THE EFFECTIVENESS AND COST-EFFECTIVENESS OF DUAL CHAMBER PACING

A. Final protocol. Note: this protocol may be subject to change.

B. Details of review team

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C. Full title of research question

The effectiveness and cost effectiveness of dual chamber pacing compared to single pacing for bradycardia

D. Clarification of research question and scope

Background

Condition

Bradycardia is a heart arrhythmia characterised by pathologically slow heart rhythm (below 60 beats per minute (b.p.m.)), originating from a range of conditions affecting the heart conduction system.[1] Bradycardia may cause heart rhythm asynchrony and insufficient blood perfusion, with intermittent specific or unspecific symptoms (dizziness, palpitations, blackout spells), possible organ damage and considerably impaired quality of life. In the medium and longer term, pathological bradycardia may cause severe cardiovascular morbidity or may progress to heart failure.

Bradycardia has two main causes, sick sinus syndrome (SSS) and atrioventricular (AV) or heart block. SSS is an irreversible dysfunction of the sinoatrial node, a small area of the atrium wall composed of specialised cells that depolarise spontaneously, acting as the natural pacemaker of the heart. SSS causes sinus pause or arrest, with delays or failure of conduction at this point.

Atrioventricular block is defective conduction at the atrioventricular node, which fails to capture depolarisation waves from the atrial tissues and to conduct impulses to the bundle of His and its branches (right and left bundle branches). AV block can progress from first degree, a benign form with minimal conduction delay, to second degree (partial) and third degree (complete) block, in which atrial and ventricular function are independent of each other. Delays in conduction may also arise in one of the sub-branches of the bundle of His (fascicular block). However, complete failure of conduction occurs only if all three fascicles become involved (trifascicular block).

Conduction defects are mainly acquired.[1] Progressive fibrosis of the nodal tissues causes sinus node disease, particularly in the elderly, whilst heart block progresses with chronic degenerative fibrosis or calcification of the proximal or distal conduction pathway. AV block commonly follows acute ischaemia, myocardial infarction or cardiomyopathy. Left bundle branch block may arise secondary to aortic stenosis, hypertension, coronary artery disease, whilst right bundle branch block may also be secondary to pulmonary embolism. Endocarditis, rheumatic fever and diphtheria may also cause complete AV block. Heart block may be caused by extrinsic factors such as intake of drugs in toxic concentrations (e.g. digitalis, verapamil or betablockers). A small number of individuals are affected by congenital defects, which may be severe (e.g. complete heart block and left bundle branch block).

There is limited information on the prevalence of conduction disorders. The prevalence of SSS is believed to be around 0.03%.[2] AV block has been variously reported as prevalent in 0.2% - 0.7% of men[3] and 0.1 - 0.8% of women.[4] Third degree AV block has been reported in 0.015 to 0.04%[5-7] in the UK and US to 0.2% in Sweden.[8] Bundle branch block was found in 1.6% of men and 0.8% of women.[4]

Treatment

Electrostimulation (pacing) is the only therapeutic approach to bradycardia. Pacing aims to re-establish normal rhythm as closely as possible, enhancing cardiac output and thereby reducing symptoms, leading to a general improvement of exercise capacity, quality of life and survival.[9] A pacemaker consists of an electrical impulse generator and one electrode, the lead, positioned on the heart chamber wall. The lead senses spontaneous depolarisation, and when this fails, it sends an electrical impulse to stimulate cardiac conduction. The pacemaker is implanted under local anaesthetic.[10] The lead is usually inserted percutaneously via the subclavian vein, then secured to the chamber wall and connected to the generator, which is positioned in a subcutaneous pocket on the chest.

Published indications for pacing[11] identify patients with complete heart block, prolonged sinus arrest and syncope as main candidates.[12] In specific circumstances, pacemakers may be recommended in asymptomatic complete heart block, SSS without syncope and with symptomatic incomplete atrioventricular block. Pacing is not recommended in asymptomatic first or second-degree heart block.

According to the British Pacing and Electrophysiology Group (BPEG) 26,151 pacemakers were implanted in UK and Ireland in 2001[13], of which 46.4% for heart

block (28.3% complete heart block, 13.9% first and second degree heart block, 4.2% bundle branch block), 27.1% for sick sinus syndrome and 26.5% for other causes (excluded from this TAR).

