Dual-chamber pacemakers for treating symptomatic bradycardia due to sick sinus syndrome without atrioventricular block, part review of Technology Appraisal 88

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GLOSSARY

Atrial fibrillation: Atrial fibrillation/flutter is a heart rhythm disorder (arrhythmia). It usually involves a rapid heart rate, in which the upper heart chambers (atria) are stimulated to contract in a very disorganized and abnormal manner.

Atrioventricular block: Defective conduction at the atrioventricular (AV) node.

Bradycardia: Slow heart rate. Bradycardia may become pathologic with decreased heart output. Symptoms of bradycardia may be specific (syncope) or chronic and non-specific (dizziness fatigue and heart failure).

Cost-effectiveness acceptability curve (CEAC): A graphical representation of the probability of an intervention being cost-effective over a range of monetary values for society's willingness to pay for an additional unit of health gain.

Incremental cost-effectiveness ratio: An expression of the additional cost of health gain associated with an intervention relative to an appropriate comparator. Expressed as the difference in mean costs (relative to the comparator) divided by the difference in mean effects. Sometimes expressed with confidence intervals.

International Normalised Ratio: A measure of the degree of anticoagulation achieved using warfarin (INR=1.0 is equivalent to no anticoagulation)

Kaplan–Meier curves: Also called product limit method. A non-parametric method of compiling life or survival tables, developed by Kaplan and Meier in 1958. This combines calculated probabilities of survival and estimates to allow for censored observations, which are assumed to occur randomly. The intervals are defined as ending each time an event (e.g. death, withdrawal) occurs and are therefore unequal.

New York Heart Association functional scale: A scale used to classify patients' cardiac disease according to the severity of their symptoms into four categories based on the limitations on physical activity; with Class I having no limitation of physical activity and Class IV having symptoms of heart failure at rest and inability to carry out any physical activity without discomfort.

Physiological pacing: Pacing mode that reproduces the natural sequence of atrioventricular contractions. This is achieved with the preservation of atrioventricular synchrony and rate-response.

Quality-adjusted life-year (QALY): A term originally developed in cancer studies to balance poor quality of life (possibly with long life expectancy) with good quality of life (possibly with short life expectancy).

Quality of life (QoL): A concept incorporating all the factors that might impact on an individual's life, including factors such as the absence of disease or infirmity as well as other factors which might affect their physical, mental and social well-being.

Rate-modulation/rate responsiveness: A feature of pacemakers in which the pacing rate varies according to the physical demands of the patient.

Sick sinus syndrome: covers a spectrum of arrhythmias with different underlying mechanisms, manifested as bradycardia, tachycardia (fast heart rate) or a mix of the two, but also as chronotropic incompetence (the inability of the heart to increase its rate appropriately with increased activity, leading to exercise intolerance).

Tachyarrhythmia: Abnormally fast heart rhythm.

Tachycardia: Increased heart rate.

LIST OF ABBREVIATIONS

Abbreviation	Description
6MWT	6-minute walking test
ABHI	Association of British Healthcare Industries
ACC	American College of Cardiology
ACE	Angiotensin converting enzyme
AF	Atrial fibrillation
AHA	American Heart Association
AV	Atrioventricular
BHF	British Heart Foundation
BNF	British National Formulary
BMI	Body-mass index
Bpm	Beats per minute
BPEG	British Pacing and Electrophysiology Group
BTS	Bradycardia-tachycardia syndrome
CC	Critical care
CI	Confidence interval
CV	Cardiovascular
CHF	Congestive heart failure
CiC	Commercial in confidence
CRD	Centre for Reviews and Dissemination
CVD	Cardiovascular disease
CDSR	Cochrane Database of Systematic Reviews
CHARM	Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity
CTOPP	Canadian Trial of Physiological Pacing
DRG	Diagnostic Related Group
DARE	Database of Abstracts of Reviews of Effects
ECG	Electrocardiogram
ESC	European Society of Cardiology
eMIT	Electronic market information tool
HF	Heart failure
HR	Hazard ratio
HES	Hospital episode statistics
HRG	Healthcare Resource Group
HTA	Health Technology Assessment

HPAI	Hospital Prescribing Audit Index
HRQoL	Health-related quality of life
IHR	Intrinsic heart rate
INR	International normalised ratio
IPD	Individual patient data
ITT	Intention to treat
Istat	National Institute of Statistics
ICER	Incremental cost-effectiveness ratio
Kpm	Kilopond metre
LA	Left atrium
LV	Left ventricle
LYG	Life-years gained
LVEF	Left Ventricular Ejection Fraction
ms	Millisecond
MeSH	Medical Subject Headings
MI	Myocardial Infarction
MOST	Mode selection trial
MTA	Multiple Technology Appraisal
NS	Not significant
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NYHA	New York Heart Association
NASPE	The North American Society of Pacing and Electrophysiology
OR	Odds ratio
ONS	Office of National statistics
PSS	Personal Social Services
PASE	Pacemaker selection in the elderly
QALY	Quality adjusted life year
RCT	Randomised controlled trial
SA	Sino-atrial
SD	Standard deviation
SE	Standard error
SAS	Specific Activity Scale
SMR	Standardised mortality rate
SSI	Somatic symptoms inventory
SPC	Summary of product characteristics

SSS	Sick sinus syndrome
TA	Technology assessment
TAG	Technology Assessment Group
TTO	Time trade-off
VAS	Visual analog scale
VP	Ventricular pacing
WTP	Willingness to pay

1 EXECUTIVE SUMMARY

1.1 Background

Bradycardia is defined as a resting heart rate below 60 beats per minute (bpm). A slow heart rate is common under various circumstances, including in some highly trained athletes; however there is also pathological bradycardia caused by conditions affecting the electrical conduction system of the heart. 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) and/or atrioventricular (AV) block. SSS is caused by dysfunction of the sinus node, the heart's natural pacemaker. SSS covers a spectrum of arrhythmias with different underlying mechanisms, manifested as bradycardia, tachycardia (fast heart rate) or a mix of the two, but also as chronotropic incompetence (the inability of the heart to increase its rate appropriately with increased activity, leading to exercise intolerance). AV block can occur independently from SSS, and so a patient suffering from symptomatic bradycardia due to SSS may also have or develop AV block. In AV block the electrical impulses from the sinus node are slowed or blocked at the AV node, which conducts electrical impulses between the atria and ventricular chambers.

Bradycardia due to SSS is more common in older people because of idiopathic degeneration or scarring of the sinus node with increasing age, however it can affect people of all ages, and it affects men and women equally. However, the prevalence of bradyarrhythmias due to SSS requiring permanent pacemaker implant is unknown.

Diagnosis of SSS is made by considering a patient's medical history and symptoms, and through the use of electrocardiograms (ECGs). Diagnosis is often difficult because symptoms and electrocardiographic abnormalities are intermittent, or may be non-specific, particularly in the elderly. People with asymptomatic SSS do not require therapy. The only effective treatment for patients suffering from symptoms is implantation of a permanent pacemaker. Pacemaker implantation will not cure or affect the prognosis of SSS; instead pacemakers are implanted with the aim of alleviating symptoms and improving the patient's quality of life.

Pacemakers are small battery driven devices which regulate abnormal heart rhythms. A pacemaker consists of a generator and one or more leads which are connected to the heart. The leads will sense the heart's electrical activity and, when it becomes too slow, an electrical impulse from the generator will initiate contraction of the heart. Single-chamber pacemakers have one lead which is attached

either to the atrium (atrial pacing) or the ventricle (ventricular pacing). Dual-chamber pacemakers have two leads; one attached to the atrium and the second to the ventricle.

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%) for implantation of a single or a dual-chamber pacemaker after AF and flutter (22.5%), complete AV block (18.8%), and second degree AV block (10.6%). Among patients with a primary diagnosis of SSS (2,490 patients) 67.5% of these patients had an implantation of a dual-chamber pacemaker, 14.8% had a single-chamber pacemaker implanted, and 2.2% had a reoperation of an existing implanted pacemaker.

In NICE technology appraisal (TA) 88 from 2005 the recommendation for patients with SSS in whom, after full evaluation, there is no evidence of impaired AV conduction was single-chamber atrial pacemakers. Since the publication of TA88 at least one large study has provided new evidence on the comparison of dual-chamber pacing with single-chamber atrial pacing in patients with SSS with no evidence of AV block.

1.2 Objectives

The aim of this Multiple Technology Appraisal (MTA) is to appraise the clinical and cost-effectiveness of dual-chamber pacemakers compared to single-chamber atrial pacemakers for treating symptomatic bradycardia in people with sick sinus syndrome (SSS) in whom there is no evidence of impaired atrioventricular conduction. This technology assessment report is an update of Technology Appraisal 88 (TA88) in relation to this indication.

1.3 Methods

The assessment comprises a systematic review of clinical and cost-effectiveness studies and a *de novo* economic analysis.

1.3.1 Clinical effectiveness systematic review

Evidence for the clinical effectiveness of dual-chamber and single-chamber atrial pacemakers was assessed by conducting a systematic review of published research evidence. The review was undertaken following the general principles published by published by the Centre for Reviews and Dissemination (CRD) and the Cochrane Collaboration.

Multiple electronic databases were searched from inception and without language restrictions. The search terms included Medical Subject Headings (MeSH) and text terms for the interventions: artificial pacemakers and pacing, dual-chamber pacemakers/pacing and single-chamber atrial pacemakers/pacing. As the scoping search using this search strategy identified all relevant trials

known from the previous MTA (TA88), search terms for the condition, i.e. bradycardia and SSS, were not used. For the review of clinical effectiveness, only RCTs were considered for inclusion in the review; systematic reviews and non-randomised studies were excluded.

Titles and abstracts returned by the search strategy were examined independently by two researchers and screened for possible inclusion. Disagreements were resolved by discussion or involvement of a third reviewer in cases where consensus could not be achieved. Full texts of potentially relevant studies were ordered. Full publications were assessed independently by two reviewers for inclusion or exclusion against pre-specified criteria, with disagreements resolved by discussion or input from a third reviewer when consensus could not be achieved. The quality of the clinical effectiveness data was assessed by two independent reviewers and checked for agreement. The study quality was assessed according to the Cochrane Handbook for Systematic Reviews of Interventions and recorded using the Cochrane Risk of Bias Tool.

Evidence on the following outcome measures was considered: mortality; heart failure; atrial fibrillation; stroke; exercise capacity; cognitive function; requirement for further surgery; adverse effects of pacemaker implantation; health-related quality of life (HRQoL). Treatment effects were analysed as odds ratios (ORs) for dichotomous data, and mean difference (MD) for continuous outcomes. Extracted data and quality assessment for each study were presented in structured tables and as a narrative summary. Where sufficient comparable data were available for each outcome measure, pair-wise meta-analysis were performed.

1.3.2 Cost effectiveness systematic review

In the cost-effectiveness review, the following databases were searched: MEDLINE (Ovid); EMBASE (Ovid); HTA database (HTA); NHS Economic Evaluations Database (NHS EED). In addition, experts in the field were contacted with a request for details of relevant published and unpublished studies of which they may have knowledge. Furthermore, the NICE website was searched for any recently published Technology Appraisals in pacing that had not already been identified via the database searches. Reference lists of key identified studies were reviewed for any potentially relevant studies.

The search strategy for MEDLINE and EMBASE included terms capturing population (pacing), interventions (dual-chamber pacemakers) and economic evaluations/costing studies with terms designed to capture a broader range of comparators (e.g. single-chamber ventricular pacemakers) than those specified in the scope. The search strategy for HTA and NHS EED combined terms for the

target condition (atrioventricular block, sick sinus syndrome) 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 to any of the searches. 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 checklist.

1.3.3 Technology Assessment Group de novo cost-effectiveness analysis

The Technology Assessment Group (TAG) constructed a *de novo* economic model in Microsoft Excel to estimate the cost-effectiveness of dual-chamber versus single-chamber atrial pacemakers in a population of patients with bradycardia as a result of SSS without AV block. The TAG economic model is a Markov cohort model consistent with that used in TA88, of which this MTA is in part an update. Furthermore, the model structure employed by the TAG, to facilitate a comparison of the cost-effectiveness of dual-chamber pacemakers versus single-chamber atrial pacemakers, is derived from that used in TA88 to assess the cost-effectiveness of these interventions in people with SSS and no AV block.

The perspective used in the economic model is that of the NHS and Personal Social Services (PSS), with costs and benefits discounted at aat 3.5% per annum and the model uses a monthly cycle length with a time horizon of 10 years. Full details of the population modelled, model structure used, inputs, outputs and sensitivity analyses are presented in the sections that follow.

Effectiveness of dual-chamber versus single-chamber device implantation on the clinical outcomes considered (atrial fibrillation, heart failure, stroke, cardiovascular and all-cause mortality) in the TAG economic model was predominantly informed by outcome data collected in the DANPACE trial. The following costs were included in the model: implant/implantation costs, monitoring and health state costs. Utility data associated with the different health states were obtained from a systematic review of the HRQoL literature.

The results of the analyses were presented for people with dual-chamber and single-chamber atrial pacemakers, as deterministic and probabilistic estimates. The sensitivity of model parameters and assumptions were tested in probabilistic sensitivity analysis (PSA), one-way sensitivity analysis (OWSA) using upper and lower limits of 95% confidence intervals around parameters, structural sensitivity analysis and through a series of scenario analyses.

1.4 Results

1.4.1 Clinical effectiveness systematic review

The systematic review of clinical effectiveness identified six RCTs of relevance to this MTA. Three of these were of a parallel group design and three were crossover trials. The parallel RCTs were trials of device whereas the crossover trials were trials of pacing mode programming.

The quality of the trials was generally good, with appropriate trial design and methodology. The crossover trials including in this review had small patient numbers (12-21 patients) and short durations (up to 3 months), which limited the outcomes that could reasonably be captured and the power to detect any differences between the pacing modes. The crossover trials provided data on exercise capacity, symptoms and quality of life measures. The parallel group RCTs were larger (50-1,415 patients) and longer (from 1 to 5.4 years mean follow up) than the crossover trials. The parallel RCTs captured mortality, heart failure, atrial fibrillation, stroke, need for reoperation, exercise capacity and adverse events of pacemaker implantation. No quality of life measures were captured in any of the parallel RCTs.

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 were predominantly influenced by the largest trial with the longest follow up, DANPACE.

Mortality

Dual chamber pacing was not associated with a statistically significant improvement in mortality in the two parallel RCTs Nielsen 2003 and DANPACE. However, the meta-analysis of mortality is unlikely to have sufficient power to identify a statistically significant difference.

Heart failure

In the three parallel RCTs (Albertsen 2008, DANPACE, and Nielsen 2003) the incidence of heart failure was captured using a wide range of measures, which limited the possibility to meta-analys data for heart failure. Dual-chamber pacing was not associated with a statistically significant difference in heart failure compared to single-atrial pacing for any of the outcome measures. In a subgroup analysis DANPACE showed that younger patients (≤ 75 years) with AAIR were at a lower risk of developing heart failure than with DDDR (HR 0.72, 95% CI: 0.53 to 1.00), and older patients (> 75 years) were at a higher risk when on AAIR (HR 1.34, 95% CI: 1.00 to 1.80).

Atrial fibrillation

There were conflicting results for atrial fibrillation from DANPACE and Nielsen 2003. Dual-chamber pacing was associated with a statistically significant increase in atrial fibrillation in Nielsen 2003 (OR 3.19, 95% CI: 1.05 to 9.67), whereas in DANPACE dual-chamber pacing was associated with a statistically significant decrease in paroxysmal atrial fibrillation (OR 0.75, 95% CI: 0.59 to 0.96), but no statistically significant difference in chronic atrial fibrillation. The disparity in the results between DANPACE and Nielsen 2003 may have many causes including differences in baseline characteristics such as pacing indication, prior history of atrial fibrillation, and PQ interval. Other factors may include differences in intervention, i.e. programming of AV delay leading to difference in % ventricular pacing. However, DANPACE is by far the largest study with the longest follow up and balanced baseline characteristics; hence it is reasonable to have more confidence in the results from DANPACE than Nielsen 2003.

Stroke

In a meta-analysis of data from DANPACE and Nielsen 2003 dual-chamber pacing was not associated with a statistically significant improvement in the rate of stroke compared to single-atrial pacing.

Exercise capacity

There were limited data (relatively small number of patients with limited follow up) on exercise capacity showing a small, but statistically significant improvement with single-chamber atrial pacing compared to dual-chamber pacing in one parallel (Albertsen 2008) and one crossover trial (Schwaab 2001). One additional short term crossover trial showed no statistically significant difference for this outcome (Gallick 1994).

Further surgery

DANPACE showed a statistically significant difference in the need for reoperations with significantly fewer participants with dual-chamber pacing needing a reoperation compared to patients 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. Albertsen 2008 reported no complications at implantation. DANPACE reported indications for reoperations of which the more frequent indications were battery depletion, lead complications and need for surgical change of pacing

mode. The latter was significantly less common in dual-chamber pacing compared to single-chamber atrial pacing.

Health-related quality of life

Health related quality of life and symptoms were assessed in two small crossover trials with limited follow up using a wide range of measures. No statistically significant difference was shown between dual-chamber and single-chamber atrial pacing for general well-being, functional status, or multi-dimensional quality of life measures including for cognitive functioning.

Changing pacing mode

In the three parallel RCTs (Albertsen 2008, DANPACE, and Nielsen 2003) single-chamber atrial pacing was associated with a statistically significant increase in patients changing pacing mode compared to patients with dual-chamber pacing (OR 0.50, 95% CI: 0.37 to 0.67). For people implanted with single-chamber atrial pacemakers, the need to change pacing mode is predominantly a result of the development of AV block requiring upgrade to a dual-chamber pacemaker.

1.4.2 Cost effectiveness systematic review

From the cost-effectiveness systematic review, the TAG 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. One was carried out in a UK setting by Castelnuovo 2005 and informed TA88 while the other is a study that was carried out in Denmark by Oddershede 2014 and is based on DANPACE and two other Danish trials.

The third cost-utility analysis was a UK study reported by Caro 2006 that compared dual-chamber pacemakers to single-chamber ventricular pacemakers. The remaining eight studies included studies that did not analyse differences in costs in relation to differences in benefits and studies which only assessed the cost-effectiveness of dual-chamber versus single chamber ventricular pacing.

Therefore, based on review of the current economic literature, the TAG considered there to be a need for a *de novo* economic analysis of dual- versus single-chamber atrial pacing in people with bradycardia as a result of SSS and no AV block.

1.4.3 Technology Assessment Group de novo cost-effectiveness analysis

The TAG carried out a *de novo* cost-effectiveness analysis. However, due to concerns around potential clinical heterogeneity as a result of different patient populations (e.g. prior history of atrial fibrillation) and different device programming used (e.g. different % ventricular pacing) in the RCTs identified, the decision was made to base the model on DANPACE. Furthermore, this was supported by clinical expert opinion as DANPACE is the largest trial with the longest follow-up period.

The base case results of the TAG's economic model demonstrate that dual-chamber pacemakers are more expensive but also more effective than single-chamber atrial pacemakers resulting in an ICER of £10,288. Probabilistic sensitivity analysis reduced this figure to £5,989 principally due to a lowering of the incremental cost. The likelihood for dual-chamber pacemakers to be cost effective was found to be over 70% at a threshold of either £20,000 or £30,000.

In order to use a conservative estimate for all subsequent analyses we focused on the deterministic results.

Structural sensitivity analysis, incorporating risk of reoperation using the available Kaplan–Meier data from DANPACE reduced the ICER from £10,288 to £7,691. A second structural sensitivity analysis, reducing the time horizon to 5 years almost doubled the base case ICER to £19,549. Based on feedback from our clinical experts a time horizon of 10 years would appear to be the most appropriate as the development of AV block is expected to increase steadily over time.

One-way sensitivity analysis showed the key drivers of cost-effectiveness in the economic model to be; lowest risk of stroke (ICER £20,643), lowest risk of paroxysmal AF (ICER £25,177), lowest risk of HF (dual pacemakers dominated by single atrial pacemakers); highest cost of implant/procedure for dual pacemaker (ICER £27,242) and lowest cost of implant/procedure for single atrial pacemaker (ICER £31,641).

A series of scenario analyses were undertaken to test the impact on the results when using alternative sources for parameter estimates or challenge assumptions in the model. The scenario analyses that raised the ICER above the base case were: assuming no difference in HF (ICER £20,948), using the risk of stroke from the TAG's meta-analysis (ICER £10,912), using spell level costs of pacemaker implantation (ICER £11,837), using monthly cost of stroke from Saka 2009 (ICER £10,901), using reprogramming/device replacement for AF of 0% (ICER £14,806), and using a discount rate of 6% (ICER £11,224).

A cumulative "worst case" scenario was also conducted that combined the monthly cost of stroke from Saka 2009, the risk of stroke from the meta-analysis conducted by the TAG, the spell level costs of implantation, reprogramming/device replacement for AF of 0%, and assuming no difference in risk of developing HF between the two types of implant. This resulted in an ICER of £49,018.

The results of the scenario analysis and the one way sensitivity analysis highlight how sensitive the results are to risk of HF, with dual-chamber pacemakers being considered cost-effective or dominated by single-chamber atrial pacemakers depending on the data used. Subgroup analysis from DANPACE identified a significant difference in HF due to age (p=0.05), all other subgroups assessed were non-significant (p>0.31). When the risk of heart failure is assessed by age, the ICER is reduced compared to the base case in patients aged >75 years (£4,918 vs £10,288, respectively), whereas dual-chamber pacemakers are dominated by single-chamber atrial pacemakers in patients aged ≤75 years (i.e. they are more costly and less effective).

