The effectiveness and cost-effectiveness of dual-chamber pacemakers compared with single-chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome: systematic review and economic evaluation

Casteluovo E, Stein K, Pitt M, Garside R, Payne E

CRD summary
No significant differences between dual-chamber and single-chamber (ventricular or atrial) pacemakers were identified for major outcomes, such as mortality and stroke, in patients with sick sinus syndrome and/or atrioventricular block. The authors’ conclusion that there are small, but potentially important, benefits associated with dual-chamber compared with ventricular pacing, is broadly supported by the data, but significant areas of uncertainty remain.

Authors’ objectives
To estimate the clinical effectiveness and cost effectiveness of dual-chamber pacemakers compared with single-chamber atrial or single-chamber ventricular pacemakers, for the treatment of bradycardia due to sick sinus syndrome or atrioventricular block.

Searching
MEDLINE, the Cochrane Library, EMBASE, Web of Knowledge, Web of Science, BIOSIS Previews, DARE, HTA, and BioMed Central were searched to November 2003. Search strategies were reported (see Appendix 2 of the report). In addition, the websites of the National Research Register, Current Controlled Trials and the US Food and Drug Administration were searched, as was the specialised register of the Cochrane Heart Group. The bibliographies of included studies and industry submissions were searched for additional studies and members of the advisory group were consulted.

Study selection
Systematic reviews or randomised controlled trials (RCTs) (parallel or cross-over), comparing dual-chamber pacemakers with single-chamber pacemakers (ventricular and/or atrial) for the treatment of symptomatic bradycardia, secondary to sick sinus syndrome, atrioventricular block, or chronic bifascicular block, were eligible for inclusion. Included participants were required to have been recruited in secondary or tertiary care centres. Participants at any stage of disease profession were considered.

Non-English language studies and studies of less than 48 hours duration were excluded. Studies in the following populations were excluded: carotid sinus syndrome and malignant vasovagal syncope; primary diagnosis of congestive heart failure or cardiomyopathy; primary diagnosis of atrial fibrillation, or atrial fibrillation from other causes without concomitant sick sinus syndrome or atrioventricular block; primary diagnosis of isolated tachycardia, or tachycardia from other causes without concomitant sick sinus syndrome or atrioventricular block.

The following outcome measures were included: mortality (all-cause and cardiovascular); stroke; atrial fibrillation; heart failure; exercise capacity; symptoms of breathlessness, fatigue, chest pain, dizziness, palpitations and sleep disturbance; functional status; quality of life; adverse events of implantation; pacemaker syndrome. The one systematic review identified was summarised separately.

The majority of included studies were comparisons of dual-chamber with ventricular pacemakers and, of these, most were cross-over trials. Mean participant age ranged from 52 to 81 years. Study populations were generally either evenly distributed between male and female, or majority male. Parallel trials had longer follow-up periods (mean of 1.5 to 3.5 years, where reported) than cross-over trials (duration 48 hours to three months). Parallel trials included both studies randomised by device and studies randomised by mode (dual-chamber pacemaker inserted and randomised to act in dual-chamber or single-chamber mode).

Studies were independently assessed for inclusion by two reviewers and disagreements were resolved by discussion.

Assessment of study quality
The methodological quality of included RCTs was assessed using criteria published in the Centre for Reviews and Dissemination (CRD) Report No. 4, which assess the potential for selection bias, performance bias, detection bias and attrition bias.

The authors did not describe the process of quality assessment, or how many reviewers were involved.

**Data extraction**

Raw data were extracted from included studies where possible, otherwise summary measures were extracted as reported. The summary effect measures used in the review were odds ratio (OR) for dichotomous outcomes (e.g. mortality, stroke), standard mean difference (SMD) for continuous outcomes (e.g. exercise capacity, symptom scores) and risk difference (RD) for incidence of pacemaker syndrome.

Data were extracted by one reviewer, using a project-specific, piloted data extraction sheet, and checked by a second.

**Methods of synthesis**

The results of included studies were summarised, in text and tables, stratified by study type (parallel or cross-over RCT), comparator (ventricular or atrial single-chamber pacing) and outcome measure. Where sufficient data were available, the results of individual trials were pooled using random-effects meta-analyses. Between study heterogeneity was assessed using the $I^2$ statistic.

**Results of the review**

Thirty four RCTs were included in the review, five parallel (n=7,183) and 29 cross-over (n=524). The quality of the parallel trials was generally reasonable, including large numbers of participants and running over three to five years. Individual quality criteria were discussed in full in the report, in relation to each included study. Cross-over trials were generally much smaller and of shorter duration. A wider range of outcomes were assessed but short duration precluded the assessment of outcomes such as mortality.

