$ 75 years) receiving single-chamber atrial pacing were at a lower risk of developing HF than those receiving dual-chamber pacing [hazard ratio (HR) 0.72, 95% CI 0.53 to 1.00]. By contrast, older people (> 75 years) with single-chamber atrial pacing were at a higher risk of HF than those with dual-chamber pacing (HR 1.34, 95% CI 1.00 to 1.80).

Atrial fibrillation

Two RCTs reported conflicting results for AF. In one RCT (177 people), dual-chamber pacing was associated with a statistically significant increase in AF (OR 3.19, 95% CI 1.05 to 9.67), whereas, in a second RCT (1415 people; DANPACE), dual-chamber pacing was associated with a statistically significant decrease in paroxysmal AF (OR 0.75, 95% CI 0.59 to 0.96) but no statistically significant difference in chronic AF. There may be multiple underlying factors leading to disparity in the results reported by two RCTs, including differences in baseline characteristics and differences in interventions (programming of AV delay). Of the identified studies, the largest RCT (DANPACE) was deemed to be more robust; thus, it is reasonable to have more confidence in this RCT than the smaller study.

Stroke

Meta-analysis of data from two RCTs indicates no statistically significant difference between dual-chamber pacing and single-chamber atrial pacing in the risk of stroke (OR 0.93, 95% CI 0.60 to 1.45).

Exercise capacity

Limited data (relatively small number of patients with limited follow-up) were available on exercise capacity. Single-chamber atrial pacing was associated with small, but statistically significant, improvements in exercise capacity in one parallel and one crossover trial. However, a second short-term crossover trial identified no statistically significant difference between devices in improvement in exercise capacity.

Further surgery

In the large RCT (DANPACE), reoperation was necessary in significantly fewer people with dual-chamber pacing than with single-chamber atrial pacing (OR 0.48, 95% CI 0.36 to 0.63).

Adverse effects of pacemaker implantation

Adverse effects of pacemaker implantation were poorly reported. One parallel RCT reported no complications at implantation. Another parallel RCT (DANPACE) reported indications for reoperation, of which the more frequent indications were need for surgical change of pacing mode, battery depletion and lead complications. Change in pacing mode was statistically significantly less common in dual-chamber pacing than in single-chamber atrial pacing ($p < 0.001$).

Health-related quality of life

Two small crossover trials reported on HRQoL and symptoms. Follow-up was limited and a wide range of measures were used to evaluate HRQoL. No statistically significant difference was found between dual-chamber and single-chamber atrial pacing for general well-being, functional status or multidimensional QoL measures, including cognitive functioning.

Changing pacing mode

In meta-analysis of data from the three parallel RCTs, dual-chamber pacing was associated with a statistically significantly lower risk of need for change in pacing than single-chamber atrial pacing (OR 0.50, 95% CI 0.37 to 0.67). Among people implanted with single-chamber atrial pacemakers, the need to change pacing mode is predominantly a consequence of the development of AV block, which requires an upgrade to a dual-chamber pacemaker.

Cost-effectiveness results

The cost-effectiveness systematic review identified 11 economic evaluations related to pacemakers and one UK costing study. Of the 11 cost-effectiveness studies, three cost–utility studies were identified, two of which evaluated dual-chamber pacemakers for treating symptomatic bradycardia due to SSS without AV block in comparison with single-chamber atrial pacemakers.

As none of the identified studies answered the decision problem, it was necessary to carry out a de novo economic analysis. Concerns around potential clinical heterogeneity in the RCTs identified and the different device programmes evaluated, as well as consultation with clinical experts, led to the decision to base the model on the largest RCT identified (DANPACE).

The base-case results demonstrate that dual-chamber pacemakers are more expensive, but are also more effective, than single-chamber atrial pacemakers, resulting in an ICER of £6506. Probabilistic sensitivity analysis produced a very similar ICER of £6068. The chance of dual-chamber pacemakers being cost-effective compared with single-chamber atrial pacemakers was found to be over 70% at a willingness-to-pay threshold of either £20,000 or £30,000.