1.5 Discussion

This MTA sought to assess the available evidence for dual-chamber pacemakers for treating symptomatic bradycardia due to SSS without AV block in comparison with single-chamber atrial pacemakers. It is a partial update of NICE TA88 (2005), which had a wider remit investigating dual-chamber pacemakers for the treatment of symptomatic bradycardia due to SSS and/or AV block. With regards to the subset of patients of interest to this research, TA88 recommends single-chamber atrial pacemakers for patients with SSS in whom, after full evaluation, there is no evidence of impaired AV conduction.

This MTA uses the best available evidence to explore the clinical and cost-effective implications for using dual-chamber pacemakers rather than single-chamber atrial pacemakers for treating symptomatic bradycardia due to SSS without AV block. DANPACE has demonstrated a significant reduction in re-operation due to need for surgical change of mode of pacing, where it was found to be significantly higher in patients implanted with a single-chamber atrial pacemaker compared with patients implanted with a dual-chamber pacemaker (9.3% vs 0.6%, $p < 0.001$). The difference is primarily due to the development of AV block requiring upgrade to a dual-chamber device. DANPACE also demonstrated a reduced risk of paroxysmal AF with dual-chamber pacing compared to single-chamber atrial pacing (OR 0.75, 95% CI: 0.59 to 0.96). No statistically significant difference was shown between the pacing modes for mortality, heart failure, stroke or quality of life. However, the risk of developing heart failure may vary with age and device.

The *de novo* economic model developed by the TAG shows that dual-chamber pacemakers are more expensive and more effective than single-chamber atrial devices resulting in a base case ICER of £10,288. The ICER remains below £20,000 in probabilistic sensitivity analysis, structural sensitivity analysis, and most scenario analyses and one-way sensitivity analyses.

A potentially important finding of this MTA is the impact that HF may have on the decision to use dual-chamber pacemakers or single-chamber atrial pacemakers for treating symptomatic bradycardia due to SSS without AVB. The results from an analysis based on age (>75 years or ≤75 years) and risk of HF, indicates that using dual-chamber pacemakers in older patients is cost-effective, with an ICER of £4,918, while using dual-chamber pacemakers is dominated (i.e. more expensive and less effective) in younger patients compared to single-chamber atrial pacemakers. However, these results are based on a subgroup analysis and should be treated with caution.

1.5.1 Strengths, limitations and uncertainties of the analyses

Strengths

- The evidence used to inform the decision problem that is the focus of this MTA has been identified following the general principles published by the Centre for Reviews and Dissemination (CRD).
- Economic analyses have been carried out in accordance with NICE guide to methods of technology appraisal and ISPOR guidance for decision analytic models.
- The economic model used to provide a framework for analysis is based primarily on the economic model constructed in TA88. In addition, parameter estimates have been informed by the best available evidence.
- Expert clinical input has been sought and received throughout the project, in particular with respect to assumptions made in clinical and economic analyses and the face validity of final results and conclusions.

Weaknesses

- The limited number of RCTs available to inform this decision question and the lack of reporting in a consistent manner in those trials identified.
- Rapid development of the technologies under investigation so that trials using current single-chamber atrial pacemakers or dual-chamber pacemakers are likely to be superseded by newer implants (and/or pacing algorithms) prior to their completion.

- A cohort approach using the adjusted trial level data from DANPACE was used to populate the efficacy parameters within the economic model rather than a microsimulation informed by individual patient data.
- The costs for the individual pacemakers under consideration were unavailable for use within the economic model and so the average costs reported within the appropriate HRG codes were used.

Uncertainties

- The results from DANPACE do not conclusively answer the clinically relevant questions concerning a difference in risk of HF, stroke, and all-cause mortality.
- As manufacturers declined the opportunity to make a submission, and were unable to supply costs for devices in the time allowed, the average costs of implant/implantation reported within the appropriate HRG codes had to be used.

1.5.2 Generalisability of the findings

- DANPACE is a relatively large trial of good quality and long follow up, which gives a reasonable evidence base for dual-chamber pacing compared with single-chamber atrial pacing for people with SSS without evidence of impaired AV conductance.
- The patient population within DANPACE was considered by our clinical experts to be a reasonable approximation of the patients in the UK.
- While the time horizon in DANPACE was reasonable, the results for patients needing a change in pacing mode and reoperation were probably conservative as the proportion of these due to the development of high grade AV block would be anticipated to increase steadily over time.
- DANPACE did not allow pacemaker algorithms designed to minimize ventricular pacing in patients with intact AV conduction, which have become more common since the start of the trial.
- The *de novo* economic model captures the costs and benefits associated with people symptomatic bradycardia with SSS without evidence of impaired AV conductance deemed suitable for dual-chamber pacing or single-chamber atrial pacing from a UK NHS perspective.

1.6 Conclusions

Implications for service provision

Feedback from our clinical experts indicates that many centres are generally implanting dual-chamber pacemakers rather than single-chamber atrial pacemakers in patients with symptomatic bradycardia due to SSS. Individual patient characteristics may dictate the use of single-chamber atrial pacemakers, e.g. concerns over potential ventricular remodelling over a prolonged period of time, but these would be in specific circumstances only. As such, it appears that there would be minimal implications for service provision if dual-chamber pacemakers are to be advocated for use in favour of single-chamber atrial pacemakers.

Suggested research priorities

Further randomised controlled trials investigating the impact of dual-chamber pacemakers compared to 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 conclusively answer these important clinical questions may be prohibitively expensive.

Assessment of the impact of treatments on patient quality of life may be of interest to the wider clinical community, particularly in patients 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.

2 BACKGROUND

2.1 Description of health problem

2.1.1 Bradycardia

Bradycardia is defined as a resting heart rate below 60 beats per minute (bpm). A slow heart rate can occur naturally under various circumstances and is not necessarily associated with a medical condition. For example, some highly trained athletes have bradycardia. However, there is also pathological bradycardia, which is caused by conditions that affect the electrical conduction system of the heart, including sick sinus syndrome (SSS) and/or atrioventricular (AV) block.[1] Bradycardia does not necessarily require treatment unless it causes symptoms. People suffering from symptomatic bradycardia can present with dizziness, confusion, palpitations, breathlessness, exercise intolerance, and syncope (blackout or fainting). However, bradycardia, and symptoms related to it, may be intermittent, or may be non-specific, particularly in the elderly.

Sick sinus syndrome

SSS is caused by dysfunction of the sinus node, the heart's natural pacemaker. The sinus node consists of a cluster of cells that is situated in the upper part of the right atrium (the right upper chamber of the heart). The sinus node generates the electrical impulses that are conducted through the heart and stimulate it to contract. SSS covers a spectrum of arrhythmias with different underlying mechanisms, manifested as bradycardia, tachycardia (fast heart rate) or a mix of the two, but also as chronotropic incompetence (the inability of the heart to increase its rate appropriately with increased activity, leading to exercise intolerance). SSS manifested as bradyarrhythmias includes sinus bradycardia, sinus arrest, sinoatrial exit block, and alternating bradyarrhythmias and tachyarrhythmias such as bradycardia-tachycardia syndrome (BTS).[1;2]

In sinus arrest or sinus pause, the sinus node transiently ceases to generate electrical impulses.[3] The pause can last from a couple of seconds to several minutes. The sinus pause usually allows escape beats or rhythms to occur, where other pacemakers in the heart initiate contraction of the ventricles. In sinoatrial exit block (SA block), the sinus node depolarises normally, but the signal is blocked before it leaves the sinus node, leading to intermittent delay (first degree SA block) or failure (second degree SA block) of atrial depolarization.

Atrioventricular block

AV block can occur independently from SSS, and so patients suffering from symptomatic bradycardia due to SSS may also have or develop AV block. In AV block, the electrical impulses from the sinus node in the right atria to the ventricular chambers are slowed or blocked at the AV node or within the His Purkinje system, which conducts electrical impulses between the atria and ventricular chambers. Although heart block can be present at birth (congenital), people are more likely to develop the condition, with the risk increasing with age, along with the incidence of heart disease. As in SA block, there are several degrees of AV block.[4] First degree AV block is usually asymptomatic and occurs when the electrical impulses slow as they pass through the AV node, but all impulses reach the ventricles. In second degree AV block, some of the electrical impulses from the sinus node are unable to reach the ventricles, a condition that is more likely to present with symptoms such as syncope. In third degree AV block (complete heart block), there are no electrical impulses between the atrial and ventricular chambers. In the absence of any electrical impulses from the atria, the ventricles produce escape beats, which are usually slow.

2.1.2 Aetiology and pathology

The resting heart rate in healthy people does not change with increasing age;[5] however, bradycardia due to SSS becomes more common in older people because of idiopathic degeneration or development of scarring of the sinus node, both of which occur with ageing.[2] However, SSS can also be caused by extrinsic factors that can mimic or exacerbate SSS, such as some types of medication (e.g., calcium channel blockers and beta blockers), electrolyte disturbances, hypothyroidism, hypothermia and toxins. SSS has also been linked with diseases and conditions that cause scarring or damage to the heart's electrical system, such as atrial fibrillation (AF) and heart failure (HF).[1;2]

AV block can also be either congenital or acquired. Acquired AV block is associated with coronary heart disease, myocardial infarction, cardiomyopathy, heart surgery, and with the use of many antiarrhythmic agents.

2.1.3 Incidence and prevalence

SSS usually occurs in older adults, but it can affect persons of all ages, and it affects men and women equally.[2] The incidence of AV conduction abnormalities also increases with advancing age.[6] However, the prevalence of bradyarrhythmias due to SSS requiring permanent pacemaker implant is unknown,[7] as is the breakdown of the prevalence of SSS with and without concurrent AV block.

Hospital episode statistics (HES) data from October 2012 to September 2013 included 2,490 patients with a primary diagnosis of SSS in NHS hospitals in England.[8]

2.1.4 Diagnosis

Diagnosis of SSS is made by considering a patient's medical history and symptoms, and through the use of electrocardiograms (ECGs). Diagnosis sometimes proves difficult because symptoms and electrocardiographic abnormalities are intermittent. When 12-lead electrocardiography does not yield a diagnosis, prolonged ECG monitoring, such as Holter monitoring (ECG monitoring for 24–48 h) or longer-duration cardiac monitoring either with event ECG recorders for weeks at a time or with an implantable loop recorder for months at a time, may help accurate diagnosis.[2;9] SSS manifested as chronotrophic incompetence is usually assessed through various exhaustive and symptom-limited exercise tests, however, there are no well-validated standards for diagnosing SSS in this setting.[5]

AV conduction is also assessed by ECG. Adequate AV conduction, that is, absence of AV block, has been defined as presence of 1:1 conduction at rates of 140 bpm.[10]

2.1.5 Prognosis and impact of health problem

The prognosis of bradycardia due to SSS depends on the aetiology. If the underlying cause is, for example, medication, hypothyroidism or electrolyte imbalance, then the bradycardia may resolve if the triggering cause is treated or removed. However, for most people, SSS is idiopathic and progressive, with a highly variable development of the disease. People with asymptomatic SSS do not require therapy. The only effective treatment for patients suffering from symptoms is implantation of a permanent pacemaker.[2] However, pacemaker implantation does not cure or affect the prognosis of SSS, and pacemakers are implanted with the aim of alleviating symptoms and improving the patient's quality of life. Pacemaker implantation is associated with considerable risk for the patient, and therefore careful consideration must be given to the balance between potential benefits and adverse effects of treatment. Although pacemaker implantation has been shown to improve quality of life for patients with bradycardia and sinus node dysfunction,[11;12] it has been noted that women and older adults may achieve lower levels of improvement in quality of life than other groups.[13] Additionally, research suggests that there may be differences between the genders at pacemaker implantation with less favourable outcomes for women in terms of complications.[14]

Patients with SSS are at risk of developing complete AV block, with considerable variation in the estimates of risk of AV block (from less than 1% up to 4.5% per year).[4;15] A patient with SSS who develops AV block will require ventricular pacing and consequently an upgrade to a dual-chamber

pacemaker if they already have a single-chamber atrial pacemaker. People with SSS may also develop BTS with AF as the tachyarrhythmia, which in turn leads to an increased risk of stroke.[2]

2.1.6 Measurements of disease

Symptomatic bradycardia, and implantation of permanent pacemakers to relieve the symptoms, can have a significant impact on a patient's quality of life.[4] Quality of life has been measured using many different generic and disease/treatment-specific measures in pacemaker trials. Recommended generic measures include SF-36, a short-form health questionnaire with 36 questions, which looks at functional health, general well-being, and physical and mental health.[16]

The Karolinska Questionnaire, which has been validated in patients paced for bradyarrhythmia, contains 16 questions on cardiovascular symptoms relevant to pacemaker patients[17] The Specific Activity Scale (SAS) is another disease-specific questionnaire for the functional classification of patients with cardiovascular disease.[18] Based on physical capacity, patients are divided into Class I (unlimited exercise capacity) to IV (very low exercise tolerance). Many pacemaker trials also use the New York Heart Association (NYHA) functional scale, which is used to classify patients' cardiac disease according to the severity of their symptoms. Similar to the SAS, patients can fall into four categories based on the limitations on physical activity, from Class I: no limitation of physical activity to Class IV: symptoms of heart failure at rest and inability to carry out any physical activity without discomfort.

2.2 Current service provision

2.2.1 Current guidelines

The National Institute for Health and Care Excellence's (NICE) technology appraisal 88 (TA88), which was published in 2005, recommends dual-chamber pacemakers for patients with symptomatic bradycardia that is due to SSS, AV block, or a combination of the two.[19] However, there were a few exceptions in which single-chamber atrial or ventricular pacemakers were preferred:

- single-chamber atrial pacemakers for patients with SSS in whom, after full evaluation, there is no evidence of impaired AV conduction;
- single-chamber ventricular pacemakers for patients with AV block with continuous AF;

- single-chamber ventricular pacemakers for patients with AV block alone, or in combination with SSS, when patient-specific factors, such as frailty or the presence of comorbidities, influence the balance of risks and benefits in favour of single-chamber ventricular pacing.

Similarly, guidelines from the American College of Cardiology (ACC) and American Heart Association (AHA), published in 2008, recommend dual-chamber pacemakers for AV block and for SSS if there is a suspected abnormality of the AV conduction or an increased risk for future AV block.[20] Single-chamber ventricular pacemakers were recommended for patients with AV block and chronic AF or other atrial tachyarrhythmias, and single-chamber atrial pacemakers recommended for patients with SSS with no suspected abnormality of the AV conduction and who are not considered to be at increased risk for future AV block.

In 2013, the European Society of Cardiology (ESC) published their guidelines on cardiac pacing and cardiac resynchronization therapy.[7] ESC recommends dual-chamber pacemakers as a first choice for patients with SSS and/or AV block, with the exception of patients with persistent AV block and continuous AF, for whom a single-chamber ventricular pacemaker is recommended.

The differences in recommendations between the more recent ESC guidelines and those of NICE and the ACC/AHA are linked to the completion and publication of the DANPACE trial,[21] which has provided new evidence on the comparison of single-chamber atrial pacing with dual-chamber pacing in SSS with no evidence of AV block. The objectives for this MTA were to formally evaluate the data from DANPACE and to identify and other evidence in this area.

2.2.2 Current pacemaker usage in the NHS

During 2012–13 in England, more than 20,000 people had a single or a dual-chamber pacemaker implanted and just over 8,000 people had a renewal of an implanted pacemaker.[22] The median length of hospital stay was 2 days for implantation of both single and dual pacemaker systems, resulting in 82,000 bed days in the UK in 2012–13. Of the newly implanted single and dual pacemakers, SSS was the fourth most prevalent primary diagnosis (9.5%), after atrial fibriallation and flutter (22.5%), complete AV block (18.8%), and second degree AV block (10.6%).[8] Among patients with a primary diagnosis of SSS (2,490 patients), 67.5% had a dual-chamber pacemaker implanted, 14.8% a single-chamber pacemaker, and 2.2% had a reoperation on an existing implanted pacemaker.[8]

The target for the implantation rate of new pacemakers in England and Wales is 700 pacemakers per million people. In 2012, the total implant rate in England and Wales fell short of this target, reaching 559 per million people in the population[23] In England, implantation rates varied between 379 to 638

new pacemaker implants per million people in different parts of the country, although a decrease in variability was noticed across the country from 2010 to 2012.[23]

2.3 Description of technology under assessment

2.3.1 Pacemakers

Pacemakers are small battery driven devices which regulate abnormal heart rhythms. A pacemaker consists of a generator and one or more leads, which are connected to the heart. The leads will sense the heart's electrical activity and, when it becomes too slow, an electrical impulse from the generator will initiate contraction of the heart.

Single-chamber pacemakers have one lead which is attached either to the atrium (atrial pacing) or the ventricle (ventricular pacing). Dual-chamber pacemakers have two leads: one lead is attached to the atrium and the second to the ventricle.

The North American Society of Pacing and Electrophysiology (NASPE) and the British Pacing and Electrophysiology Group (BPEG) have established nomenclature to describe the different pacing modes of pacemakers, which comprises a four-letter combination (Table 1).[24] The first letter indicates which chamber or chambers are paced, and the second letter specifies which chamber(s) are sensed. Letter I and II are usually, but not necessarily, the same. The third letter describes the mode of response to sensing. The pacemaker can be: inhibited (I), if it senses a spontaneous depolarisation; triggered (T), if it senses that no depolarisation has occurred (uncommon); and both inhibited and triggered (D).

Table 1: Definition of Generic Anti-bradycardia pacing codes (NASPE/BPEG)[24]

Position	**I**	**II**	**III**	**IV**
Category	Chamber paced	Chamber sensed	Response to Sensing	Rate modulation
Codes	A = Atrium V = Ventricle D = Dual (Atrium and Ventricle)	A = Atrium V = Ventricle D = Dual (Atrium and Ventricle)	O = None T = Triggered I = Inhibited D= Dual (Triggered and Inhibited)	O = None R = Rate-modulated

In an AAI or VVI pacemaker, the pacemaker senses an atrial or ventricular event and withholds its signal. DDI pacemakers will inhibit the output of the device in either chamber where it senses a signal. The most common example of the letter D in the third position is in DDD pacemakers, which have dual functionality. On sensing an atrial signal, the DDD pacemaker initially inhibits the atrial output, which triggers a timer that, after a set time interval (AV delay), initiates a ventricular output. If the DDD device senses a ventricular signal during the triggering interval, the pacemaker also inhibits the ventricular output. The fourth letter specifies whether the pacemaker is programmed to sense and increase the heart rate in response to physical, mental or emotional activity. This is termed rate response.

Modern pacemakers have numerous programmable features that can be altered to optimize pacemaker function. Programming is a complex and rapidly evolving technical area, and a detailed description of pacemaker programming is beyond the scope of this report, thus a few key parameters are summarised below.

- *Rate responsiveness*. As mentioned above, some pacemakers can be programmed to vary the pacing rate in response to the patient's activity level. Rate responsive pacemakers control heart rate by sensing body movement, breathing, or by closed loop stimulation. Closed loop stimulation determines the appropriate heart rate based on intracardiac impedance measurements, which reflect information from the autonomic nervous system.

- *AV delay*. The AV delay is the time interval between an atrial paced or sensed event, and the delivery of a ventricular pacing stimulus in dual chamber pacemakers. If intrinsic conduction is more rapid than the duration of the programmed AV delay, the intrinsic signal will inhibit ventricular pacing.

- *Mode switching*. Dual-chamber pacemakers may have an additional feature called mode switching.[25] Mode-switch algorithms track tachyarrhythmias, such as AF, and when these occur trigger a non-tracking mode, or ventricular pacing to avoid tachycardia. Atrial arrhythmias would otherwise cause sustained high ventricular rates. When the atrial rate falls below the rate programmed for mode switch, the pacemaker changes back to a tracking mode.[25]

2.3.2 Implant procedure and follow-up

Pacemakers are usually implanted under local anaesthetic. An incision is made below the collarbone to facilitate lead implantation and a pocket created under the skin to hold the pacemaker device. The

pacing lead is inserted in to the heart through a major vein. One end of the lead is securely lodged in the tissue of the heart and the other end is connected to the pacemaker. The position of the lead is checked using X-ray imaging. Testing and programming of the pacemaker may sometimes be done wirelessly and can be changed at any time. The hospital stay is usually brief and the implant procedure could be carried out as day surgery or might require a single overnight stay in hospital. Implantation of a dual-chamber pacemaker may take longer than a single-chamber pacemaker, because dual-chamber pacemakers require the insertion and placement of two leads. The requirement for an additional lead in dual versus single-chamber pacemakers might lead to an associated increased risk of complications, such as lead displacement.[26]

People with permanently implanted pacemakers require regular follow-up to check: the function of the pacemaker leads; the frequency of utilisation and the battery life of the pacemaker; and for abnormal heart rhythm.[27] The battery life of a pacemaker is about 5 to 8 years; after this time, replacement of the pacemaker will be required. Replacement of the pacemaker involves making an incision over the previous site of insertion, removing the old pacemaker generator, checking the lead(s), and, if satisfactory, attaching a new generator to the existing lead(s). Problems with pacemaker leads, such as loss of contact between the lead and the heart, require reoperation. Where repair of a fault with a lead is necessary, the old lead may be left in place but disconnected from the pacemaker and a new lead implanted. Removal of old leads can be complicated by the formation of scar tissue connecting the lead to the vein and/or the heart.