Dual-chamber versus single-chamber ventricular pacing:

Dual chamber pacing was not associated with significant improvement in mortality, stroke, heart failure, or functional capacity measured by specific activity scale.

Dual chamber pacing significantly reduced the incidence of atrial fibrillation, pooled OR 0.76 (95% CI: 0.65, 0.90, p=0.001, three parallel RCTs). Dual chamber pacing significantly improved exercise capacity, SMD 0.35 (95% CI: 0.17, 0.52, p<0.0001, 20 crossover RCTs). No differences were found in exercise capacity by age.

Quality of life was assessed in 17 trials (four parallel and 13 cross-over) using a wide range of instruments. Results were variable with some evidence of improvement associated with dual-chamber pacing, mostly from cross-over studies. Three parallel trials used Short Form 36 to assess quality of life. One trial found significant improvements associated with dual-chamber pacing in some components (physical function, physical role, social function, energy, mental health and pain) at 48 month follow-up. Twelve cross-over studies measured general well-being in a variety of ways and found improvements associated with dual-chamber-pacing, SMD 1.59 (95% CI: 0.95, 2.23, p<0.00001), but significant between study heterogeneity ($I^2$ 83.6%).

The incidence of pacemaker syndrome varied between 4% (inferred) and 26%. Dual-chamber pacing significantly relieved the symptoms of pacemaker syndrome when these occurred and pacemaker syndrome was an major reason for cross-over in the parallel trials. The majority of complications were perioperative. Dual chamber pacing was associated with higher rates of lead dislodgement (4.2% versus 1.4%) and inadequate pacing (1.3% versus 0.3%). Other complication rates were similar. Subgroup analyses from the large parallel trials showed no evidence of differential effects of dual-pacing in identifiable patient groups.

Dual-chamber versus single-chamber atrial pacing:

No significant differences were found in mortality, stroke, heart failure, overall exercise capacity, functional status, or quality of life.
One cross-over study (n=19) found a small, statistically significant effect on exercise duration in favour of atrial pacing (mean 423 +/- 127 seconds versus 402 +/- 102 seconds, p < 0.05).

One parallel study (n=177) found a higher incidence of atrial fibrillation with dual-pacing, 25 participants (20%) versus 4 participants (7.4%) in the atrial pacing arm (p = 0.03).

All trials showed the potential for atrioventricular block to develop with time, but short duration limited the potential to capture the impact of progressive atrioventricular block on outcomes.

Cost information
The five-year cost of a dual-chamber system was estimated to be around £7,400. Taking into account the costs of complications and subsequent clinical events, this was estimated to be around £700 higher than for single-chamber devices.

At five years, dual-chamber pacing in sick sinus syndrome and atrioventricular block was considered likely to yield additional QALYs (quality adjusted life-years), at a cost of less than £10,000 per QALY. However, there was considerable uncertainty associated with this estimate. More conservative assumptions gave an estimated cost per QALY of £30,000.

Atrial pacing dominated dual-chamber pacing under all assumptions.

Authors' conclusions
Dual-chamber pacing results in small, but potentially important, benefits in populations with sick sinus syndrome and/or atrioventricular block, compared with ventricular pacing. The evidence comparing dual-chamber with atrial pacing is much smaller and less robust. Pacemaker syndrome is important in determining cost-effectiveness, but variation in diagnosis and assessment of severity make it difficult to quantify. There is currently insufficient evidence to identify specific groups who may benefit most from dual-chamber pacing.

CRD commentary
The review addressed a clearly stated research question, defined by appropriate inclusion criteria. Extensive searches were made to identify relevant studies but the subsequent exclusion of non-English language publications leaves open the possibility of language bias. Measures to minimise error and/or bias were reported for the selection of studies and the extraction of data but not the assessment of validity. The methodological quality of included studies was extensively assessed and reported. Meta-analyses, where used, were appropriate and full details of the included studies were reported. No significant effects were identified for major outcomes such as mortality and stroke. The authors’ conclusion that there are small, but potentially important, benefits associated with dual-chamber compared with ventricular pacing is broadly supported by the data, but significant areas of uncertainty remain.

Implications of the review for practice and research
Practice: The authors did not state any recommendations for practice.

Research: The authors stated that further trials and an individual patient data meta-analysis of dual-pacing versus atrial pacing are required (one trial in-progress is identified in the report and an individual patient data meta-analysis is currently in progress). Research on the effectiveness of pacemakers in children is required, as currently there is no evidence in this area. Further research is needed on the classification, diagnosis and utility associated with pacemaker syndrome.

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Bibliographic details
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.