The emulation of normal heart rhythm crucially depends on the selection of pacemaker type in combination with programming features. Pacemaker characteristics and functions are incorporated in the Generic Code for Anti-bradycardia pacing (NBG)[14] of the NASPE/BPEG[11], composed of 3-5 letters, as follows:

Position I.	Chamber sensed	A = atrium V = ventricle D = dual (A+V)
Position II.	Chamber paced	A V or D
Position III.	Response to sensing	O =None T= triggered I = inhibited D = dual
Position IV.	Rate modulation	O = None or R = rate modulation
Position V.	Multi-site pacing	A V or D.

Single chamber pacemakers have one lead, which senses and paces either the atrium or the ventricle. The most used types are codes VVI and VVIR (ventricular pacemakers) or AAI and AAIR (atrial pacemakers). Dual chamber pacemakers have an additional lead positioned on the atrium, thus sensing and pacing both chambers (i.e. codes DDD, DDDR).

Electrostimulation is usually inhibited in single-chamber pacemakers when a spontaneous depolarisation occurs, whilst this may either inhibit or trigger pacing in dual chamber devices, according to the chamber where depolarisation is sensed. Rate modulation is a programming feature that adjusts pacing frequency to patient effort. It can be included in either single or dual chamber pacemakers. Additional programming may be performed non-invasively after implant.

Adverse effects

Broadly, there are two types of pacemaker-related complications associated with a) the operative procedure or b) the dynamics of electrostimulation.

Early peri-operative complications include pneumothorax, haemothorax and haematoma, lead displacement and early infections of the insertion site. Later complication of lead displacement, cardiac perforation or infections, either local, due to mechanical erosion of the pocket or systemic, including endocarditis or septicaemia, have also been reported. Asymptomatic and symptomatic subclavian venous thrombosis are also possible. Furthermore, mechanical malfunctioning, rupture or insulation defects of the lead and generator may occur.

In the presence of atrio-ventricular dyssynchrony or retrograde conduction (ventriculo-atrial conduction), pacemaker syndrome (PS) may arise.[15] PS is a complex of clinical signs and symptoms of variable severity attributable to haemodynamic deterioration, including hypotension, symptomatic depressed cardiac output (i.e. shock, fatigue, dyspnoea, dizziness, palpitations, neck pulsation, syncope) and, in the longer term, congestive heart failure.

Complications are generally addressed with early revision or re-implantation of pacemakers. Pacemaker syndrome may be treated with early upgrade from single to dual chamber pacing. Another common reason for upgrade is unrecognised or progressive disease in either atrial or ventricular conduction for patients with an initial diagnosis of SSS or AV only. Routine replacement is necessary at the end of the expected life of a generator (5 to 9 years on average).

Dual chamber pacing

Guidelines for pacemaker implantation in the UK[12] suggest that dual chamber pacing may be preferable to single chamber pacing except in patients with pre-existing atrial fibrillation. It has previously been reported[15;16] that dual chamber pacemakers may bring advantages over single chamber pacemakers in maintaining adequate cardiac output, reducing mortality, occurrence of atrial fibrillation, strokes, heart failure and pacemaker syndrome, particularly in patients with intact AV conduction, and improving exercise capacity. New data may become available[17] very soon to address continuing uncertainty.

In 2001, dual chamber pacemakers accounted for 59.5% of the total implants in the UK and EIRE. 38.7% were ventricular, with the residual 1.8% being atrial pacemakers.[13] The use of rate modulated devices has steadily increased from early negligible rates in the 1990s to 23.6% (dual chamber) and 18.8% (ventricular single chamber) in 2001. The latter have partially substituted ventricular, non-rate modulated pacemakers whose utilisation steadily declined from 93.6% (1980) to 19.9% (2001). Dual chamber pacemakers are more common in younger patients, with an average age of 70-74 years at first implant compared to 77-81 years for ventricular devices (74.5 years overall).

It is generally believed that the use of pacing and particularly dual chamber in the UK lags behind other European Countries, for all pacing types, with population specific rates of 322.1 implants per million population in England and 297 per million in Wales, compared to rates of around 450/million[13] in Europe and North America. Furthermore, available data suggest that up to 23% of patients with SSS and 30% with AV block receive ventricular pacemakers.[13] The reasons of this difference are unclear.

Scope

The Technology Assessment Report will assess the clinical and cost effectiveness of dual chamber pacemakers for patients with symptomatic bradycardia of congenital or acquired origin, secondary to sick sinus syndrome, atrioventricular block or other causes. Only permanent therapeutic pacing will be considered. The TAR will attempt to:

- Estimate the advantage of dual chamber pacing on single chamber pacing in reducing mortality and morbidity;
- Determine the role of dual chamber pacing in enhancing quality of life and reducing pacemaker syndrome;

- Identify groups of patients for whom dual chamber pacing might be particularly suitable;
- Estimate the cost-effectiveness or cost-utility of dual chamber pacing and identify key determinants;
- Identify implications for service provision in the NHS.