2.3.3 Complications

Most complications occur during or soon after implantation of a pacemaker. Some of the more common complications are lead displacement (1.4–2.1%) and puncture of the lung when placing the leads, which can lead to pneumothorax (1.9%) or haemothorax.[28;29] One of the most serious, but rarer, complications that can arise during the implant procedure is cardiac perforation. There is also the risk of infection of the pacemaker pocket or the leads.[29;30] Complications occurring at a later date mainly involve dysfunction of the pacemaker or of the leads, that is, failure to pace or sense appropriately. Other late complications include infection or erosion of the pacemaker site or its leads.[30]

Reoperation may be required as a result of a complication, such as lead displacement, infection or pacemaker erosion, but it can also be due to a need for pacemaker upgrade (single to dual) or pacemaker replacement due to changed clinical needs, or end of battery life.[26] The complication rate associated with a reoperation is substantially higher than that associated with initial implantation.[31]

2.3.4 Costs associated with intervention

The cost of pacemaker implantation is made up of several elements:

- price of the generator and leads;
- implant procedure (setting and personnel);
- personnel involved prior to and following implantation;
- regular routine follow up;
- management of peri-operative complications;
- management of late complications;
- replacement or upgrade at the end of the life of the pacemaker or in response to changing clinical need.

Further details on the costs associated with pacemaker implantation are given in Section 5.2.11 of this report.

3 DEFINITION OF THE DECISION PROBLEM

3.1 Decision problem

Population

The population of interest to this review is people with symptomatic bradycardia due to sick sinus syndrome (SSS) without atrioventricular (AV) block, that is, with intact AV conduction, and who required permanent pacemaker implantation.

Intervention and comparator

The review considered permanent implantable dual-chamber pacemakers programmed to dual-chamber pacing compared with permanent implantable pacemakers (single or dual) programmed to atrial pacing.

All programmable features such as rate responsiveness, mode switch, and ventricular pacing (VP) minimizing features were allowed.

Outcomes

The outcomes of interest considered for this review included:

- mortality (all-cause);
- heart failure (HF);
- atrial fibrillation (AF);
- stroke;
- exercise capacity;
- cognitive function;
- requirement for further surgery;
- adverse effects of pacemaker implantation (including peri- and post-operative complications, AF and device replacement);

- health-related quality of life (HRQoL).

3.2 Overall aims and objectives of assessment

The aim of this Multiple Technology Appraisal (MTA) is to appraise the clinical and cost-effectiveness of dual-chamber pacemakers for treating symptomatic bradycardia in people with sick sinus syndrome (SSS) in whom there is no evidence of impaired AV conduction, and to update the recommendations of Technology Appraisal 88 (TA88)[19] in relation to this indication.

4 ASSESSMENT OF CLINICAL EFFECTIVENESS

4.1 Methods for reviewing effectiveness

The clinical effectiveness of single-chamber atrial and dual-chamber pacemakers for the treatment of symptomatic bradycardia due to sick sinus syndrome (SSS) without atrioventricular (AV) block was assessed by conducting a systematic review of published research evidence. The review was undertaken following the general principles published by the Centre for Reviews and Dissemination (CRD) and the Cochrane Collaboration.[32;33]

4.1.1 Identification of studies

To identify relevant randomised controlled trials (RCTs), multiple electronic databases were searched, including MEDLINE, EMBASE, and The Cochrane Library (including the Cochrane Database of Systematic Reviews [CDSR], Cochrane Central Register of Controlled Trials [CENTRAL], Database of Abstracts of Reviews of Effects [DARE], and Health Technology Assessment Database [HTA database]). Bibliographies of retrieved studies identified as relevant were manually reviewed for potentially eligible studies. In addition, experts in the field were contacted with a request for details of published and unpublished studies of which they may have knowledge. Furthermore, submissions submitted to NICE were assessed for unpublished data.

The search terms included Medical Subject Headings (MeSH) and text terms for the interventions: artificial pacemakers and pacing; dual-chamber pacemakers/pacing; and single-chamber atrial pacemakers/pacing. As the scoping search using this search strategy identified all relevant trials known from the previous MTA, search terms for the condition (i.e., bradycardia and SSS) were not used. To keep in line with the original MTA, which focused on RCT evidence, the search strategy included an RCT filter developed and validated by Scottish Intercollegiate Guidelines Network.[34] No language or date restriction was applied to the searches. Electronic databases were initially searched on 7 January 2014 and results uploaded into Reference Manager Version 11.0 and deduplicated. An update search was carried out 12 May 2014. Full details of the terms used in the searches are presented in Appendix 1 Literature search strategies.

Two reviewers independently screened all titles and abstracts according to the inclusion criteria (Table 2**Error! Reference source not found.**). Full paper manuscripts of any titles/abstracts of otential relevance were obtained and assessed independently by two reviewers. If a study was only reported as a meeting abstract or if full paper manuscripts could not be obtained, the study authors were contacted to gain further details. Studies for which insufficient methodological details were

available to allow critical appraisal of study quality were excluded. Discrepancies between the two reviewers were resolved by consensus, with involvement of a third reviewer when necessary.

4.1.2 Inclusion and exclusion criteria

Inclusion criteria and exclusion criteria for the review of effectiveness were based on the decision problem outlined in Table 2. The review included RCTs of parallel and crossover design. Systematic reviews and non-randomised studies were excluded.

The intervention was permanent implantable dual-chamber pacemakers compared with single-chamber atrial pacemakers or dual-chamber pacemakers programmed primarily to atrial pacing. Studies were not excluded based on programming of the pacemakers; both rate and non-rate responsive programming were included. The review also allowed other programmable features, such as prolonging or eliminating the AV interval in order to minimize ventricular pacing.

RCTs were included if the relevant pacing modes were compared in a population with symptomatic bradycardia, documented SSS, bradycardia-tachycardia syndrome, and normal AV conduction. Studies were excluded if none of the outcomes of interest was reported.

Table 2. Inclusion criteria, based on the decision problem, for studies evaluating clinical effectiveness

	Inclusion criteria
Study design	Randomized controlled trials of parallel or crossover design
Intervention	Permanent implantable dual-chamber pacemakers
Population	People with symptomatic bradyarrythmias due to sick sinus syndrome without atrioventricular block
Comparator	Permanent implantable single-chamber atrial pacemakers
Outcomes	Mortality (all-cause); Heart failure; Atrial fibrillation; Stroke; Exercise capacity; Cognitive function; Requirement for further surgery; Adverse effects of pacemaker implantation (including peri- and post-operative complications, atrial fibrillation and device replacement); Health-related quality of life (HRQoL).

4.1.3 Data abstraction strategy

Data were extracted independently by two reviewers using a standardised data extraction form. Information extracted included details of the study's design and methodology, baseline characteristics of participants, and results, including clinical outcome efficacy and any adverse events reported. Where there was incomplete information, the study authors were contacted with a request for further details. Discrepancies were resolved by discussion, with involvement of a third reviewer if necessary. Data extraction forms for the included studies are provided in Appendix 2 Data abstraction.

4.1.4 Critical appraisal strategy

The quality of the clinical effectiveness studies were assessed independently by two reviewers. Any disagreements were resolved by consensus and if necessary a third reviewer was consulted. The study quality was assessed according to recommendations by the CRD[32] and the *Cochrane Handbook for Systematic Reviews of Interventions*[33] and recorded using the Cochrane Risk of Bias Tool.[35]

4.1.5 Methods of data synthesis

Details of results on clinical effectiveness and quality assessment for each included study are presented in structured tables and as a narrative summary. The possible effects of study quality on the effectiveness data and review findings are discussed. Standard pair-wise meta-analysis was performed to evaluate the clinical effectiveness for several outcomes based on intention-to-treat (ITT) analysis. ITT was defined as patients being analysed in the trial arm to which they were allocated at randomisation regardless of whether they changed pacing mode, withdrew or were lost to follow-up.

Dichotomous outcomes data were meta-analysed using Mantel-Haenzsel odds ratio (OR) with 95% confidence interval (CI) and a random effects model. Individual trial data were analysed and presented in the same way as meta-analysed data for comparison where appropriate. In addition, if hazard ratios were presented in the original publication of a trial, these have been reproduced in this report for comparison. Missing data were imputed and analysed as treatment failures.

For the dichotomous outcomes reported in this review (mortality, HF, AF, stroke, further surgery, and adverse events), only RCTs with a parallel group design have been considered, excluding RCTs with a crossover design. RCTs with a crossover design are most appropriate for symptomatic treatment of chronic or relatively stable conditions, such as symptomatic bradycardia treated by artificial pacing with a permanently implanted pacemaker.[36] However, crossover trials are only appropriate when looking at treatment effects that are likely to be reversible and short-lived, and inappropriate when

studying outcomes where an outcome event may alter the baseline risk, that is, on entry to the second phase the patients systematically differ from their initial state.[36]

Data for the continuous outcomes exercise capacity, cognitive functioning, and quality of life were primarily reported in included crossover trials. Data from parallel and crossover RCTs have been reported separately. It was planned *a priori* to analyse continuous outcome data from crossover studies using the mean difference (or the difference between the means) of dual-chamber and single-chamber atrial pacing, and the standard deviation (SD) or standard error (SE) for the within-person differences. However, the included crossover trials reported means and SD for treatment-specific outcomes, but did not report paired results. One crossover trial provided individual patient data (IPD) for exercise capacity (Gallick 1994[37]) and one for quality of life (Lau 1994[38]) from which the mean difference and SE for within-person difference could be obtained. However, because of the lack in reporting of relevant data across the included crossover trials, meta-analysis of data was not performed.

Meta-analysis was carried out using Review Manager,[39] with the use of a random-effects model. Statistical heterogeneity between included studies was assessed using the I^2 test. In the presence of heterogeneity (I^2 > 30%), possible sources were investigated, including differences between individual studies' populations, methods or interventions. The possibility of publication bias and/or small study effects was not investigated because of the low number of included studies.

4.1.6 Stakeholder's submissions

A joint manufacturers' submission from the Association of British Healthcare Industries (ABHI) was expected for this MTA; however, the only submission to NICE in relation to this MTA was from the British Cardiovascular Society. As such this report does not contain confidential information from stakeholders. No data additional to the studies identified in the systematic review were presented in the submission.

4.2 Results

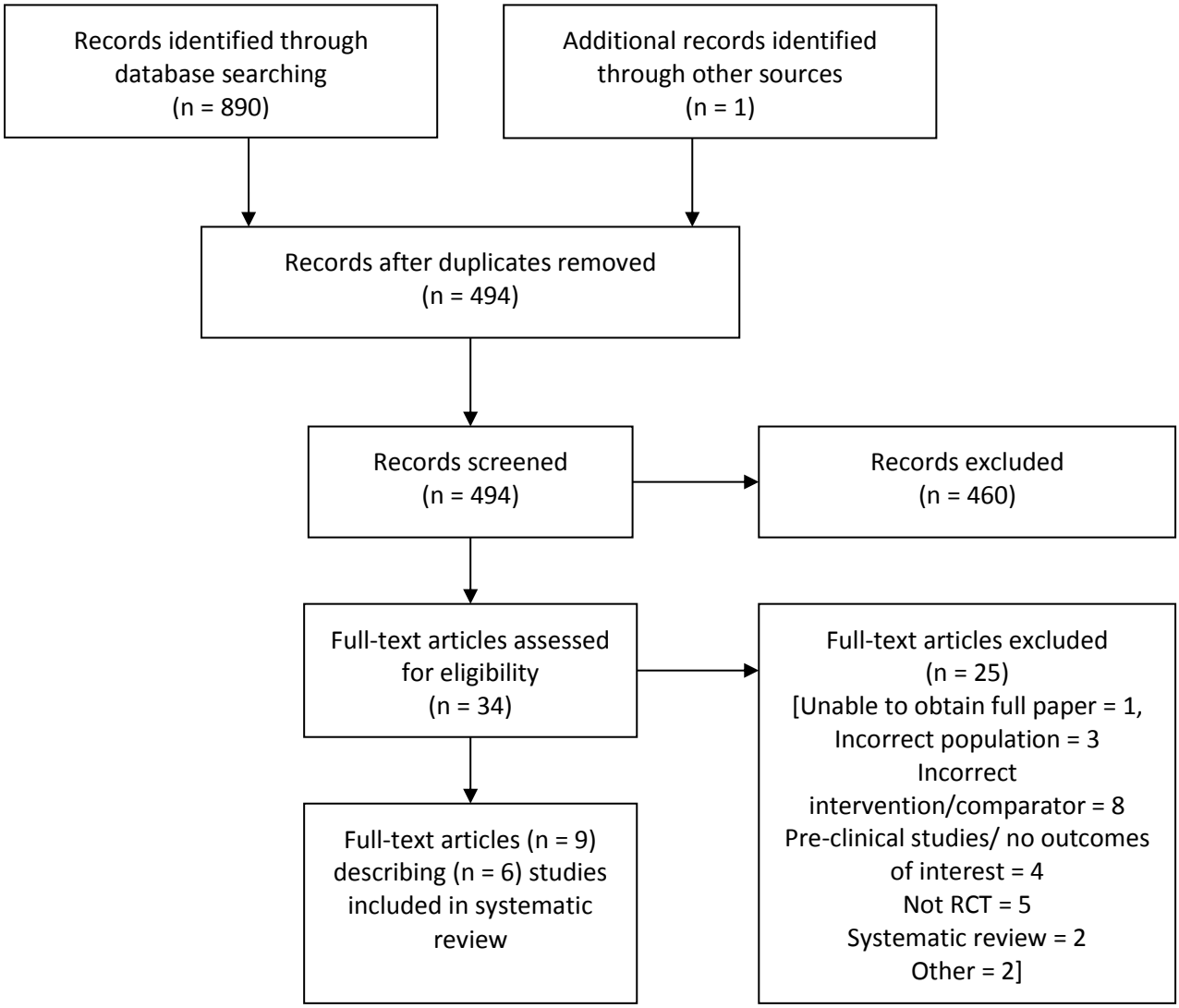
4.2.1 Quantity and quality of research available

Database searches retrieved 492 records (post deduplication). One additional reference was identified through hand searching, giving a total of 493 references that were screened for inclusion (Figure 1). Full references were sought for 34 of these, which were potentially eligible for inclusion. Of the records identified as potentially relevant, only one reference was unobtainable.[40] However, this reference was identified in the original MTA TA88 and excluded because it was a pre-clinical

study.[19] Of the remaining 33 records, 9 references describing 6 studies were included in the review. Characteristics of the studies included in the review are given in Table 3. A list of excluded references (with reason for exclusion) is presented in Appendix 4 Table of excluded studies.

No additional studies were retrieved from submissions made to NICE as part of the appraisal of this technology.

Figure 1. PRISMA flow diagram for studies included and excluded from the clinical effectiveness review.



Randomised controlled trial characteristics

A summary of study characteristics (populations, interventions, comparator and follow up) is shown in Table 3.

Table 3. Summary of studies included in the review of the clinical effectiveness literature.

Study	Population	Intervention	Comparator 1	Comparator 2	Randomisation	Country	N patients	Follow up	Supplementary publications
Parallel group RCTs									
Albertsen 2008[41]	sinus arrest/sino-atrial block, BTS, sinus bradycardia	DDD(R)	AAI(R)	N/A	device	Denmark	50	12 months	None identified
DANPACE[42]	sino-atrial block/sinus-arrest, sinus bradycardia, bradycardia-tachycardia	DDDR	AAIR	N/A	device	Denmark, UK, Canada	1,415	Mean 5.4 ± 2.6 years	Andersen et al.[43] Nielsen et al.[44] Riahi et al.[45]
Nielsen 2003[46]	sinus bradycardia, sino-atrial block, BTS	DDDR-s	AAIR	DDDR-l	device	Denmark	177	Mean 2.9 ± 1.1 years	Kristensen et al.[47]
Crossover RCTs									
Gallick 1994[37]	sinus node disease	DDDR	AAIR	N/A	programming	NR	12	< 1 day	None identified
Lau 1994[38]	sick sinus syndrome	DDDR	AAIR	N/A	programming	NR	15	3 months	None identified
Schwaab 2001[48]	sinus bradycardia	DDDR	AAIR	N/A	programming	Germany	21	3 months	None identified

Abbreviations used in table: BTS, bradycardia-tachycardia syndrome; DDDR-s, DDDR with a short programmed atrioventricular (AV) delay; DDDR-l, DDDR with a long programmed AV delay; N/A, not applicable; RCTs, randomized controlled trials.

Six RCTs described and reported in nine publications, were included in the review. The review included one trial (Gallick 1994[37]) that was identified but excluded from the original MTA, TA88.[19] In TA88, studies of less than 48 hours duration, like Gallick 1994, were excluded, whereas no time limitation was specified for the purposes of this review. This review also includes two trials that have been completed and published since TA88; Albertsen 2008 and DANPACE.[41;42]

Information about and results from DANPACE have been published in three publications included in this review: the protocol; the primary publication; and one publication focusing on subgroup analyses of HF data.[42;43;45] One other included trial (Nielsen 2003) was reported in a main publication and an additional paper focusing on AF and thromboembolism analyses.[46;47]

Study design

Three RCTs with a parallel group design (Albertsen 2008, DANPACE, and Nielsen 2003)[41;42;46] and three crossover RCTs (Gallick 1994, Lau 1994, Schwaab 2001)[37;38;48] were identified as relevant and were included in this review.

The follow-up period varied greatly among the included studies. Of the parallel group RCTs, Albertsen 2008 had a set follow up of 12 months,[41] DANPACE had a follow up of up to 10 years with an average of 5.4 ± 2.6 years,[42] and, in Nielsen 2003 the follow up ranged from 6 days to 5.3 years (mean 2.9 ± 1.1 years).[46]

The follow up in the crossover trials was shorter than in the parallel studies. In Lau 1994 and Schwaab 2001, patients spent 4 weeks in each pacing mode before crossing over to the other pacing mode.[38;48] Gallick 1994 studied the immediate effects of pacing mode during exercise: haemodynamic effects were measured during bicycle exercise first in one pacing mode and after 0.5 to 1 hour rest the exercise was repeated in the other pacing mode.[37]

Intervention and comparator

The three parallel RCTs randomised patients to receive single or dual-chamber pacemakers.[41;42;46] In the crossover trials, all patients were implanted with a dual-chamber pacemaker and then randomised to a pacing programme of dual-chamber or single-chamber atrial pacing, followed by the alternate pacing mode.[37;38;48]

Most trials randomised patients before pacemaker implantation, including the trials randomising patients by device (parallel RCTs),[41;42;46] and two of the studies randomising by pacing programme

(Lau 1994[38] and Schwaab 2001[48]). The remaining trial, Gallick 1994[37], randomised patients who had recently had a dual pacemaker implanted.

The single and dual pacemakers used in the included trials were from several different manufacturers including: Medtronic; St. Jude Medical; ELA Medical Inc.; Guidant (Boston Scientific); Boston Scientific; Pacesetter (St. Jude Medical); Cardiac Pacemakers Inc.; Telectronics Pacing Systems (St. Jude Medical); and Intermedics Inc (Boston Scientific).

The included trials compared DDD(R) with AAI(R) pacing. However, Nielsen 2003[46] included two DDDR trial arms with different programmed AV delay: DDDR-s with a short AV delay (<150 ms) and DDDR-l with a fixed long AV delay (300 ms). Data for these two study arms have been combined in analyses in this review. However, for each outcome, the impact of combining the study arms has either been explored in a sensitivity analysis or data from each study arm have been presented separately.

DANPACE[42] was the only trial that specifically stated that programmable features prolonging or eliminating the AV interval, in order to minimize ventricular pacing, were not permitted in the trial.

In all the included studies, all or the majority of patients within each study received pacemakers programmed with the rate adaptive function activated. The rate adaptive function was activated in all patients in Albertsen 2008[41], DANPACE[42], Gallick 1994[37], Lau 1994[38] and Schwaab 2001.[48] In Nielsen 2003, all but two patients had the rate adaptive function active.[46]

The programmed AV delay in the dual-chamber pacing mode differed greatly across the studies and between study arms, as shown in Table 4. The studies had, for each study arm with dual-chamber pacing, an AV delay that was either set at a specific value (Nielsen 2003[46] and Gallick 1994[37]), in a range (Albertsen 2008[41], DANPACE[42] and Lau 1994[38]), or optimised according to a programmed algorithm (Schwaab 2001[48]). Gallick 1994[37], Lau 1994[38] and the DDDR-s arm in Nielsen 2003[46] employed relatively short AV delays, up to 150 ms. By contrast, the DDDR-l arm in Nielsen 2003[46] had an AV delay of 300 ms. The AV delay in Albertsen 2008[41] and DANPACE[42] was around 220 ms.

The mode switch function was active in all three parallel group RCTs.[41;42;46] In Schwaab 2001, mode switch was activated in some patients, but the number of patients was not specified.[48] Gallick

1994[37] and Lau 1994[38] did not report mode switch settings; however, mode switching may not have been available at the time of these trials.

Table 4. Dual pacemaker programming

Study	Intervention	Rate adaptive	AV delay	Mode switch
Parallel group RCTs				
Albertsen 2008	DDDR	On	Maximum 220–225 ms	On
DANPACE	DDDR	On in all but 2 patients	140–220 ms	On
Nielsen 2003	DDDR-s	On	150 ms	On
	DDDR-l	On	300 ms	On
Crossover RCTs				
Gallick 1994	DDDR	On	100 ms	NR
Lau 1994	DDDR	On	96 ± 7 to 140 ± 5 ms	NR
Schwaab 2001	DDDR	On	AV-delay was optimised based on the maximum time velocity integral of the aortic flow	On, but not in all patients
Abbreviations used in table: AV delay, atrioventricular delay; ms, millisecond; NR, not reported; RCTs, randomized controlled trials.				