As the deterministic results and the probabilistic results were so similar, all subsequent analyses were based on the deterministic model. Structural sensitivity analysis incorporating risk of reoperation using the available Kaplan–Meier data from the DANPACE trial [Nielsen JC, Thomsen PE, Hojberg S, Moller M, Vesterlund T, Dalsgaard D, *et al.* A comparison of single-lead atrial pacing with dual-chamber pacing in sick sinus syndrome. *Eur Heart J* 2011;**32**:686–96] reduced the ICER from £6506 to £3425. One-way sensitivity analysis (OWSA) indicates that the results are most sensitive to parameter uncertainty around the lowest risk of HF (dual-chamber pacemakers dominated by single-chamber atrial pacemakers), the highest cost of implant/procedure for dual-chamber pacemaker (ICER £23,010) and the lowest cost of implant/procedure for single-chamber atrial pacemaker (ICER £27,409).

A series of scenario analyses was undertaken to interrogate the impact on the results of using alternative sources for parameter estimates and challenging assumptions in the model. Scenario analyses that raised the ICER above the base case assumed no difference in HF (ICER £22,213), using the risk of stroke from the meta-analysis carried out by the review authors (ICER £6438), using monthly cost of HF from NICE's TA88 (ICER £7140), using reprogramming/device replacement for AF of 0% (ICER £10,872) and using a discount rate of 6% (ICER £6938).

A cumulative worst-case scenario resulted in an ICER of £48,738; the analysis combined the monthly cost of HF from NICE's TA88, the risk of stroke from the meta-analysis conducted by the review authors, the spell-level costs of implantation and the reprogramming/device replacement for AF of 0%, and assumed no difference in risk of developing HF between the two types of implant.

The results of the scenario analysis and the OWSA highlight how sensitive the results are to risk of HF. Subgroup analysis from the DANPACE trial [Nielsen JC, Thomsen PE, Hojberg S, Moller M, Vesterlund T, Dalsgaard D, *et al.* A comparison of single-lead atrial pacing with dual-chamber pacing in sick sinus syndrome. *Eur Heart J* 2011;**32**:686–96] identified a potentially important difference in HF resulting from age. When risk of HF is assessed by age, in patients aged > 75 years dual-chamber pacemakers dominate single-chamber atrial pacemakers (i.e. are less expensive and more effective), whereas, in people aged ≤ 75 years, dual-chamber pacemakers are dominated by single-chamber atrial pacemakers.

Conclusions and recommendations for future research

Dual-chamber pacemakers appear to be cost-effective compared with single-chamber atrial pacemakers for treating symptomatic bradycardia due to SSS without AV block. The majority of sensitivity analyses undertaken in the health economic evaluation had very little impact on the base-case ICER or resulted in an ICER of around £20,000 or less.

A potentially important finding of the review is the potential influence of age on risk of HF and the choice of pacemaker. A subgroup analysis based on age (> 75 years or ≤ 75 years) and risk of HF indicates that using dual-chamber pacemakers in older people dominates single-chamber atrial pacemakers, whereas using dual-chamber pacemakers is dominated in younger people. It should be noted that these results are based on a subgroup analysis and should be interpreted with caution.

Suggested research priorities

Further RCTs investigating the impact of dual-chamber pacemakers compared with single-chamber atrial pacemakers focusing on their impact on HF, stroke and all-cause mortality would be desirable. However, the size of trials required to answer conclusively these important clinical questions may make them prohibitively expensive.

Assessment of the impact of treatments on QoL may be of interest to the wider clinical community, particularly in people with SSS and with and without AV block. Further research into the cost of implantation and the adverse events associated with implanting a dual-chamber or single-chamber atrial pacemaker may also be warranted.

Study registration

This study is registered as PROSPERO CRD42013006708.

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