All randomised controlled trials and randomised crossover trials of dual chamber pacemakers compared to single chamber pacemakers will be included in the review of effectiveness.

A review of published cost-effectiveness or cost-utility models will be included. In addition, a cost-utility or cost-effectiveness analysis will be carried out if sufficient data are available.

Intervention

Dual chamber permanent pacemakers, rate adaptive and non-rate adaptive, with any type of programming algorithms and with or without atrial tracking algorithms.

Comparator

Single chamber permanent pacemakers, rate and non-rate adaptive, with any programming algorithm.

Population of interest

Individuals recruited in secondary and tertiary centres with a diagnosis of sinus node disease, atrioventricular or intraventricular block and individuals with symptomatic bradycardia from other causes will be included. No upper or lower age limit will be applied.

Inclusion criteria

Permanent therapeutic dual chamber pacing in:

- Patients with a primary diagnosis of acquired symptomatic bradycardia, secondary to sick sinus syndrome and AV block. Chronic bifascicular block will be included;
- Patients at any stage of disease progression will be considered, subject to their meeting the requirements for eligibility for permanent pacing.

Exclusion criteria

Permanent therapeutic dual chamber pacing in:

- Patients with carotid sinus syndrome and malignant vasovagal syncope;
- Patients with a primary diagnosis of congestive heart failure or cardiomyopathy without concomitant sick sinus syndrome or atrioventricular block;

- Patients with a primary diagnosis of atrial fibrillation, or atrial fibrillation from other causes without concomitant sick sinus syndrome or atrioventricular block;
- Patients with a primary diagnosis of isolated tachycardia or tachycardia from other causes without concomitant sick sinus syndrome or atrioventricular block.

Permanent pacing in any patient group if pacing is:

- Bi-ventricular;
- Bi-atrial;
- Triple chamber;
- Any type of temporary or diagnostic pacing.

Dual chamber pacing with any of the above if results for dual chamber pacing are not reported separately.

Outcomes

The review will report on patient-centred outcomes, including:

- Effectiveness, primary endpoints: all-cause deaths
- Effectiveness, secondary endpoints: short and long-term exercise capacity and other relevant patients centred outcomes (e.g. cognitive function); cardiovascular morbidity (non-fatal strokes, embolism, atrial fibrillation, progression to heart failure); rates of hospitalisation for heart failure; role of pacemaker dependency on effectiveness;
- Adverse events: early and late complications (i.e. pneumothorax, operative infections, septicaemia, subclavian thrombosis, late infections, pocket erosion, cardiac perforation, rates of lead displacement, change of pacing mode because of lead or programming problems, lead or generator malfunctioning); rates and time to onset of pacemaker syndrome;
- Quality of life: patients' perceived quality of life, using disease-specific, generic or preference-based measures;
- Efficiency: Cost-effectiveness, cost-benefit and cost-utility analysis.

Patient preferences

Where available, information on patients' preference will be extracted from trial reports.

Time perspective

Studies with a duration of at least 48 hours.

E. **Report methods**

Search strategy

A preliminary search has revealed that a systematic review was conducted on dual versus single pacing by a research group in Birmingham.[16] However, further large trials have been concluded since publication. The Birmingham Review will therefore be included and updated in the TAR.

The review will proceed from a systematic electronic search conducted on the sources listed below to identify published randomised controlled parallel trials or cross-over trials that compare dual to single chamber pacing in patients eligible for inclusion.

Searches will be carried out in

- Electronic databases, including MedLine Pubmed, Embase, The Cochrane Library (including the Cochrane systematic Review Database, Cochrane Controlled Trials Register), the Cochrane Heart Group Specialised Register, Science Citation Index, Web of Science Proceedings, DARE, NHS EED, HTA database;
- Trial Registers in the UK and abroad (Current Controlled Trials, NIH Clinical Trials Database);
- HTA websites (CCOHTA, HTA);
- Websites of regulatory agencies (FDA and MDA);
- Websites of Medical Associations (NASPE, BPEG) and associated databases (National Pacemaker Database, UK);
- Manufacturers of pacing devices;
- Research groups or other groups with special interest in pacing identified through literature searches and contact with experts;
- Bibliographies of identified studies;
- Websites of patients' associations (British Heart Foundation).