Population

Most of the parallel and crossover RCTs included patients with symptomatic bradycardia or SSS in combination with certain ECG criteria, for example, indicating normal AV conduction.

Schwaab 2001 had slightly different inclusion criteria: patients had to have chronotrophic incompetence, have experienced at least two documented episodes of atrial tachyarrhythmia, be on antiarrhythmic medication for prevention of atrial flutter or AF, as well as being eligible for a dual-chamber pacemaker for symptomatic bradycardia.[48]

The parallel RCTs (Albertsen 2008, DANPACE, and Nielsen 2003) had similar exclusion criteria, excluding patients if they had chronic AF, AV block, carotid sinus syndrome, vasovagal syncope, bundle branch block, surgery, a short life expectancy, dementia or cancer.[41;42;46] Lau 1994[38] did not report specific exclusion criteria, and Gallick 1994[37] excluded patients with evidence of AV node disease or who were unable to exercise.

Summaries of the characteristics of the study populations in the included RCTs are presented in Table 5 (parallel RCTs) and Table 6**Error! Reference source not found.** (crossover RCTs). More detailed aseline characteristics can be found in Appendix 2 Data abstraction.

The parallel RCTs (Albertsen 2008, DANPACE, and Nielsen 2003) varied in size from 50 to 1,415 randomised patients. [41;42;46] The crossover studies (Gallick 1994, Lau 1994, and Schwaab 2001) were smaller, with between 12 and 21 participants.[37;38;48] The RCTs all included patients with SSS or sinus node dysfunction (SND). The parallel RCTs Albertsen 2008[41] and Nielsen 2003[46] reported the breakdown of pacing indication of the participants for sinus arrest/sino-atrial block, BTS, and sinus bradycardia, with some imbalances between the trial arms: most notably there were more people with BTS in the two dual-chamber pacing arms than in the AAIR arm in Nielsen 2003.[46]

Mean age was similar across the three parallel RCTs (Albertsen 2008, DANPACE, and Nielsen 2003), and between study arms (72–74 years).[41;42;46] The participants in the crossover trials (Gallick 1994, Lau 1994, and Schwaab 2001) had a slightly lower mean age of 61–70 years. [37;38;48] Only DANPACE reported previous history of AF, with around 44% of the participants having a history of AF in each trial arm.[42] Previous stroke was captured in Albertsen 2008 and DANPACE. In the smaller study by Albertsen,[41] the number of patients with prior stroke was low but with a notable difference between groups in the proportion of people with prior stroke (5/24 patients in the AAIR arm and only 1/26 in the DDDR arm). In DANPACE, there was no statistically significant difference between the trial arms in the proportion of patients having experienced a stroke at trial entry (7.5% and 8.6% respectively).[42] In the parallel RCTs that reported NYHA class at baseline (Albertsen 2008, DANPACE and Nielsen 2003) the majority of participants were NYHA class I or II (96%) with no or mild symptoms of HF. [41;42;46]

Table 5. Patient baseline characteristics of included parallel RCTs

Patient characteristics	**Albertsen 2008**		**DANPACE**		**Nielsen 2003**		
	DDDR n (%)	**AAIR n (%)**	**DDDR n (%)**	**AAIR n (%)**	**DDDR-s n (%)**	**DDDR-l n (%)**	**AAIR n (%)**
Number of participants	26	24	708	707	60	63	54
Age (Mean ± SD)	73 ± 13	72 ± 10	72.4 ± 11.4	73.5 ± 11.2	74 ± 9	74 ± 9	74 ± 9
Sex (male)	8 (31)	10 (42)	267 (37.7)	235 (33.2)	23 (43)	26 (43)	24 (38)
Sinus arrest/sinus-atrial	16	14	NR	NR	17	16	19

block								
Brady-tachy syndrome		12	11	NR	NR	38	36	27
Sinus bradycardia		8	4	NR	NR	5	11	8
Previous history of atrial fibrillation		NR	NR	318	303	NR	NR	NR
Previous stroke		1	5	53	61	NR	NR	NR
NYHA class, n	I	18	19	522	503	38	46	32
	II	8	3	158	172	22	14	18
	III	0	2	24	29	0	3	2
	IV	0	0	2	0	0	0	1
Anticoagulant drugs		NR	NR	89	108	5	11	5
Beta blockers		11	6	132	159	5	7	4
Diuretics		11	14	263	304	NR	NR	NR
Ca^{2+} channel blockers		5	5	142	137	7	11	14
ACE inhibitors		10	11	170	160	NR	NR	NR
Cardiac glycoside		NR	NR	62	73	9	11	11
Sotalol		NR	NR	44	43	8	10	7
Amiodarone		NR	NR	24	25	NR	NR	NR
Aspirin		14	20	361	369	40	36	35
Class I antiarrhythmics		NR	NR	20	14	NR	NR	NR
Abbreviations used in table: ACE inhibitor, angiotensin-converting-enzyme inhibitor; NR, not reported; NYHA, New York Heart Association; SD, standard deviation.								

Table 6. Patient baseline characteristics of included crossover RCTs

Patient characteristics	**Gallick 1994**	**Lau 1994**	**Schwaab 2001**
	n (%)	**n (%)**	**n (%)**
Number of participants	12	15	21
Age (Mean ± SD)	61 ± SE 4	62 ± 2	70 ± 7
Sex (male)	8 (67)	5 (42)	11 (58)
Previous history of AF	NR	Some of the patients	NR
Previous stroke	NR	NR	NR
NYHA class	NR	NR	NR
Beta blockers	4	1	NR
Class I antiarrhythmics	NR	NR	2

Ca^{2+} channel blockers	4	2	NR
ACE inhibitors	NR	1	NR
Cardiac grycoside	3	3	NR
K^{+} channel blockers	NR	1	18
Aspirin	NR	1	NR
Nitrates	NR	2	NR
Abbreviations used in table: ACE inhibitor, angiotensin-converting-enzyme inhibitor; AF, atrial fibrillation; NR, not reported; NYHA, New York Heart Association.			

Outcomes

The outcomes of interest to this review that were reported in the included studies are listed in Table 7. For several of the outcomes, the trials had used different scales or measurements, which have been reported separately. These include HF, exercise capacity, and HRQoL.

Table 7. Outcomes of interest reported in included trials

Outcome	**Parallel RCTs**			**Crossover RCTs**		
	Albertsen 2008	**DANPACE**	**Nielsen 2003**	**Gallick 1994**	**Lau 1994**	**Schwaab 2001**
All-cause mortality		✓	✓	N/A	N/A	N/A
CV mortality			✓	N/A	N/A	N/A
Heart failure	✓	✓	✓	N/A	N/A	N/A
Atrial fibrillation		✓	✓	N/A	N/A	N/A
Stroke		✓	✓	N/A	N/A	N/A
Exercise capacity	✓			✓		✓
Cognitive functioning						✓
Further surgery		✓		N/A	N/A	N/A
Adverse events	✓	✓				
Health related quality of life					✓	✓
Abbreviations used in table: CV, cardiovascular; N/A not applicable.						

Randomised controlled trial quality

This section describes the trial designs and methodology employed in the trials, which may give rise to an increased risk of bias in terms of selection, detection, performance, and attrition bias. Additionally, other potential sources of bias, such as statistical methods used, are also assessed. Table 8 and Table 9 summarises the results of critical appraisal of the included parallel and crossover RCTs, respectively. A more detailed describtption of the quality assessment of the trials can be found in Appendix 3 Quality assessment.

Table 8. Summary of risk of bias assessments of parallel RCTs included in review

Outcome	**Potential source of bias**	**Albertsen 2008**	**DANPACE**	**Nielsen 2003**
		Risk assessment[a]		
	Random sequence generation	?	?	?
	Allocation concealment	?	✓	?
	Selective reporting	✓	x	✓
Mortality	Blinding of participants and personnel	N/A	✓	✓
	Blinding of outcome assessment	N/A	✓	✓
	Incomplete outcome data	N/A	?	✓
Stroke	Blinding of participants and personnel	N/A	✓	✓
	Blinding of outcome assessment	N/A	✓	✓
	Incomplete outcome data	N/A	?	✓
Atrial fibrillation	Blinding of participants and personnel	N/A	?	?
	Blinding of outcome assessment	N/A	?	?
	Incomplete outcome data	N/A	?	✓
Heart failure	Blinding of participants and personnel	?	?	?
	Blinding of outcome assessment	x	?	?
	Incomplete outcome data	✓	?	✓
Requirement of further surgery	Blinding of participants and personnel	N/A	?	N/A
	Blinding of outcome assessment	N/A	?	N/A
	Incomplete outcome data	N/A	✓	N/A
Exercise capacity	Blinding of participants and personnel	?	N/A	N/A
	Blinding of outcome assessment	x	N/A	N/A
	Incomplete outcome data	✓	N/A	N/A

Adverse events	Blinding of participants and personnel	?	N/A*	N/A
	Blinding of outcome assessment	?	N/A*	N/A
	Incomplete outcome data	✓	N/A*	N/A

[a] Key for risk assessment: ✓ = low risk of bias; ? = unclear risk of bias; and x = high risk of bias.

* DANPACE did not report adverse events at implantation at randomisation; however, the indications for reoperations during follow up were detailed, which have been reported as adverse events in this review.

Abbreviation used in table: N/A, not applicable.

Table 9. Summary of risk of bias assessments of crossover RCTs included in review

Outcome	**Potential source of bias**	**Gallick1994**	**Lau 1994**	**Schwaab 2001**
		Risk assessment[a]		
	Random sequence generation	?[a]	?	?
	Allocation concealment	?	?	✓
	Selective reporting	✓	?	x
Exercise capacity	Blinding of participants and personnel	?	N/A	✓
	Blinding of outcome assessment	?	N/A	✓
	Incomplete outcome data	✓	N/A	✓
Cognitive function	Blinding of participants and personnel	N/A	N/A	✓
	Blinding of outcome assessment	N/A	N/A	✓
	Incomplete outcome data	N/A	N/A	✓
Health-related quality of life	Blinding of participants and personnel	N/A	✓	✓
	Blinding of outcome assessment	N/A	✓	✓
	Incomplete outcome data	N/A	✓	✓

[a] Key for risk assessment: ✓ = low risk of bias; ? = unclear risk of bias; and x = high risk of bias.

Abbreviation used in table: N/A, not applicable.

Selection bias

None of the full publications of the included trials described how the randomisation sequence had been generated. However, based on correspondence with the trialists for Albertsen 2008, randomisation was performed in a 1:1 ratio.[41] Each patient was asked to draw one envelope, containing the allocation, from a batch of 10. Albertsen 2008, DANPACE and Schwaab 2001 gave

some details about how the allocation sequence had been concealed from staff involved in the enrolment and assignment of participants. In these studies, the allocation was performed using sealed envelopes before pacemaker implantation (Albertsen 2008[41], DANPACE[42]) or programming of the first pacing mode (Schwaab 2001[48]). Nielsen 2003, Gallick 1994, and Lau 1994 did not describe allocation concealment.[37;38;46]

Performance and detections bias

Participants and investigators were blinded to the pacing mode in Lau 1994 and Schwaab 2001.[38;48] Albertsen 2008, Nielsen 2003 and Gallick 1994 did not describe the trial design regarding blinding.[37;41;46] Based on correspondence with the trialists of DANPACE it was confirmed that this study was an open label trial with participants, trialists and outcome assessors aware of the type of pacemaker and pacing mode in each patient.[42]

In Nielsen 2003, physical examinations and echocardiography were carried out unblinded,[46] unlike Albertsen 2008 where echocardiographic analyses were done blinded to the pacing mode.[41] However, blinding of echocardiography will have only limited impact on the outcomes of interest captured in Albertsen 2008: HF, exercise capacity and adverse events.[41] In DANPACE, a committee adjudicated stroke and thromboembolic events unaware of the assigned pacing mode.[42] Gallick 1994 did not specify the blinding status of any outcome assessors.[37]

Attrition bias

As mentioned previously, DANPACE and Nielsen 2003 had variable length of follow-up of study participants. In both studies, patients were followed up from enrolment to death or end of study, with no loss to follow up.[42;46] In Albertsen 2008, one patient randomised to single-chamber atrial pacing was lost to follow up, which has been accounted for as a treatment failure in the TAG's analyses.[41]

Despite the low number of patients lost to follow up, the number of patients changing pacemaker or pacing mode from the one to which they were randomised was relatively high and uneven between the trial arms in all three parallel RCTs.[41;42;46] In all three trials, a larger number of patients in the single-chamber atrial pacing arm switched to (predominantly) DDDR pacing compared with the number of patients in the dual-chamber pacing arm switching to another pacing mode.

Among the crossover trials, three patients in Lau 1994[38] and two patients in Schwaab 2001[48] were excluded from the trials: reasons for exclusion in Lau 1994 were pacemaker failure (2) and patient

non-compliance (1), and, in Schwaab 2001, development of chronic atrial fibrillation (1) and death (1). As expected, the crossover trials had to exclude participants who did not complete both intervention periods.

Reporting bias

In an early publication of DANPACE outlying the protocol for the study,[43] one of the secondary end points listed was a quality of life evaluation, comprising elements from the general health questionnaire SF-36. However, no result of this outcome was published in either of the identified references linked to this study.[42;45]

All three crossover trials (Gallick 1994, Lau 1994 and Schwaab 2001) reported results for each pacing mode separately, with mean and SE or SD.[37;38;48] Exact p values were not provided for the within patient difference for any of the outcomes: the p value was either not reported, described as non-significant, or reported to be less than a certain value. Lau 1994[38] reported IPD for general well-being (as measured by a visual analogue scale [VAS]) and Gallick 1994[37] reported IPD for exercise time, which were used to calculate the within patient difference for these outcomes. The lack of reporting of p value for the paired t-test for other outcome data in the crossover trials rendered the data unsuitable for meta-analysis.

Statistical analysis

Both DANPACE[42] and Nielsen 2003[46] were suspended before reaching the target number of participants and are consequently under-powered to show a statistically significant difference in the primary outcome; all-cause mortality in DANPACE and changes in left atrium (LA) size and left ventricle (LV) size and function in Nielsen 2003. A total of 450 patients were to be included in Nielsen 2003,[46] but recruitment was stopped after randomisation of 177 patients because recruitment for DANPACE had started. However, recruitment for DANPACE was also stopped early, at 1,415 randomised patients compared with the target of 1,900 patients. [42] This was due to the increasing use of dual-chamber pacemakers with features that prolong or eliminate the AV interval to minimize ventricular pacing in patients with SSS, which were not permitted in the trial, which led to a decrease in the recruitment rate. Also, a planned interim analysis showed that no statistically significant difference could be reached with respect to the primary outcome of all-cause mortality even with the planned 1,900 patients.

Overall trial quality

Overall trial design and methodology were appropriate in the included trials: however, detailed descriptions of randomisation and allocation concealment were sparse. The parallel RCTs were either open label or it was unclear if and how patients, trial personnel and outcome assessors were blinded to the pacing modes. Blinding is likely to have a limited effect on the result of objective outcomes such as mortality, stroke and adverse events; however, for more subjective outcomes, including patient reported outcomes, such as quality of life and HF questionnaires and exercise capacity, there is an increased risk of introducing bias into the results. The two crossover RCTs reporting results on quality of life were both described as double blind. The risk of attrition bias was generally low as few patients were lost to follow up in the parallel RCTs and the crossover trials excluded a small number of patients from the analyses. However, the number of patients in the parallel RCTs who changed pacing mode during the follow up period was uneven between the pacing modes, which may lead to a conservative estimate of the effect of pacing mode.

4.2.2 Assessment of effectiveness

Change in pacing mode

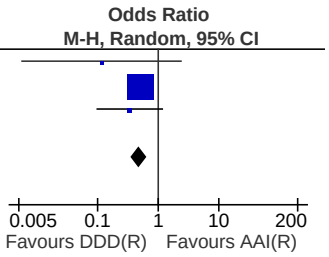
Several patients in the parallel RCTs (Albertsen 2008, DANPACE and Nielsen 2003) changed pacing mode during the study from the one to which they were randomised.[41;42;46] Among the 857 patients randomised to DDDR and 785 to AAIR in the three trials, significantly more people with single-chamber atrial pacing changed pacemaker and pacing mode compared with the dual-chamber pacing group (OR 0.50, 95% Confidence Interval [CI]: 0.37 to 0.67, Figure 2). There was no statistical heterogeneity in the meta-analysis of the three trials and only modest uncertainty; however, the result was mainly driven by the largest and longest trial, DANPACE.

Most patients who changed from AAI(R) changed to DDD(R). The primary reasons for the implantation of a dual-chamber pacemaker in patients with a single-chamber atrial pacemaker were development of high degree AV block, or Wenckebach block during implantation. However, there were also a small number of patients who switched from AAIR to VVI. Patients randomised to DDD(R) who changed pacing mode during implantation or during follow up primarily changed to VVI pacing because of development of persistent atrial fibrillation. One patient was lost to follow up in the AAIR arm of Albertsen 2008, who has been included in this analysis as changing pacing mode.

Figure 2. Results from analysis of change in pacing mode

Study or Subgroup	Dual-chamber pacing Events	Total	Atrial pacing Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Albertsen 2008	0	26	3	24	1.0%	0.12 [0.01, 2.37]
DANPACE 2011	69	708	122	707	92.9%	0.52 [0.38, 0.71]
Nielsen 2003	5	123	6	54	6.1%	0.34 [0.10, 1.16]
Total (95% CI)		**857**		**785**	**100.0%**	**0.50 [0.37, 0.67]**
Total events	74		131			

Heterogeneity: Tau² = 0.00; Chi² = 1.33, df = 2 (P = 0.51); I² = 0%
Test for overall effect: Z = 4.50 (P < 0.00001)



Percent atrial and ventricular pacing

The rate of atrial and ventricular pacing (%) varied greatly among the studies, study arms and pacing mode (Table 10). Differences between studies in the rate of paced atrial or ventricular beats may be associated with differences in other outcome measures. Ventricular pacing has been associated with an increased incidence of AF.[49]

In DANPACE and Nielsen 2003, the percentage of atrial and ventricular pacing was calculated using the mean of the number of paced beats at each follow-up, which was captured by the pacemaker event counters.[42;46] Schwaab 2001 used stored pacemaker histograms to capture % paced beats in the atrium and ventricle.[48] Albertsen 2008[41] and Lau 1994[38] did not describe how % atrial and ventricular pacing was captured, and Gallick 1994[37] did not report data on % atrial or ventricular pacing.

Schwaab 2001 had the highest rate of atrial and ventricular pacing, with patients being paced in both the atrium and ventricle for almost every beat.[48] The amount of atrial pacing was balanced between the trial arms in Schwaab 2001[48] (95–96%) and in DANPACE[42] (58–59%). By contrast, in Albertsen 2008[41] the % atrial pacing was higher in the DDDR (62%) than the AAIR group (53%), and in Nielsen 2003[46] there were similar amounts of atrial pacing in the AAIR (69%) and DDDR-l (67%) group but less in DDDR-s (57%). Lau 1994 did not report % atrial pacing.[38]

The variation between the trials in % ventricular pacing was even greater than for atrial pacing. The ventricular pacing in the dual-chamber pacing arm was 64–66% in Albertsen 2008[41], DANPACE[42] and Lau 1994.[38] However, the dual-chamber pacing arm with the long AV delay in Nielsen 2003[46] (DDDR-l) had only 17% ventricular pacing compared with a ventricular pacing % of above 90% in the dual-chamber pacing arm with short AV delay (DDDR-s) in the same trial. Ventricular pacing was

also above 90% in Schwaab 2001.[48] The programmed AV delay varied between the included studies, which may explain some of the variation in % ventricular pacing.

Table 10. Percent atrial and ventricular pacing

Study	Pacing mode	AV delay	% ventricular pacing	% atrial pacing
Parallel RCTs				
Albertsen 2008	DDDR	paced AV delay max 220–225 ms	66	62
	AAIR	N/A	2 patients, 3% and 99%, respectively*	53
DANPACE	DDDR	mean max paced AV delay 225 ± SD 39 ms	65 ± SD 33	59 ± 31
	AAIR	N/A	103/122 patients, 53 ± SD 35*	58 ± 29
Nielsen 2003	DDDR-s	150 ms	90	57
	DDDR-l	300 ms	17	67
	AAIR	N/A	NR*	69
Crossover RCTs				
Gallick 1994	DDDR	100 ms	NR	NR
	AAIR	N/A	N/A	NR
Lau 1994	DDDR	96 ± 7 to 140 ± 5 ms	64 ± 11	NR
	AAIR	N/A	N/A	NR
Schwaab 2001	DDDR	AV-delay was optimised based on the maximum time velocity integral of the aortic flow	99 ± 2	95 ± 5
	AAIR	N/A	N/A	96 ± 5

* % ventricular pacing for patients in the single-chamber atrial pacemaker group who upgraded to dual-chamber pacemaker

Abbreviations used in table: AV delay, atrioventricular delay; ms, millisecond; N/A, not applicable; NR, not reported; RCTs, randomized controlled trials.

All-cause mortality

DANPACE and Nielsen 2003 reported all-cause mortality.[42;46] With 831 people randomised to DDDR pacing and 761 patients to AAIR pacing in total, there were fewer deaths among patients with

dual-chamber pacing than single-chamber atrial pacing, but the difference was not statistically significant (OR 0.97, 95% CI: 0.67 to 1.41; Figure 3).

The large DANPACE trial, which stopped recruitment before reaching the planned 1,900 patients, was not powered to detect a difference in mortality between the two pacing modes.[42] However, from a planned interim analysis of DANPACE, it was calculated that no statistically significant difference in all-cause mortality would have been observed even if all 1,900 patient had been recruited. As the meta-analysis of DANPACE and Nielsen 2003 considers only 1,592 patients it is unlikely to have sufficient power to identify a statistically significant difference. The breakdown of the number of deaths in the two DDD trial arms in Nielsen 2003 is shown in Table 11.[46]

Figure 3. Results from analysis of all-cause mortality

Study or Subgroup	Dual-chamber pacing Events	Total	Atrial pacing Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
DANPACE 2011	193	708	209	707	83.0%	0.89 [0.71, 1.13]
Nielsen 2003	28	123	9	54	17.0%	1.47 [0.64, 3.38]
Total (95% CI)		**831**		**761**	**100.0%**	**0.97 [0.67, 1.41]**
Total events	221		218			

Heterogeneity: Tau² = 0.03; Chi² = 1.30, df = 1 (P = 0.25); I² = 23%
Test for overall effect: Z = 0.15 (P = 0.88)

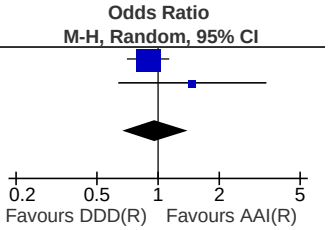


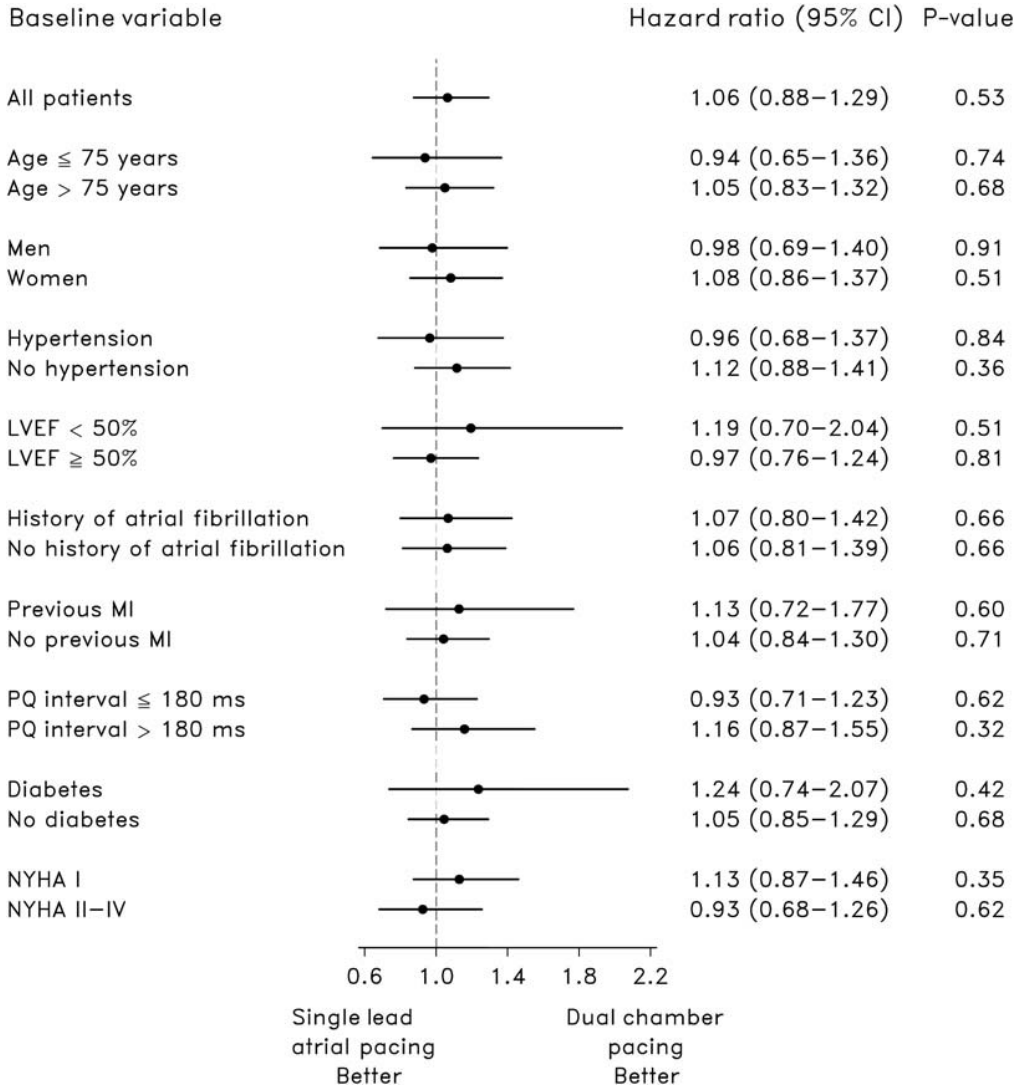
Table 1. Results of all-cause mortality by trial arm in Nielsen 2003[46]

Outcome	Dual-chamber pacing				Atrial pacing		p value
	DDDR-s		DDDR-I		AAIR		
	n	N	n	N	n	N	
Mortality	14	60	14	63	9	54	0.51
Abbreviations used in table: n, number of patients with an events; N, total number of patients.							

DANPACE, for which the primary outcome was all-cause mortality, presented this outcome as a HR.[42] The HR presented in the full publication was in line with the meta-analysis of mortality OR of the two included trials. The unadjusted HR for AAIR pacing versus DDDR pacing was 1.06 (95% CI: 0.88 to 1.29, p = 0.53). The HR after adjustment for baseline variables (age, gender, prior history of atrial fibrillation, prior myocardial infarction, left ventricular ejection fraction [LVEF] < 50%, and hypertension) was 0.94 (95% CI: 0.77 to 1.14, p = 0.52) for AAIR pacing versus DDDR pacing. The all-cause mortality incidence was similar in all predefined subgroups (age > or ≤ 75 years; gender; hypertension; LVEF < or ≥ 50%; history of atrial fibrillation; previous myocardial infarction; PQ

interval > or ≤ 180 ms; diabetes; NYHA I or II–IV), with the smallest p value for interaction of 0.45 (Figure 4).

Figure 4. Subgroup analyses of all-cause mortality in DANPACE[42]



Abbreviations used in figure: CI, confidence interval; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association functional class.

In Albertsen 2008, which did not report mortality as an outcome, one patient was lost to follow up in the AAIR group, who may have died within the follow up period.[41]

Heart failure

HF was reported in all three parallel RCTs (Albertsen 2008, DANPACE and Nielsen 2003). However, the outcome measures varied between the studies (Table 12).[41;42;46] In the three trials, HF was captured as: NYHA class at end of follow up; number of patients taking diuretics; HF leading to hospitalisation; number of cases of new HF (defined as new NYHA class IV or new NYHA class III with the presence of oedema and/or dyspnoea); number of patients with an increase in consumption of diuretics; and number of patients with an increase in at least one NYHA class.

All the outcome measures for HF with a reported measure of uncertainty consistently showed no statistically significant difference between dual-chamber and single-chamber atrial pacing (Table 12). However, because of low event rates or relatively small sample sizes the uncertainty was large around the HF outcome measures reported by Nielsen 2003[46] (patients with increased consumption of diuretics, patients with at least one NYHA class increase) and HF leading to hospitalisation, reported by DANPACE.[42]

Predefined subgroup analyses in DANPACE showed a statistically significant difference between single-chamber atrial pacing and dual-chamber pacing for patients aged ≤ 75 years and patients aged > 75 years in the number of patients developing new heart failure.[42] In the younger subgroup (≤ 75 years) patients with AAIR were at a lower risk of developing heart failure than with DDDR (HR 0.72, 95% CI: 0.53 to 1.00), and in the older subgroup (> 75 years) patients were at a higher risk when on AAIR (HR 1.34, 95% CI: 1.00 to 1.80). All other subgroup analyses were non-significant (gender; hypertension; LVEF < or ≥ 50%; previous myocardial infarction; PQ interval > or ≤ 180 ms; NYHA I or II–IV; diuretics, p > 0.31).

Table 12. Results of reported measures of heart failure

Study		**Time point**	**Dual-chamber pacing**				**Atrial pacing**		**Estimate of effect**	**p value**
			n	**N**	**n**	**N**	**n**	**N**		
Albertsen 2008					DDD(R)		AAI(R)			
NYHA class	I II III IV	Baseline	N/A	N/A	18 8 0 0	26	19 3 2 0	24	NR	NR

	I II III IV	End of follow up	N/A	N/A	14 10 1 1	26	18 5 0 0	23*	NR	NR
DANPACE					DDDR		AAIR		AAIR vs DDDR	
NYHA class	I II III IV	Baseline	N/A	N/A	522 158 24 2	708	503 172 29 0	707	NR	NR
NYHA class	I II III IV	End of follow up	N/A	N/A	341 260 61 4	666	364 231 67 4	666	NR	0.43
Patients on diuretics		End of follow up	N/A	N/A	328	708	324	707	NR	0.89
Heart failure (leading to hospitalisation)		End of follow up	N/A	N/A	28	708	27	707	HR 1.06	0.84
New heart failure (new NYHA IV or III + symptoms)		End of follow up	N/A	N/A	169	708	170	707	Unadjusted	
									HR 1.00	0.87
									Adjusted	
									HR 1.09	0.44
Nielsen 2003			DDDR-s		DDDR-l		AAIR			
Patients with increased consumption of diuretics		End of follow up	19	60	13	63	15	54	NR	0.34
Patients with at least one NYHA class increase		End of follow up	18	60	29	63	17	54	NR	0.17

Data for the one patient lost to follow up in the AAIR arm of Albertsen 2008 have not been imputed.[41]

Abbreviations used in table: n, number of patients with an events; N, total number of patients; NYHA, New York Heart Association; N/A, not applicable; NR, not reported.

Atrial fibrillation

DANPACE and Nielsen 2003 reported results on the incidence of AF.[42;46] In both DANPACE and Nielsen 2003, AF was diagnosed by standard 12-lead ECG at planned follow up visits. In DANPACE, AF was defined as either paroxysmal (the first diagnosis of AF detected in the ECG and verified by

the pacemaker telemetry at a planned follow-up visit) or chronic (AF at two consecutive follow-up visits and at all subsequent follow-up visit). The results of paroxysmal and chronic AF have been combined to simplify the comparison with the results from Nielsen 2003 (Table 13), but they are also reported separately (Table 14).

Nielsen 2003 showed that the risk of developing AF with dual-chamber pacing was significantly higher than with single-chamber atrial pacing (OR 3.19, 95% CI: 1.05 to 9.67, Table 13).[46] A sensitivity analysis of the DDDR-l and DDDR-s trial arms analysed separately, similarly show a larger proportion of patients developing AF in either dual-chamber pacing arms than in the trial arm paced with a single-chamber atrial pacemaker (Table 13). In the sensitivity analysis the single-chamber atrial pacing group has been split in two, so as to avoid double counting of patients.

Table 13. Results of analysis and sensitivity analysis of atrial fibrillation in Nielsen 2003[46]

Study	**Outcome**	**Dual-chamber pacing**		**Atrial pacing**		**Effect estimate DDDR vs AAIR***	
		n	**N**	**n**	**N**	**OR**	**95% CI**
Nielsen 2003	Atrial fibrillation	25	123	4	54	3.19	1.05-9.67
Sensitivity analysis	Subgroup	n	N	n	N	OR	95% CI
Nielsen 2003	DDDR-l	11	63	2	27	2.64	0.54–12.84
	DDDR-s	14	60	2	27	3.80	0.80–18.10

*OR and 95% CI calculated by TAG.

Abbreviations used in table: CI, confidence interval; n, number of patients with an events; N, total number of patients; OR, odds ratio.

In contrast to the results in Nielsen 2003,[46] in DANPACE, the risk of developing paroxysmal AF was significantly lower with dual-chamber pacing compared with single-chamber atrial pacing (OR 0.75, 95% CI: 0.59 to 0.96; Table 14).[42] By contrast, there was no statistically significant difference identified between dual-chamber and single-chamber atrial pacing when focusing on the number of patients who developed chronic AF (OR 0.96, 95% CI: 0.68 to 1.33, Table 14): there was substantial uncertainty identified in this analysis.

The HRs for paroxysmal and chronic AF reported in DANPACE (unadjusted and adjusted for age, gender, prior history of AF, prior myocardial infarction, LVEF < 50%, and hypertension), comparing single-chamber atrial pacing with dual-chamber pacing support the analyses (Table 15).

Table 14. Results of analysis of chronic and paroxysmal atrial fibrillation based on data from DANPACE[42] (effect estimate generated by TAG)

Study	**Outcome**	**Dual-chamber pacing**		**Atrial pacing**		**Effect estimate DDDR vs AAIR***	
		n	**N**	**n**	**N**	**OR**	**95% CI**
DANPACE	Paroxysmal AF	163	708	201	707	0.75	0.59–0.96
	Chronic AF	76	708	79	707	0.96	0.68–1.33

*OR and 95% CI calculated by TAG

Abbreviations used in table: AF, atrial fibrillation; CI, confidence interval; n, number of patients with an events; N, total number of patients; OR, odds ratio.

Table 15. Results of unadjusted and adjusted analysis of chronic and paroxysmal atrial fibrillation in DANPACE[42]

Study	**Outcome**	**Dual-chamber pacing**		**Atrial pacing**		**Unadjusted effect estimate AAIR vs DDDR**		**Adjusted effect estimate AAIR vs DDDR**	
		n	**N**	**n**	**N**	**HR**	**95% CI**	**HR**	**95% CI**
DANPACE	Paroxysmal AF	163	708	201	707	1.27	1.03–1.56	1.24	1.01–1.52
	Chronic AF	76	708	79	707	1.02	0.74–1.39	1.01	0.74–1.39

Abbreviations used in table: n, number of patients with an events; N, total number of patients; HR, hazard ratio; CI, confidence interval; AF, atrial fibrillation.

There are several possible reasons for the disparity in the result of AF between DANPACE and Nielsen 2003, including differences in baseline characteristics of patients enrolled in the studies, and differences in pacemaker programming.[42;46] Various hypotheses have been put forward around factors that may have an effect on the incidence of AF:

- *Previous history of AF*. In DANPACE the strongest predictor of paroxysmal AF was prior history of AF (HR 3.23, 95% CI: 2.59 to 4.03, p = 0.001).[42] Though, the DDDR and AAIR pacing arms being well balanced for previous AF at baseline. Nielsen 2003 did not report previous history of AF; however, they did report a breakdown of the underlying pacing indications including BTS, in which the tachyarrhythmia often is AF. In Nielsen 2003 there was an imbalance in the number of patients with BTS, with a larger proportion among patients in the two dual-chamber pacing arms than in the single-chamber pacing arm. Nielsen 2003 showed a correlation between BTS at implantation and an increased risk of AF (relative risk 3.3 [95% CI: 1.3 to 8.1], p = 0.01).[46]
- *PQ interval*. The result of a subgroup analysis of 650 patients in the DDDR group in DANPACE indicates that a longer baseline PQ-interval (> 180 ms) is associated with an increased risk of AF (p < 0.001).[42] There was a slight difference in PQ-interval at baseline between the studies, however, the PQ-interval was well balanced between the different trial arms within each study (Table 16).[42;46]

Table 16. PQ interval at baseline in DANPACE[42] and Nielsen 2003[46]

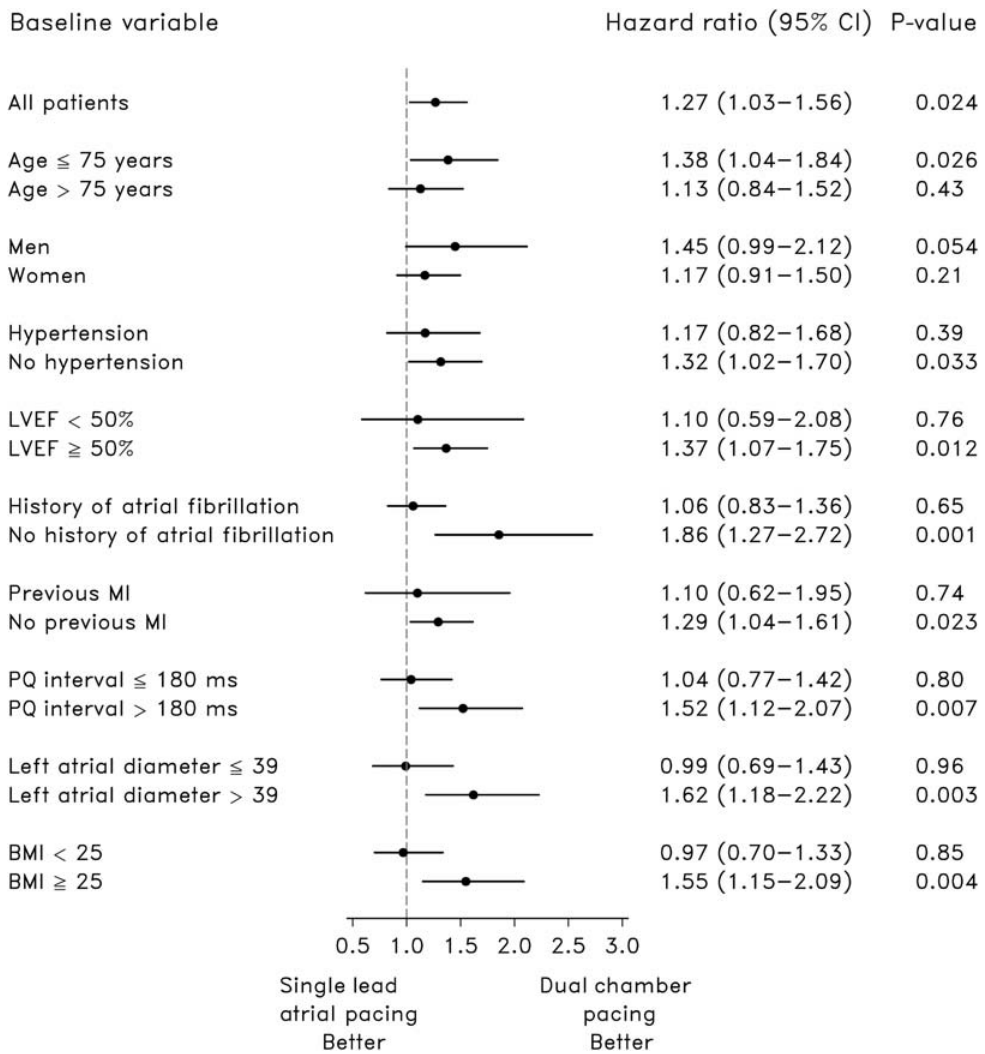
Baseline characteristic	Nielsen 2003			DANPACE	
	DDDR-s	DDDR-l	AAIR	DDDR	AAIR
PQ baseline (ms)	183 ± 28	184 ± 27	186 ± 27	179 ± 30	179 ± 29
Abbreviation used in table: ms, millisecond.					

- *Programmed AV interval and % ventricular pacing*. Both DDDR and AAIR preserve AV synchrony. However, in AAIR, normal ventricular activation pattern is preserved, whereas DDDR causes some degree of unnecessary ventricular pacing with changes to the ventricular activation and contraction pattern, which has been associated with an increased risk of AF.[49;50] The programmed AV delay is closely linked to the resulting % ventricular pacing; the DDDR-l arm in Nielsen 2003[46] had a programmed AV delay of 300 ms and just 17% ventricular pacing, whereas the DDDR-s arm had an AV delay of 150 ms and 90% ventricular pacing. In DANPACE[42] the patients in the DDDR arm had an AV delay and % ventricular pacing in the middle of the range observed in Nielsen 2003[46] (225 ± 39 ms and 65 ± 33 %, respectively) (Table 10). However, in Nielsen 2003, there were significantly more patients with AF in both the DDDR-l and the DDDR-s arms than in the AAIR group, despite having low and high % ventricular pacing, respectively.[46] A subgroup analysis of 650 patients with a

DDDR pacemaker in DANPACE showed no statistically significant association between % ventricular pacing or the length of the AV delay and risk of AF.[44]

Both DANPACE and Nielsen 2003 seem to be of good quality, although there are some differences in the methods (e.g., programmed AVI) and in the baseline characteristics of the patients in the two studies. However, DANPACE[42] is almost 10 times the size of Nielsen 2003[46] and it has a longer mean follow up (5.4 ± 2.6 compared with 2.9 ± 1.1 years, respectively); thus, it is reasonable to have more confidence in the results from DANPACE compared with the Nielsen 2003 study.

Figure 5. Subgroup analyses of paroxysmal atrial fibrillation in DANPACE[42]



Abbreviations used in figure: BMI, body mass index; CI, confidence interval; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

Subgroup analyses of paroxysmal AF in DANPACE showed a statistically significant difference between the subgroups of patients with and without a prior history of AF, body-mass index (BMI) ≥ or < 25, and a left atrial diameter > or ≤ 39 mm at baseline (Figure 5).[42] In these three subgroups the incidence of paroxysmal AF was lower with DDDR than AAIR pacing in patients without a prior history of AF, a higher body-mass index, and a dilated left atrium at baseline ($p < 0.05$). The subgroup analysis of patients with different PQ interval > or ≤ 180 ms indicated a lower risk of paroxysmal AF with DDDR than AAIR pacing in patients with a longer PQ interval ($p = 0.084$). The p values for all other interaction were greater than 0.34.