Inclusion and exclusion criteria

Two researchers will independently initially assess the result of searches for inclusion against title and abstract. Disagreement will be resolved by consensus and where necessary, by the intervention of a third reviewer. Full text of studies included at this stage will be obtained and evaluated for inclusion in the review.
Studies of effectiveness will be included if they are conducted with appropriate randomisation methods. Randomised controlled studies, cross-over randomised studies and systematic reviews of effectiveness will be included, subject to other inclusion criteria detailed elsewhere in this protocol.
Cost-effectiveness, cost-utility and cost-benefit studies of dual chamber pacing of patients with heart block and or sick sinus syndrome, compared to single chamber pacing in the same patients group will be included.

The literature review will also inform the choice of parameters used in the economic evaluation of dual chamber pacing conducted in the TAR. For some outcomes (for example, long term safety, resource use and costs or patient preferences) it is unlikely that a sufficient number of controlled studies exist. Non randomised uncontrolled studies will be included if they provide the best available estimate of selected parameters included for review i.e. when RCT evidence is lacking or uninformative. Studies including cost or utility estimates will be considered if they provide estimates of relevant parameters suitable for the cost-utility analysis carried out in the review.

Exclusions:

- Non randomised studies of effectiveness, case series and case reports, n of 1 trials, case-control studies and cohort studies;
- Studies in which insufficient methodological detail is reported to allow critical appraisal;
- Studies not reporting relevant patients outcomes;
- Studies on patients with clinical indications for pacing other than those considered in this TAR;
- Pre-clinical studies, models or electrophysiology experimentation on human or other biological material;
- Animal models;
- Studies not published in English, and for which translation in English is not available.

Data extraction strategy

Data will be extracted by one researcher and checked by a second researcher, with differences resolved by consensus.

Quality assessment strategy

The quality of studies included will be assessed using the criteria stated in the NHS CRD Report N.4.[18] Cost-effectiveness and cost-utility studies will be assessed following the methodology reported in Sculpher and colleagues[19] and Weinstein and colleagues.[20]

Methods of analysis/synthesis

Meta-analysis will be performed if estimates of effectiveness and other outcomes derived from RCTs are retrieved in sufficient number and fulfil criteria for homogeneity. The meta-analysis will be performed on intention-to-treat data, using random effect models. Sources of heterogeneity will be identified, their impact explored and included in the analysis when appropriate.
If meta-analysis proves to be unfeasible or inappropriate, results of included studies will be tabulated and discussed.

Separate subgroup analysis will be considered if adequate and sufficient information is retrieved, i.e. with reference to children or the elderly population.

Methods for estimating qualify of life, costs and cost-effectiveness and/or cost/QALY

Resource consumption and cost data will be extracted from studies included in the TAR. Where data gaps remain, additional cost estimates will be sought from standard sources and suitable published studies.
Additional resource use or cost data may be derived from NHS Trusts.
Costs will be discounted at 6% and benefits at 1.5%, with an alternative scenario with costs and benefits both discounted at 3.5%.

An independent cost-utility or cost-effectiveness model will be developed, comparing dual chamber to single chamber pacing for the target patients group. Ideally, the model will consider the long-term outcomes, costs and quality of life of dual chamber pacing, if sufficient data are available.

F. Handling the company submission(s)

Information provided by manufacturers will be included in the review if inclusion criteria are met.

Any economic analyses and associated models submitted by technology sponsors will be critically analysed following the criteria for quality assessment of cost-effectiveness or cost-utility studies referenced above. Should the number of models be large, a simple comparison of the results will be done with the analysis carried out as part of the TAR.

Any 'commercial in confidence' data taken from the company submission will be underlined in the HTA report and will be followed by an indication of the relevant company name e.g. in brackets. The report will state that data have been removed.

G. Project management

Timetable/milestones - submission of:

Draft protocol: 12 November 2003
Final Protocol: 3 December 2003
Progress report: 10 March 2004
Draft report for referees: April 2004
Final Draft report: 26 May 2004

Competing interests

None

Advisory Group

An advisory group is currently being formed, and will act as an expert resource through the TAR process. In addition, the Technology Assessment Report will be subject to external review by at least two experts acting on behalf of the NHS HTA Programme. These referees will be chosen according to academic seniority and content expertise and will be agreed with NCCHTA. We recognise that the NICE secretariat and Appraisal Committee will undertake methodological review. In addition, an external methodological referee will be asked to review the report on behalf of the HTA Programme. Referees will review a complete and near final draft of the TAR and will understand that their role is part of external quality assurance. The Advisory Group and Referees will be required to sign a copy of the NICE *Confidentiality Acknowledgement and Undertaking* which we will hold on file. Comments from referees and the Technical lead, together with our responses will be made available to NCCHTA in strict confidence for editorial review and approval.

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