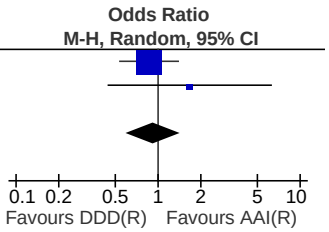
Stroke

DANPACE and Nielsen 2003 captured the number of patients suffering a stroke as an outcome. In Nielsen 2003, the diagnosis of stroke was given when neurological symptoms of presumably cerebral ischemic origin persisted for more than 24 h, or if patients died within 24 h from an acute cerebrovascular event.[46] The definition of stroke In DANPACE was similar: the sudden development of focal neurological symptoms lasting more than 24 h.[42] As for several other outcomes, the number of events was low, the uncertainty considerable, and no statistically significant difference was shown (OR 0.93, 95% CI: 0.60 to 1.45, Figure 6Figure 6.).

Figure 6. Results from analysis of stroke

	Dual-chamber pacing		Atrial pacing			Odds Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
DANPACE 2011	34	708	39	707	88.6%	0.86 [0.54, 1.39]
Nielsen 2003	11	123	3	54	11.4%	1.67 [0.45, 6.24]
Total (95% CI)		**831**		**761**	**100.0%**	**0.93 [0.60, 1.45]**
Total events	45		42			

Heterogeneity: Tau² = 0.00; Chi² = 0.85, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 0.31 (P = 0.75)



DANPACE reported an unadjusted HR for stroke of 1.13 (95% CI: 0.72 to 1.80, $p = 0.59$) for patients with single-chamber atrial pacing compared with dual-chamber pacing.[42] The HR when adjusted for age, gender, prior history of AF, hypertension, and prior stroke was similar (HR 1.11, 95% CI: 0.70 to 1.77, $p = 0.65$).

The breakdown of the number of patients suffering a stroke in the trial arms in Nielsen 2003 is shown in Table 17.[46]

Table 17. Results of stroke by trial arm in Nielsen 2003[46]

Outcome	Dual-chamber pacing				Atrial pacing		p value
	DDDR-s		DDDR-l		AAIR		
	n	N	n	N	n	N	
Stroke	7	60	4	63	3	54	0.32
Abbreviations used in table: n, number of patients with an events; N, total number of patients.							

Exercise capacity

Exercise capacity was measured in the parallel RCT Albertsen 2008[41] and the crossover trials Gallick 1994[37] and Schwaab 2001.[48] Albertsen 2008 used the 6-minute walking test (6MWT) to test exercise tolerance / capacity.[41] The 6MWT measures the distance an individual is able to walk over a total of 6 minutes on a hard, flat surface. In Gallick 1994, exercise capacity was tested through an upright bicycle exercise.[37] The initial workload was 200 kpm, which was increased incrementally by 200 kpm every 3 minutes. The aim was to achieve a peak heart rate ≥ 85% predicted by age, and the outcome measure was exercise time. Schwaab 2001 used bicycle ergometry by incremental exercise test to exhaustion, using workload increments of 15 Watt/min.[48] Outcome measures included total exercise duration and maximum workload.

Gallick 1994[37] presented individual patient data for exercise duration whereas Schwaab 2001[48] presented only data for the individual treatment periods, but results of paired t tests of the within patient difference were only reported as significant or not, without numerical detail of p values.

In Albertsen 2008 there was no statistically significant difference between the trial arms in the 6MWT at baseline, but, at 12 months' follow up, patients with a single-chamber atrial pacemaker walked significantly further than patients with a dual-chamber pacemaker (Table 18).[41] Although the result was statistically significant and the mean difference just reached the minimal clinically important difference of 54–80 meters,[51] there was substantial uncertainty around this value. One patient in the single-chamber atrial pacing group was lost to follow up during the study, which may have had a small impact on the overall result.

Schwaab 2001 also showed a significantly better exercise capacity with single-chamber atrial pacing compared with dual-chamber pacing for bicycle exercise duration and workload.[48] However, Gallick 1994 did not detect a statistically significant difference between the pacing modes for a similar

bicycle test.[37] It is noteworthy that Gallick 1994 evaluated pacemakers over a markedly shorter test period, with both pacing modes tested in the same day with 0.5 to 1 hour rest between modes, which may partly explain the difference in result between Gallick 1994 and Schwaab 2001. However, as with the 6MWT in Albertsen 2008, there was substantial uncertainty around the result of the exercise testing in both Schwaab 2001 and Gallick 1994.

Table 18. Results of reported measures of exercise capacity

Parallel RCT	**Timeframe**	**Dual-chamber pacing**			**Atrial pacing**			**p value**
		mean	**SD**	**N**	**mean**	**SD**	**N**	
Albertsen 2008								
Six-minute walking test (m)	Baseline	415	76	26	444	105	24	NS
	12 months	446	96	26	500	89	23	<0.05

Crossover RCT	**N**	**Dual-chamber pacing**		**Atrial pacing**		**Within patient difference**	
		mean	**SD**	**mean**	**SD**	**mean**	**p value**
Gallick 1994							
Exercise duration* (sec)	12	416	140	411	122	6	0.74
Schwaab 2001							
Exercise duration (sec)	19	402	102	423	127	-21	<0.05
Maximum workload (Watt)	19	96	27	103	31	-7	<0.05

*Calculated from individual patient data.

Abbreviations used in table: N, total number of patients; NS, not significant; SD, standard deviation.

Further surgery

One of the outcomes in DANPACE was pacemaker reoperation during follow up.[42] The need for pacemaker reoperation was decided by the physician in charge of follow-up. There were significantly fewer participants in the DDDR arm needing a reoperation compared with the AAIR arm (OR 0.48, 95% CI: 0.36 to 0.63, Table 19) during the relatively long-term follow up in DANPACE (5.4 ± 2.6 years). The difference in reoperations between the pacing modes was statistically significant with only modest uncertainty around the result. Need for surgical change of pacing mode was the only reason for reoperation for which the difference between the pacing modes was statistically significant (Table

20). The reported unadjusted and adjusted HRs for AAIR versus DDDR pacing are also listed in Table 19.

Table 19. Results of unadjusted and adjusted analysis of reoperations in DANPACE[42]

Dual-chamber pacing		Atrial pacing		Effect estimate DDDR vs AAIR*		Unadjusted effect estimate AAIR vs DDDR		Adjusted effect estimate AAIR vs DDDR	
n	N	n	N	OR	95% CI	HR	95% CI	HR	95% CI
84	708	156	707	0.48	0.36 to 0.63	1.99	1.53 to 2.59	2.00	1.54 to 2.61

*OR and 95% CI calculated by TAG

Pacemaker reoperation was adjusted for age, gender, prior history of AF, prior myocardial infarction, LVEF < 50%.

Abbreviations used in table: CI, confidence interval; HR hazard ratio; n, number of patients with an events; N, total number of patients; OR, odds ratio.

Table 20. Results per indication for reoperation in DANPACE[42]

Indication	Dual-chamber pacing		Single-chamber atrial pacing		p value
	n	N	n	N	
Battery depletion	42	708	59	707	0.09
Need for surgical change of mode of pacing	4	708	66	707	<0.001
Lead complications	30	708	37	707	0.42
Surgical or mechanical complications	7	708	10	707	0.52
Infection	3	708	3	707	0.98
Skin erosion	3	708	1	707	0.31
Device failure	2	708	2	707	0.99

Abbreviations used in table: n, number of patients with an events; N, total number of patients.

Adverse effects of pacemaker implantation

Although all three parallel group RCTs randomised patients by device, only two of the trials reported data on adverse effects linked to pacemaker implantation: Albertsen 2008 and DANPACE.[41;42] Albertsen 2008 looked at complications around implantation; in the 50 randomised participants there

were no lead displacements, infections or haematomas at pacemaker implantation (Table 21).[41] No other peri- or postoperative adverse effects of pacemaker implantation were reported. One patient in the single-chamber atrial pacing group was lost to follow up during the study that could have had an adverse event after withdrawing from the trial.

DANPACE did not report adverse effects at implantation at randomisation; however, the indications for reoperations during follow up were detailed.[42] Of 1,415 patients, 240 underwent one or more reoperations during the follow up period (Table 19). The more frequent indications for reoperation were battery depletion, lead complications and need for change of pacing mode (Table 20). Less common adverse effects leading to reoperation were surgical or mechanical complications, infection, skin erosion, or device failure. The only indication that was significantly different between the dual-chamber and single-chamber atrial pacemaker arm was surgical change in pacing mode.

Table 21. Complications at implantation in Albertsen 2008[41]

Complication	Dual-chamber pacing		Atrial pacing	
	n	N	n	N
Lead displacements	0	26	0	24
Infections	0	26	0	24
Haematomas	0	26	0	24
Abbreviations used in table: n, number of patients with an events; N, total number of patients.				

Health related quality of life and symptoms

Quality of life was studied in the crossover trials Lau 1994 and Schwaab 2001.[38;48] Both studies used different instruments to measure symptoms, quality of life and functional status. Lau 1994 used: visual analogue scale (VAS) for general well-being; SAS functional questionnaire for physical capacity (described in Section 2.1.6); 12-item General Health Questionnaire, symptom questionnaire; and the somatic symptoms inventory (SSI) adapted for local use from the Bradford Somatic Inventory.[38] The 12-item General Health Questionnaire is a measure of current mental health. Each item is rated on a four-point scale (less than usual, no more than usual, rather more than usual, or much more than usual). The symptom questionnaire assessed the incidence and frequency of dyspnoea, palpitations, dizziness, chest pain, sleep disturbance, and neck pulsations, rated between 1 (all the time) and 5 (never). The SSI measures: adequacy of daily life activities, emotional adjustment, social interactions (frequency, range and quality), work adjustment, sleep, fatigue and appetite.

Schwaab 2001 used three different self-administered questionnaires relevant to this review: VAS for general well-being, physical, emotional, and cognitive functioning; VAS Karolinska questionnaire including 16 questions on cardiovascular symptoms relevant to pacemaker patients; and SAS functional questionnaire.[48]

Lau 1994[38] presented individual patient data for general well-being, however, for all other outcomes of interest, Lau 1994 and Schwaab 2001[48] presented data for only the individual treatment periods, but results of paired t tests of the within patient difference were only reported as significant or not, without numerical detail of p values.

General wellbeing and functional status

General well-being was similar across Lau 1994 and Schwaab 2001.[38;48] There was no statistically significant difference between the pacing mode in either trial (**Error! Reference source not found.** 2). For functional status, the results were also similar between the trials with no statistically significant difference between the pacing modes. Although both trials were relatively small and with limited follow up, and there was a substantial amount of uncertainty around these results.

Table 22. Results for general well-being, visual analogue scale

Outcome	**Dual-chamber pacing**		**Atrial pacing**		**Within patient difference**	
	mean	**SD**	**mean**	**SD**	**mean**	**p value**
General well-being						
Lau 1994*	7.1	1.2	6.8	1.3	0.25	0.32
Schwaab 2001	67	20	67	23	0	NS
SAS						
Lau 1994	1.5	0.2	1.4	0.2	0.1	NS
Schwaab 2001	1.6	0.74	1.6	0.67	0	NS

*Calculated from individual patient data.

Abbreviations used in table: NS, not significant; SD, standard deviation.

Multi-dimensional measures

In Schwaab 2001, one of the multi-dimensional quality of life questionnaires (self-perceived health status) included a section on cognitive function, an outcome specified in the scope of this review.[48] Schwaab 2001 was the only included study to capture this outcome. There was no statistically significant difference between dual-chamber and single-chamber atrial pacing mode for cognitive functioning or the other elements of the self-perceived health status questionnaire in Schwaab 2001 (Table 23). Similarly there was no statistically significant difference between the pacing modes for tests of mental well-being (12-GHQ, SSI), or for most symptoms in either Lau 1994 or Schwaab 2001 (Table 23).[38;48] Schwaab 2001 did report patients experienced less dizziness with single-chamber atrial pacing than with dual-chamber pacing ($p < 0.05$), where Lau 1994 did not find a difference for the same symptom.

The results of the multi-dimensional quality of life measures are limited by the same factors as the results for general well being and functional status: both trials were relatively small and with limited follow up, and there was a substantial amount of uncertainty around the results.

Table 23. Results for multi-dimensional quality of life measures

Outcome	**Dual-chamber pacing**		**Single-chamber atrial pacing**		**Within patient difference**	
	mean	**SD**	**mean**	**SD**	**mean**	**p value**
Lau 1994						
12-item General Health Questionnaire	14.3	SE 2.2	15.2	SE 2.1	–0.9	NS
The somatic symptoms inventory	71.5	SE 3.3	70.2	SE 3.5	1.3	NS
Activities of daily living	31.2	2.0	32.8	2.1	–1.6	NS
Emotional adjustment	24.2	1.7	23.2	1.8	1.0	NS
Social interactions						
Frequency	11.3	1.1	11.8	1.2	–0.5	NS
Range	2.1	0.2	2.2	0.3	–0.1	NS
Quality	21.5	1.2	22.4	1.1	–0.9	NS
Work adjustment	0.4	0.1	0.3	0.1	0.1	NS
Sleep	0.3	0.1	0.3	0.1	0.0	NS

Fatigue	0.6	0.1	0.6	0.1	0.0	NS
Appetite	0.2	0.1	0.1	0.1	0.1	NS
Symptoms (1–5)						
Dyspnoea	3.4	0.45	3.95	0.25	–0.55	NS
Palpitations	4.25	0.25	3.95	0.3	0.3	NS
Dizziness	4.25	0.25	3.95	0.3	0.3	NS
Chest pain	4.55	0.25	4.6	0.25	–0.05	NS
Sleep disturbance	4.2	0.25	4.6	0.2	–0.4	NS
Neck pulsations	4.95	0.1	4.95	0.1	0	NS
Schwaab 2001						
Self perceived health status (%)						
General well-being	67	20	67	23	0	NS
Physical functioning	59	25	56	25	3	NS
Emotional functioning	63	27	63	27	0	NS
Cognitive functioning	56	23	51	27	5	NS
Karolinska questionnaire (%)						
Chest pain	73	20	76	19	–3	NS
Palpitations	78	17	79	20	–1	NS
Dizziness	71	16	82	11	–11	< 0.05
Dyspnoea	67	24	71	20	–4	NS
Abbreviations used in table: NS, not significant; SD, standard deviation; SE, standard error.						

4.3 Discussion

4.3.1 Summary of quantity and quality of research available

The systematic review of clinical effectiveness identified six RCTs of relevance to this MTA. Three of these were of a parallel group design and three were crossover trials. The trials all evaluated the efficacy of dual-chamber pacing compared with single-chamber atrial pacing in people with symptomatic bradycardia due to SSS, with no evidence of impaired AV conduction.

Both parallel group and crossover trials are appropriate designs for the evaluation of pacing modes. In crossover trials, it is easy to switch between pacing modes with implantation of dual-chamber pacemakers, and there is negligible concern for carry over effects or the need for a wash-out period between pacing modes. Crossover trials have an advantage over parallel group trials due to higher

power to detect a difference between interventions for the same number of participants. However, the crossover trials including in this review had small patient numbers (12–21 patients) and short durations (up to 3 months), which limited the outcomes that could reasonably be captured and the power to detect any differences between the pacing modes. The crossover trials provided data on exercise capacity, symptoms and quality of life measures.

The parallel group RCTs were larger (50–1,415 patients) with longer follow up (mean follow-up from 1 to 5.4 years mean) than the crossover trials. The parallel RCTs captured mortality, HF, AF, stroke, need for reoperation, exercise capacity and adverse events of pacemaker implantation. No quality of life measures were reported in any of the parallel RCTs. The parallel RCTs were trials of device whereas the crossover trials were trials of pacing mode programming.

The quality of the trials was generally high, with appropriate trial design and methodology. The trials appeared to be appropriately randomised with a low number of participants excluded or lost to follow up. DANPACE was an open-label trial whereas the blinding in the other two parallel RCTs was unclear. However, blinding is likely to have a limited effect on the result of objective outcomes such as mortality, stroke, AF and adverse events captured in these trials. For more subjective outcomes, including patient reported outcomes such as quality of life and HF questionnaires, and exercise capacity, there is an increased risk of introducing bias in the results. However, the two crossover RCTs reporting results on quality of life were both described as double blind. The baseline characteristics were similar between the trial arms and across the parallel, and crossover RCTs. However, in Nielsen 2003, there were more people with brady-tachy syndrome in the dual-chamber pacing groups than in the single-chamber atrial pacing group. DANPACE was the only one of the included trials reporting previous history of AF, which was balanced between the trial arms. The number of patients in the parallel RCTs who changed pacing mode during the follow up period was uneven between the trial arms, which may lead to a conservative estimate of the effect of pacing mode for certain outcomes.

4.3.2 Summary of assessment of clinical effectiveness

- Dual chamber pacing was associated with a statistically non-significant improvement in mortality in Nielsen 2003 and DANPACE. The meta-analysis strengthens this conclusion. However, the meta-analysis is unlikely to have sufficient power to identify a statistically significant difference.

- In the three parallel RCTs (Albertsen 2008, DANPACE, and Nielsen 2003) the incidence of heart failure was captured using a wide range of measures, which limited the possibility to meta-analys data for heart failure. Dual-chamber pacing was not associated with a statistically significant difference in heart failure compared to single-atrial pacing for any of the outcome measures. In a subgroup analysis DANPACE showed that younger patients (≤ 75 years) with AAIR were at a lower risk of developing heart failure than with DDDR (HR 0.72, 95% CI: 0.53 to 1.00), and older patients (> 75 years) were at a higher risk when on AAIR (HR 1.34, 95% CI: 1.00 to 1.80).

- There were conflicting results for AF from DANPACE and Nielsen 2003. Dual-chamber pacing was associated with a statistically significant increase in AF in Nielsen 2003 (OR 3.19, 95% CI: 1.05 to 9.67), whereas in 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 improvement in chronic AF. The disparity in the results between DANPACE and Nielsen 2003 may have many causes, including differences in baseline characteristics such as pacing indication, prior history of AF, and PQ interval. Other factors may include differences in intervention, which is, programming of AV delay leading to difference in % ventricular pacing. However, DANPACE is by far the largest study with the longest follow up and balanced baseline characteristics; thus, it is reasonable to have more confidence in the results from DANPACE than Nielsen 2003.

- In a meta-analysis of data from DANPACE and Nielsen 2003 dual chamber pacing was not associated with a statistically significant improvement in the risk of stroke.

- There were limited data (relatively small number of patients with limited follow up) on exercise capacity showing a small, but statistically significant improvement with single-chamber atrial pacing compared with dual-chamber pacing in one parallel (Albertsen 2008) and one crossover trial (Schwaab 2001). One additional short-term crossover trial showed no statistically significant difference for this outcome.

- In the three parallel RCTs (Albertsen 2008, DANPACE, and Nielsen 2003), single-chamber atrial pacing was associated with a statistically significant increase in patients changing pacing mode compared with patients with dual-chamber pacing (OR 0.50, 95% CI: 0.37 to 0.67). For people implanted with a single-chamber atrial pacemaker, the need to change

pacing mode was predominantly a result of the development of AV block requiring upgrade to a dual-chamber pacemaker.

- DANPACE was the only trial which specifically looked at reoperations, which showed a statistically significant difference in the need for reoperations with significantly fewer participants with dual-chamber pacing needing a reoperation compared with patients with single-chamber atrial pacing (OR 0.48, 95% CI: 0.36 to 0.63). In line with the results of change in pacing mode, the difference in reoperations was primarily driven by a surgical need for change of pacing mode in patients with single-chamber atrial pacemakers.

- Adverse effects of pacemaker implantation were poorly reported. Albertsen 2008 reported no complications at implantation. DANPACE reported indications for reoperations of which the more frequent indications were battery depletion, lead complications and need for surgical change of pacing mode. The latter was significantly less common in dual-chamber pacing compared with single-chamber atrial pacing.

- HRQoL and symptoms were assessed in two small crossover trials with limited follow up using a wide range of measures. No statistically significant difference was shown between dual-chamber and single-chamber atrial pacing for general well-being, functional status, or multi-dimensional quality of life measures including for cognitive functioning.

4.3.3 Generalisability of results

DANPACE is a relatively large trial of good quality and good follow up, which gives a reasonable evidence base for dual-chamber pacing compared with single-chamber atrial pacing for people with SSS without evidence of impaired AV conductance. The additional studies identified in this review had small sample sizes and short follow-up in comparison, giving them little weight to inform the question of dual-chamber pacing versus single-chamber atrial pacing. Although the time horizon in DANPACE was reasonable, the results for patients needing a change in pacing mode and reoperation were probably conservative as the proportion of these due to the development of high grade AV block would be anticipated to increase steadily over time. Additionally, DANPACE did not allow pacemaker algorithms designed to minimize ventricular pacing in patients with intact AV conduction, which are becoming more common since this trial. Although the DDDR pacemakers in DANPACE were programmed in a way intended to reduce unnecessary ventricular pacing, ventricular pacing was still 65 ± 33 %, which may offset some of the benefit of implanting a dual-chamber pacemaker.

4.3.4 Conclusions

This review has shown dual-chamber pacing to be associated with a lower risk of AF and fewer reoperations than single-chamber atrial pacing. No statistically significant difference was shown between the pacing modes for mortality, stroke, quality of life, or heart failure. However, for patients younger than 75 years of age the risk of heart failure seems to be higher with a dual-chamber pacemaker than a single-chamber atrial pacemaker, and for patients older than 75 years the risk seems to be lower with dual-chamber pacing compared with single-chamber atrial pacing.

Hence, there are arguments in favour of both dual-chamber pacing and single-chamber atrial pacing in patients with SSS without evidence of impaired AV conduction.

With single-chamber atrial pacing:

- patients who do not go on to develop AV block have been paced appropriately and avoid any unnecessary ventricular pacing, which may have adverse consequences for cardiac function;
- the risk of heart failure may be lower than for dual-chamber pacing if the patient is younger than 75 years of age;
- the implantation procedure is generally shorter than for dual-chamber pacemakers;
- the follow-up takes less time than for dual-chamber pacemakers;
- the risks of complications associated with pacemaker implantation may be lower than for dual-chamber pacemakers due to only one lead being inserted.

With dual-chamber pacing:

- patients who do go on to develop AV block will be protected by the presence of a ventricular lead and will not need a further operation to upgrade the pacemaker and insert a second lead, which is associated with higher risk of complications than for first time implant;
- the risk of developing AF is lower than with single-chamber atrial pacemaker;
- the risk of heart failure may be lower than for single-chamber atrial pacing if the patient is older than 75 years of age.

In conclusion, in patients with SSS without evidence of impaired AV conduction, the risk of developing complete AV block and the lack of tools to identify patients at high risk of developing the condition argues for the implantation of a dual-chamber pacemaker programmed to minimise

unnecessary ventricular pacing. However, considerations have to be made around the risk of developing heart failure which may depend on age and device.

5 ASSESSMENT OF COST-EFFECTIVENESS

5.1 Systematic review of existing cost-effectiveness evidence

This section describes the Technology Assessment Group's (TAG's) review of the existing cost-effectiveness evidence for pacing in the management of bradycardia. Sections 5.1.1, 5.1.2 and 5.1.3 provide narrative summaries of UK-specific economic evaluations (Section 5.1.1), non-UK specific economic evaluations (Section 5.1.2) and costing studies (Section 5.1.3) identified in the review. A joint manufacturers' submission was expected from the Association of British Healthcare Industries (ABHI) but it was not submitted for consideration as part of this MTA. Section 5.1.4 summarises the available evidence and draws conclusions about the published assessments of cost-effectiveness.

A systematic review of MEDLINE (Ovid), EMBASE (Ovid), HTA database (HTA, Cochrane Library) and NHS EED (Cochrane Library) was carried out in December 2013. The review aimed to identify published economic evaluations or costing studies of relevance to the decision problem that is the focus of this MTA.

To facilitate the identification of all potentially relevant information, the MEDLINE and EMBASE search strategies combined terms capturing population (pacing), interventions (dual-chamber pacemakers) and economic evaluations/costing studies with terms designed to capture a broader range of comparators (e.g., single-chamber ventricular pacemakers) than those specified in the scope: economic evaluations or costing studies in patients receiving single-chamber ventricular pacing were considered likely to be informative in the development of a *de novo* economic evaluation.

The search strategy for HTA and NHS EED combined terms for the target condition (AV block, SSS) with terms for the intervention (pacemaker). All databases were searched from inception: full details of the search terms are presented in Appendix 1 Literature search strategies.

In addition to searches of the above databases, additional sources of potentially relevant publications were explored:

- experts in the field were contacted with a request for details of relevant published and unpublished studies of which they may have knowledge;
- the NICE website was searched for any recently published Technology Appraisals in pacing that had not already been identified via the database searches;

- reference lists of key identified studies were reviewed for any potentially relevant studies.

No restrictions on language or setting were applied to any of the searches. The titles and abstracts of papers identified through the searches were independently assessed for inclusion by two health economists using the criteria outlined in Table 24.

Table 24. Inclusion and exclusion criteria for the systematic review of economic evaluations and costing studies

Inclusion criteria	Exclusion criteria
• all full economic evaluations (cost-effectiveness, cost-benefit, cost-consequence or cost minimisation) • all UK resource use or costing studies • any setting (to be as inclusive as possible) • disease area is AV block and/or SSS • intervention is pacing	• abstracts with insufficient methodological details • systematic reviews
Abbreviations used in table: AV, atrioventricular; SSS, sick sinus syndrome.	

The systematic review was updated in June 2014. The search strategy remained the same as outlined above; however, results were limited from 16 December 2013 to 6 June 2014 to identify additional relevant studies.

A total of 228 papers were identified from the December 2013 search (Figure 7). Of these papers, 112 were excluded on the basis of title and abstract and 90 were duplicates. Therefore, a total of 26 papers were identified as potentially relevant and were reviewed in full. Of the 26 papers, 15 were excluded after review of the full paper. For a description of the reason for exclusion of the ordered papers, see Appendix 4 Table of excluded studies. Eleven papers from the December 2013 search were identified as relevant to the review of the economic literature. A further nine papers were identified from the update search in June 2014. Of these, seven were excluded on the basis of title and abstract, one was a duplicate, and one paper was identified as potentially relevant and reviewed in full. One additional paper was identified as relevant to the review of the economic literature.

Of the 12 studies identified from the searches, 11 were economic evaluations and one was a UK-specific costing study (Table 25 shows a summary of studies, full extraction tables are provided in Appendix 2 Data abstraction).

Figure 7. Identified economic evaluation and costing studies

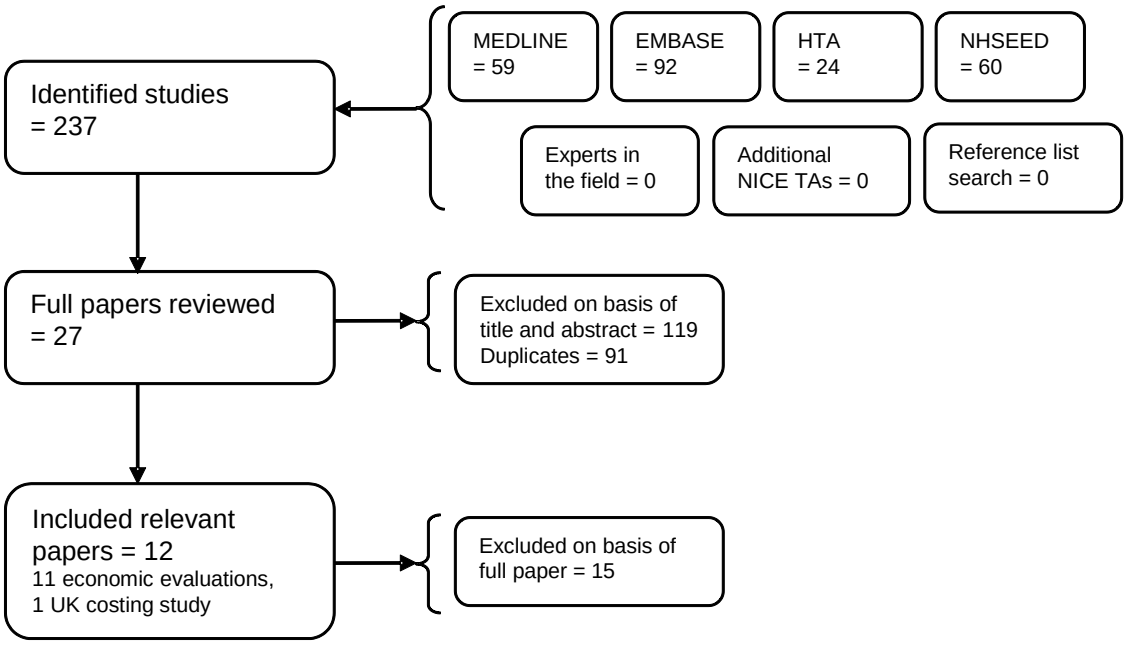


Table 25. Summary of studies included following review of the published economic literature

Study	Identified in TA88	ReportingTA88	Additional studies
	Mahoney 1994	Castelnuovo 2005	Clarke 1998
			Deniz 2008
			O'Brien 2005
	Sutton 1996	Caro 2006	Oddershede 2014
			Osman 2010
			Rinfret 2005
			Ray 1992
			Wiegand 2001
Abbreviation used in table: TA, Technology Appraisal.			

Of the 11 economic evaluations identified, five were UK studies,[52-56] and two were carried out in the USA,[57;58] with the remaining four studies carried out in Denmark,[59] Italy,[60] Canada[61] and Germany.[62]

With the exception of studies carried out by Caro et al.[52] and Castelnuovo et al.,[53] the identified UK-specific economic evaluations were simple comparisons of costs and benefits. That is, differences in

costs were not analysed in relation to differences in benefits. Furthermore, single centre costs were predominantly used and estimates of benefit informed either by retrospective analysis of patient records[54;55] or unadjusted pooling of incidence data identified in a literature review.[56]

The analyses carried out by Caro et al.[52] and Castelnuovo et al.[53] were evaluations of cost-utility. Caro et al. focused on the cost-utility of dual-chamber (DDD/DDDR) versus single-chamber ventricular pacemakers (VVI/VVIR) in people with bradycardia resulting from sino-atrial node dysfunction (SND) or AV block. The study reported by Castelnuovo et al. relates to TA88, of which this MTA is in part a review and update, and therefore considers, amongst others, the question that is the scope of this MTA. That is, the cost-utility of dual-chamber versus single-chamber atrial pacemakers in people with SSS and no AV block; atrial pacing is estimated to dominate (be less expensive and more effective than) dual-chamber pacing over a 10-year time horizon. A narrative review of all UK-specific economic evaluations is presented in Section 5.1.1, with quality assessment against the NICE reference case, and Philips checklist presented in Appendix 3 Quality assessment.

The six non-UK economic evaluations identified were of varying quality and relevance.[57-62] One study[59] considered the cost-effectiveness of dual-chamber versus single-chamber atrial pacing making it the most relevant non-UK economic evaluation. The remaining four studies considered the cost-effectiveness of dual-chamber versus single-chamber ventricular pacing.[57;58;60;61] Of these, two studies compared DDD or AAI devices with VVI devices.[57;61] A narrative review of these studies is presented in Section 5.1.2, with quality assessment against the NICE reference case, and Philips checklist presented in Appendix 3 Quality assessment.

The single UK-specific costing study[63] identified in the TAG's systematic review of the economic literature provides information on the cost of devices incurred by a single centre in 1991 and is therefore of limited use to inform an up-to-date economic evaluation.

5.1.1 Narrative summary of included UK economic evaluations

Caro 2006

Caro et al.[52] estimated the cost-utility of dual-chamber pacemakers versus single-chamber ventricular pacemakers in people with bradycardia as a result of SND or AV block. The analysis was carried out from a UK NHS perspective, using costs from 2003 discounted at 6% per annum over a 5-year time

horizon: benefits, namely quality adjusted life years (QALYs), were discounted at a rate of 1.5% per annum.

Model structure and assumptions

A discrete event simulation approach was used to estimate the incremental cost-effectiveness ratio (ICER) of the dual- versus single-chamber pacemakers considered. The model simulated two hypothetical populations of patients: population A and population B. With the exception of age (sampled from 2002 UK pacemaker implantation population statistics) and systolic blood pressure (sampled from the Framingham Heart Study for patients with AF), the characteristics of each (n = 1,000) hypothetical patient in population A were sampled from distributions derived from the baseline characteristics of people enrolled into the Canadian Trial of Physiological Pacing (CTOPP). Each patient in population A was 'cloned' to produce population B. Both populations entered the simulation at the point of pacemaker implantation: population A received a dual-chamber (DDD or DDDR) pacemaker and population B received a single-chamber ventricular (VVI or VVIR) pacemaker.

Thereafter, simulated patients were exposed to the risk of one of four events: onset of AF; an implantation-related complication; pacemaker syndrome; or death. The time to each possible event was estimated through samples of the corresponding failure time distribution: each event was assumed to be independent of other simulated events. The simulation selected and processed the consequences of each event in the order in which they were estimated to occur, with death resulting in no future events and the onset of AF resulting in exposure to the risk of stroke.

Outcome data

The onset of AF with respect to device type was estimated from data collected in the CTOPP trial.[64;65] Analysis indicated that dual-chamber pacing was associated with an 18% and 27% reduction in the onset of AF (lasting more than 15 min) and chronic AF (permanent AF), respectively. Data from MOST[66] were used to inform the rate of post-operative complications associated with dual-chamber devices, whereas complication rates associated with single-chamber ventricular devices were derived from application of the HR (0.42) versus dual-chamber pacing observed in CTOPP.[64] The incidence and severity (i.e., whether symptoms were severe enough to warrant pacemaker upgrade) of pacemaker syndrome in patients implanted with single-chamber ventricular devices were estimated from data reported in MOST and CTOPP. Mortality observed in the CTOPP trial was used to inform simulated life expectancy. After the onset of AF, the risk of stroke was estimated using the

Framingham risk equation,[67] patients receiving anticoagulation treatment (assumed to be 65% of the patients with chronic AF, based on data from CTOPP) incurred a relative risk reduction of 0.55; based on a study by Hart et al[68]. QoL utility weights are reportedly derived from "data collected using the time trade-off approach during MOST", but details of utility value derivation are not provided nor cited.

Resource use and cost data

Direct medical costs incurred by the UK NHS were included in the analysis and encompassed costs of: device; initial implantation; device replacement; anticoagulation; and stroke. With the exception of device costs, standard NHS cost resources were used (NHS reference costs, Summary of product characteristics [SPC]): device costs were obtained from a personal communication from the Consortium of Pacemaker Manufacturers. The cost of anticoagulation included warfarin therapy. The costs of monitoring and laboratory tests were obtained from a personal communication with the Department of Coagulation, Sheffield Haemophilia and Thrombosis Centre, Royal Hallamshire Hospital. The cost of stroke, initial implantation and replacement implantations were derived from relevant Healthcare Resource Group (HRG) codes.

Summary of results

The average (based on 100 simulations) additional cost associated with a dual-chamber pacemaker versus a single-chamber ventricular pacemaker was estimated to be £43 per patient, over 5 years. This additional cost was estimated to be associated with an average gain in QALYs of 0.09 per person, resulting in an average ICER of £477 per QALY gained. Univariate sensitivity analysis revealed that the cost-effectiveness results are sensitive to assumptions regarding the proportion of patients requiring pacemaker replacement as a result of pacemaker syndrome. Multivariate sensitivity analysis indicated robust cost-effectiveness estimates, with 29% of simulations resulting in the dominance of dual-chamber pacemakers over single-chamber ventricular pacemakers, and 31% indicating an ICER of less than £1,000 per QALY. No simulations estimated an ICER of more than £10,000 per QALY.

Critique

The study by Caro et al.[52] provides a useful example of a simulation approach in a disease area similar to that specified in the scope of this MTA. The model structure used represents a reasonable approximation of the health condition under evaluation, but is limited by the exclusion of HF and the use of a time horizon shorter than the expected lifetime of the interventions considered. With the

exception of QoL utility weights, data that forms the basis of the economic evaluation are generally well described; however, it is unclear how data sources were identified. Assessment of parameter uncertainty has been carried out to sufficient depth to understand the potential impact of model parameters on the cost-effectiveness results; however, assessment of structural or methodological uncertainty is missing.

Castlenuovo 2005

The review and economic evaluation carried out by Castelnuovo et al.[53] informed TA88, an MTA of which this review is in part an update. Consequently, the scope of the review reported by Castelnuovo et al. was broader than the decision problem that is the focus of this MTA. Castelnuovo et al. considered the clinical and cost-effectiveness of dual- versus single-chamber pacemakers for the management of bradycardia as a result of SSS and/or AV block. The analysis was carried out over 5- and 10-year time horizons from the perspective of the UK NHS. Costs (from 2003) were discounted at a rate of 6% per annum and benefits (QALYs) were discounted at a rate of 1.5% per annum, according to the NICE reference case of the time.

Model structure and assumptions

A series of Microsoft Excel-based Markov models was used to assess the cost-effectiveness of three different treatment choices:

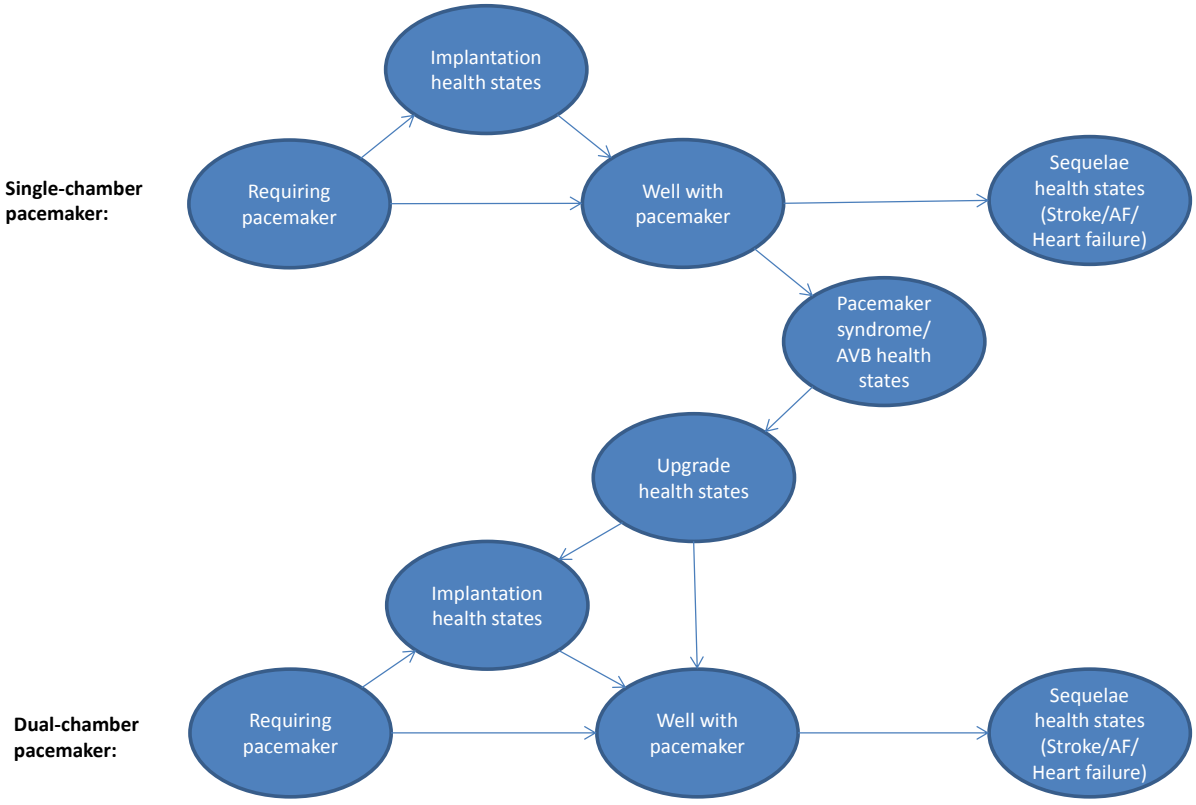
1. Dual-chamber pacemakers versus single-chamber ventricular pacemakers in people with AV block;
2. Dual-chamber pacemakers versus single-chamber ventricular pacemakers in people with SSS;
3. Dual-chamber pacemakers versus single-chamber atrial pacemakers in the SSS population.

The patient population of each analysis were assumed to be homogenous, that is had either SSS or AV block. A simplified outline of the structure of the Markov models is displayed in Figure 8. Health states were designed to reflect disease course and potential outcomes following pacemaker implantation. People receiving a dual-chamber pacemaker were initially exposed to the risk of perioperative and subsequent complications and over the longer term to the risk of AF, HF or stroke. People who developed AF were exposed to a higher risk of HF or stroke than people without AF. In addition, people with a dual-chamber device (either initially or following upgrade) who went on to develop AF had their device reprogrammed to act as a single-chamber ventricular device. Mortality was also accounted for within the model, with people exposed to the risk of death from any-cause,

perioperative mortality, death from stroke or death from HF. The subsequent disease pathways for people experiencing HF or stroke were not explicitly modelled: broad assumptions regarding the ongoing cost and utility associated with these health states were made.

People receiving a single-chamber pacemaker were exposed to the same risks as people receiving a dual-chamber pacemaker. However, people receiving a single-chamber ventricular pacemaker were also at risk of developing pacemaker syndrome, which could result in upgrade to a dual-chamber pacemaker. Similarly, people receiving a single-chamber atrial pacemaker were at risk of developing AV block, necessitating upgrade to a dual-chamber pacemaker.

Figure 8. Overview of model structure used in TA88



Outcome data

RCT data were used to inform the incidence of perioperative and subsequent complications, incidence and severity of pacemaker syndrome, progression to AV block (in people with SSS) and the onset of AF. Operative complication rates were taken from CTOPP[64] and PASE,[69] with complication rates

from an upgrade procedure assumed to be twice that of an initial procedure. The incidence and severity of pacemaker syndrome in people implanted with a single-chamber ventricular device were estimated based on data from MOST and CTOPP.[64;70] Progression to AV block (1.9% per annum) in people with SSS was sourced from Nielsen et al.[46] The likelihood of developing AF was taken from data presented in MOST, UKPACE (commercial in confidence) and Neilsen et al.[46]

The incidence of stroke and HF in people without AF and receiving single-chamber ventricular or dual chamber pacemakers was synthesised in a meta-analysis from evidence identified in the clinical-effectiveness review that formed part of the work undertaken for TA88.[19] The incidence of HF and stroke for people without AF receiving single-chamber atrial pacing was taken from the study reported by Nielsen et al.[46] In people with AF, the likelihood of experiencing stroke or HFG was estimated from data presented in Chugh et al.[71] and Wang et al.,[72] respectively. Table 26 provides a summary of the outcome data used to inform the Markov models that formed the basis of the economic evaluation considered in TA88.

Table 26 Summary of outcome data used in TA88

Outcome	**Single-chamber ventricular pacing**		**Single-chamber atrial pacing**		**Dual-chamber pacing**	
	Input	**Source**	**Input**	**Source**	**Input**	**Source**
Incidence of perioperative complications[a]	3.3%	CTOPP[64]	3.3%	CTOPP[64]	6.6%	CTOPP[64]
Perioperative mortality[b]	0.25%	PASE[69]	0.25%	PASE[69]	0.25%	PASE[69]
Subsequent complications	0.1%	Assumption	0.1%	Assumption	0.1%	Assumption
Subsequent complications mortality	0.5%	Assumption	0.5%	Assumption	0.5%	Assumption
Incidence of mild pacemaker syndrome	• 44% (1 month); • 77% (6 months); • 23%	PASE[73]	N/A	N/A	N/A	N/A

	(thereafter).					
Severe pacemaker syndrome	16.5% of pacemaker syndrome cases	CTOPP[64]	N/A	N/A	N/A	N/A
Progression to AVB	N/A	N/A	1.9% per annum	Nielsen[46]	N/A	N/A
AF onset	**SSS** • 12% (6 months); • 27% (thereafter). **AV block** CiC from UKPACE	MOST[70]	**SSS** • 12% (6 months); • 27% (thereafter). **AV block** CiC from UKPACE	MOST[70]	**SSS** • 12% (6 months); • 27% (thereafter). **AV block** CiC from UKPACE	MOST[70]
Progression to stroke (no AF)	1.25% per annum	Castelnuovo[53]	RR versus dual-chamber 0.62	Nielsen[46]	1.07% per annum	Castelnuovo[53]
Progression to stroke (with AF)	3.2% per annum	Chugh[71]	3.2% per annum	Chugh[71]	3.2% per annum	Chugh[71]
Stroke mortality	33% per annum	Appelros[74]	33% per annum	Appelros[74]	33% per annum	Appelros[74]
Heart failure (no AF)	2.6% per annum	Castelnuovo[53]	RR versus dual-chamber 1.07	Nielsen[46]	2.5% per annum	Castelnuovo[53]
Heart failure (with AF)	3.3% per annum	Wang[72]	3.3% per annum	Wang[72]	3.3% per annum	Wang[72]
Heart failure mortality	20.8% per annum	MacIntyre[75]	20.8% per annum	MacIntyre[75]	20.8% per annum	MacIntyre[75]

[a]Dual-chamber rate doubled for upgrade procedures

[b] doubled for upgrade procedures

Abbreviations used in table: AF, atrial fibrillation; AV, atrioventricular; CiC, commercial in confidence; CTOPP, Canadian Trial of Physiological Pacing; MOST, Mode Selection Trial in Sinus Node Dysfunction; N/A, not applicable; PASE, Pacemaker Selection in the Elderly; RR, relative risk; SSS, sick sinus syndrome; TA, Technology Appraisal.

Resource use and cost data

Costs associated with the intervention, procedure (including complications), device reprogramming; management of pacemaker syndrome, AV block, AF, stroke and HF were included in the economic evaluation carried out by Castelnuovo et al. (Table 27).[53] Intervention costs were sourced from an economic evaluation carried out alongside the, at the time unpublished, UKPACE trial. Procedure (including complications) costs were calculated from HRG codes reported in the resource cost initiative database (NHS Executive. The new NHS reference costs. Leeds: NHS Executive; 2002). The cost of device reprogramming was assumed to comprise a cardiological consultation, pacing check and an ECG. Costs associated with device upgrade, severe pacemaker syndrome and AV block were excluded as they were assumed to involve the same type of resource use and, therefore cost, as device reprogramming. Costs associated with mild pacemaker syndrome were assumed to be equivalent to those associated with a routine follow-up visit.

Broad assumptions were made regarding the resource use and cost associated with the management of AF, stroke and HF. Estimates of treatment allocation for people with AF were taken from two studies, with costs for antithrombotics taken from a cross sectional community study carried out in 1998[76] and costs for digioxin, β-blockers and calcium channel blockers based on the AFFIRM trial[77-79]. In addition, people with chronic AF were assumed to have eight visits per year to their general practitioner (GP). Those on warfarin were assumed to require a further two specialist outpatient visits and a further eight anticoagulation clinic visits. Resources used after a stroke were derived from a UK study of resource use in people living with stroke[80] and combined with 2003 community care and NHS reference costs. The resource use and cost assumed to be associated with HF is stated as being "based on assumptions regarding hospital admission and drug use".[53]

Table 27. Summary of costs used in TA88

Cost	Single-chamber pacing	Dual-chamber pacing
Device	VVI: £690 VVIR: £1,099 Atrial lead: £175 Ventricular lead: £172	DDD: £1,365 DDDR: £2,107 Atrial lead: £175 Ventricular lead: £172
Device implantation	£4,025	£4,925
Perioperative complications	£816	£894

Subsequent complications	£816	£894
Upgrade to dual-chamber	£4,925	N/A
Reprogramming dual-chamber to act as single chamber ventricular	N/A	£176
Cost (per cycle)	**Single-chamber pacing**	**Dual-chamber pacing**
Follow up	£40	£40
Mild pacemaker syndrome	£40 (ventricular pacing only)	N/A
Severe pacemaker syndrome	£176 (ventricular pacing only)	N/A
AV block prior to upgrade	£176	N/A
AF	£41	£41
Stroke	£820	£820
Heart failure	£152	£152
Abbreviations used in table: AF, atrial fibrillation; AV, atrioventricular; N/A, not applicable.		

Health-related quality of life

QoL was incorporated into the model with the use of weights (utilities) associated with time spent in each of the model's health states, adjusting the value of that time with respect to the severity of the health state. The majority of these weights were identified from a study by Lopez-Jimenez et al., which reported health values elicited and valued by a subset of patients enrolled in the PASE trial.[11] Table 28 summarises the utility weights used for each health state in the TA88 models.

Table 28: Summary of utility values used in TA88

Health state	Utility	Source
Pacemaker implant	0.76	Lopez-Jimenez et al.[11]
Perioperative complications	0.75	Assumption based on Lopez-Jimenez et al.[11], 0.01 less than pacemaker implant
Subsequent complications		
Well with pacemaker	0.925	Lopez-Jimenez et al.[11]
Mild pacemaker syndrome	0.80	Equivalent to people with NYHA Class I or II heart failure, Lopez-Jimenez et al.[11]
Severe pacemaker syndrome	0.62	Equivalent to people with NYHA Class III or IV heart failure,

		Lopez-Jimenez et al.[11]
AV block prior to upgrade	0.76	Lopez-Jimenez et al.[11]
Upgrade to dual-chamber pacemaker	0.915	Lopez-Jimenez et al.[11]
Perioperative complications during upgrade		
AF	0.875	Hogenhuis et al.[81]
Reprogramming dual-chamber to single-chamber ventricular following onset of AF	0.875	Assumed equal to AF
Stroke	0.64	Tengs et al.[82]
Heart failure	0.39	Lopez-Jimenez et al.[11]
Abbreviations used in table: AF, atrial fibrillation; AV, atrioventricular; NYHA, New York Heart Association.		

Summary of results

For each of the three treatment choices considered in TA88, the ICERs estimated deterministically are as follows:

- dual versus single-chamber ventricular pacemakers in people with AV block, £8,458 per QALY over 5 years, £5,483 per QALY over 10 years;
- dual versus single-chamber ventricular pacemakers in people with SSS, £9,552 per QALY over 5 years, £5,732 per QALY over 10 years;
- dual versus single-chamber atrial pacemakers in people with SSS, dual-chamber pacemakers are dominated by (i.e., are more costly and less effective than) single-chamber atrial pacemakers over 5 and 10 years.

Univariate sensitivity analysis identified the cost of implantation and the incidence, duration and utility associated with mild pacemaker syndrome as key drivers of the deterministic cost-effectiveness results. In addition, mortality and the incidence of AF were noted as having a moderate effect on the ICERs associated with each treatment choice. Probabilistic sensitivity analysis highlighted a high degree of uncertainty in the models, with results spread across the four quadrants of the cost-effectiveness plane.

Critique

Overall, the work carried out by Castelnuovo et al. is of high quality. The model structure used coherently maps the clinical pathway of the health condition under consideration and all model assumptions have been clearly stated and justified. The use of shorter (5 years) and longer (10 years) time horizons is useful for understanding the potential impact of the broad assumptions made regarding the sequelae of AF, HF and stroke. The health states considered are generally appropriate. However, no rationale is provided for the exclusion of subsequent complications following upgrade to a dual-chamber pacemaker. Data on which the models are based were predominantly identified systematically, with quality assessment of source data carried out and choices between sources justified. However, the identification of some data sources, for example, Chugh et al. for the progression to stroke after AF, has not been explained. Treatment effects have been appropriately synthesised using the best techniques and data available at the time. Extrapolation has been described and justified and the potential impact explored in sensitivity analysis. All costs and QoL weights included in the model have been clearly justified and calculated. However, the utility associated with an upgrade procedure (0.915, after application of a disutility of 0.01 to the utility associated with being well with pacemaker [0.925]) seems high and may overestimate the benefit of single-chamber pacemakers. In general, results have been sufficiently explained and contextualised by the existing literature and areas of remaining uncertainty, for example, conflicting trial results, have been highlighted.

Clarke 1998

Clarke et al.[54] carried out a retrospective follow-up of patients implanted with single-chamber atrial pacemakers in a single centre between 1992 and 1996. The aim of the study was to ascertain the rate of development of AV block and estimate potential cost-saving from use of single-chamber atrial pacing instead of dual-chamber pacing in people with SND and no AV block. Retrospective analysis of case notes identified 81 patients implanted with a single-chamber atrial pacemaker between 1992 and 1996. Of these, eight patients died during the analysis period and case notes were unobtainable for five patients. Fifteen (22%) of the 68 patients for whom case notes were available required a revision procedure. Of these, 10 patients (67%) required revision as a result of complications or manufacturer recall and four (5.8%) patients required revision following the development of AV block. Based on these data and on the cost of implantation (£2,885 and £3,844 for single and dual-chamber pacemakers, respectively), Clarke et al. estimated cost-savings of £103,000 a year associated

with the use of single-chamber atrial pacemakers instead of dual-chamber pacemakers in people with SND and no AV block.

Critique

The cost savings estimated by Clarke et al. seem to be based on the assumption that an additional cost (i.e., the cost of upgrade) would be accrued by only patients developing AV block. The additional cost associated with revision procedures after experiencing complications does not seem to have been taken into account. In addition, the sample size (n = 68) is small and based on the experience of a single healthcare centre, therefore, these data cannot be assumed to reliably inform the rate of development of AV block in people with SND.

Osman 2010

The aim of the study reported by Osman et al.[55] was to assess the safety and potential cost savings associated with same day procedures (as opposed to procedures followed by an overnight stay) for implantation of new pacemaker devices (i.e., first pacemaker implants). The study used retrospective safety and cost data from a single centre to assess the level of complications associated with a same day procedure in patients scheduled for a new pacemaker implant.

Summary of results

Records from 780 patients intended for same day implantation of a new pacemaker were identified for the period of April 2001 to December 2006. Table 29 summarises the immediate (occurring < 24 hours after implantation) and early (occurring > 24 hours and < 6 weeks after implantation) complications recorded and the reason for any unplanned overnight stay.

Table 29. Unplanned overnight hospital stays and complications following same day new pacemaker implantation as reported by Osman et al.[55]

Reasons for unplanned overnight hospital stays	Immediate (< 24 hours post-implant) complications	Early (> 24 hours and < 6 weeks post-implant) complications
• Hematoma (12 patients); • Pneumothorax (3 patients); • Observation at physician's request (13 patients);	• Displaced atrial leads (2 patients); • Elevated ventricular threshold (1 patient); • Sensing problems on the atrial	• Lead displacements (5 patients); • High pacing thresholds (6 patients);

• Social reasons (7 patients); • The development of angina (3 patients); • AF (1 patient); • Warfarin with INR > 2.0 (2 patients);	lead (2 patients); • Haematoma (1 patient).	• Wound infection (3 patients); • Sensing problems (2 patients); • Subclavian vein thrombosis (1 patient).
Abbreviations used in table: AF, atrial fibrillation; INR, international normalised ratio.		

The cost associated with an overnight stay (£203.60) was obtained from the centre's finance department. Based on this and on retrospective assessment of procedures carried out from November 2005 to November 2006 (109 procedures, of which 2 required an unplanned overnight stay), the authors concluded that savings of £21,785 (109 x £203.60-2 x £203.60) were made for the year November 2005 to November 2006.

Critique

The study by Osman et al. provides a useful insight into the potential complications associated with pacemaker implantation procedures in the UK. Although the cost information provided is limited to the cost of an overnight stay, details are given regarding, for example, the use of pre- and peri-implantation antibiotics, which may be useful to inform a *de novo* economic evaluation.

Sutton 1996

Sutton et al.[56] carried out a comparison of costs and benefits associated with atrial (AAI/DDD) versus ventricular (VVI) pacing in people with SSS or AV block. The analysis was carried out over a 10-year time horizon; however, no discounting was applied to costs or benefits. A generic unit of currency, based on 1991 UK prices, is used to inform all estimates of cost. Furthermore, the perspective of the analysis is not explicitly stated.

Model structure and assumptions

The authors state that a "computer model" was developed to estimate the incidence and prevalence of complications considered within the analysis, namely: AF; AV block; stroke and any resulting disability; HF; pacemaker upgrade; and mortality. The number of surviving patients with AF, stroke, disability as a result of stroke, or HF was calculated and recorded annually for:

- patients with SSS initially implanted with a VVI device;
- patients with SSS upgraded to a DDD device;
- patients with SSS initially implanted with a DDD device;
- patients with AV block initially implanted with a VVI device;
- patients with AV block upgraded to a DDD device;
- patients with AV block initially implanted with a DDD device.

In addition, the following assumptions were made in relation to the analysis:

- stroke is assumed to occur in 30% of AF cases;
- 30% of stroke cases are assumed to result in long-term disability;
- mortality is assumed to be equivalent for patients with and without HF or AF.
- no generator change or lead replacement is required within the 10-year time horizon.

Outcome data

A literature review was carried out to inform estimates of the incidence of AF, AV block, HF, stroke and mortality. Outcome data used in the analysis carried out by Sutton et al. are summarised in Table 30. It is unclear how estimates of mortality have been derived, that is, the authors report an average mortality (based on 13 studies) of 6.4% and 3.6% per annum in SSS patients paced with VVI and DDD devices, respectively. However, the estimates of mortality used to inform the analysis are 6% and 3% for SSS patients paced with VVI and DDD devices, respectively. Furthermore, the source of mortality estimates for AV block patients paced with VVI (7% per annum) and DDD (5% per annum) devices is not stated. In addition to the lack of clarity regarding estimates of mortality, the proportion of patients assumed to experience stroke is 30%, whereas evidence from the literature review suggests a 39% stroke/AF ratio. Finally, the source(s) used to estimate the incidence of pacemaker syndrome is (are) not provided.

Table 30. Summary of outcome data used in analysis by Sutton et al. (adapted from Table 3; pg 577)[56]

Outcome	SSS		AV block	
	VVI	DDD	VVI	DDD
Year 1				
AF	10%	2%	5%	1%
Stroke	3%	0.6%	1.5%	0.3%
Disability	0.9%	0.2%	0.45%	0.09%
Heart failure	6%	2%	6%	25
Pacemaker syndrome	2%	0%	2%	0%
Mortality	6%	3%	7%	5%
Year 2 onwards				
AF	7%	1.5%	3%	0.5%
Stroke	2.1%	0.45%	0.9%	0.15%
Disability	0.63%	0.14%	0.27%	0.045%
Heart failure	6%	2%	6%	2%
Pacemaker syndrome	2%	0%	2%	0%
Mortality	6%	3%	7%	5%
Abbreviations used in table: AF, atrial fibrillation; AV, atrioventricular; SSS, sick sinus syndrome.				

Resource use and cost data

As noted above, a generic unit of currency is used to inform all estimates of cost. The reference cost for this currency is the 1991 UK price of a VVI device, which is set as 100 currency units. Table 31 summarises the costs used in the analysis by Sutton et al.

Table 31. Cost and sources used to inform cost-benefit analysis by Sutton et al.[56]

Cost component	VVI	DDD	Source
Pulse generator	100	166	Survey of 6 manufacturer's active on the UK market
Leads	13	26	
Implantation[a]	117	148	Single centre costs

Follow-up	4	8	
Upgrade[b]	340		
AF treatment	10	10	
Stroke[c]	100	100	
Disability	1733	1733	Local area costs of long-term care
Heart failure[d]	243	243	UK drug prices, single centre care costs

[a] 2 overnight stays assumed per procedure, with 45 mins and 60 mins operating time assumed for single-chamber and dual-chamber, respectively.

[b] includes dual-chamber device costs, plus 60 mins of operating time and one night inpatient stay, plus "waste of resources involved in disposing of the redundant generator".

[c] assumed to include 7 days of inpatient care.

[d] includes the cost of therapy with ACE inhibitor and frusemide at average doses plus one week of inpatient care per year.

Abbreviation used in table: AF, atrial fibrillation.

Summary of results

Based on the inputs listed above, the analysis carried out by Sutton et al. estimated that survival is increased with atrial pacing. By contrast, 2- and 5-fold reductions are estimated in HF and disability from stroke, respectively. Assessment of costs associated with atrial and ventricular pacing suggests that there are equal cost implications to both pacing modes 3 years after implantation. However, in SSS patients, the 10-year cumulative cost of VVI pacing is 12 times that of DDD pacing. Furthermore, the 10-year cumulative cost of VVI pacing in patients with AV block is 8 times that of DDD pacing in the same indication.

Univariate sensitivity analysis was carried out to assess the impact of AF incidence, mortality, stroke incidence (as a proportion of AF incidence), disability costs and the incidence of HF on the modelled cost estimates. In SSS patients, the cost of DDD pacing increases with increasing disability costs and increasing stroke incidence, but at a faster rate than the cost of VVI pacing. Conversely, DDD costs increase at a lower rate than VVI costs with increasing AF and HF incidence. However, it is important to note that sensitivity analysis around the incidence of AF assumes no difference between VVI and DDD pacing, an assumption that is unlikely to be reflected in clinical practice.

In AV block patients, the cost of DDD pacing increases more rapidly than the cost of VVI pacing with increasing AF and HF incidence. Conversely, costs of DDD pacing increase more slowly than the cost of VVI pacing with increasing disability costs and stroke incidence.

Critique

The study by Sutton et al., while based predominantly on a review of the literature, is limited in that estimates of incidence obtained from the literature are simply pooled (i.e., an average taken) without adjustment for patient characteristics. This is likely to introduce potentially considerable bias into estimates of ongoing incidence and prevalence of common pacemaker sequelae. In addition, the use of a generic currency unit based on unpublished costs does not facilitate uprating of costs to current prices. Therefore, while providing a potentially useful source of health states and structural assumptions that may be used to inform a *de novo* economic evaluation, the analysis carried out by Sutton et al. is not informative due to methodological limitations.

5.1.2 Narrative summary of included non-UK economic evaluations

Oddershede 2014

Oddershede et al.[59] considered the cost-utility, from a Danish health care system perspective, of dual- versus single-chamber atrial pacemakers in people with SSS and preserved AV conduction. Costs and benefits (QALYs) were discounted at a rate of 3.5% per annum over a period of 60 years to estimate lifetime costs and effects. A Markov model constituting four health states (“well”, “first stroke”, “second stroke” and “dead”) was used to analyse cost-effectiveness. Patients without a history of stroke entered the model in the health state “well”, whereas those with a history of stroke entered the model in the health state “first stroke”. The model had monthly cycles and allowed patients to develop up to seven strokes.

The authors estimated cost-effectiveness using three approaches – “adjusted” and “unadjusted” approach using data from DANPACE and an “adjusted pooled approach” using data from the DANPACE pooled with two other Danish clinical trials. Patients were divided according to predicted survival probability into three groups to account for heterogeneity, with Group 1 categorised as the group at highest risk of death and Group 3 at the lowest. risk of death A Cox proportional hazards model was used to estimate the characteristics of the three groups. Survival probability was reported to change with:

- age;
- gender;
- previous myocardial infarction;
- history of AF;
- proportion of patients entering the model at the health state “first stroke”.

The cost-effectiveness of DDDR was assessed by calculating net-monetary benefit, which combines lifetime costs and QALYs. Therefore, a net monetary benefit greater than zero indicated that DDDR was cost-effective. Probabilistic sensitivity analysis was carried out to test the robustness of the results.

Outcome data

Stroke occurrence and death were the outcomes of interest. The authors justified not including HF based on the findings reported by Riahi et al., who found no ststaitically significant difference in occurrence of HF by pacing mode.[45] Patient level data on clinical effectiveness from the DANPACE trial was pooled with data from two other Danish RCTs reported by Andersen et al. and Nielsen et al.[46;50;83]

Resource use and cost data

Resource use with initial pacemaker implantation was collected from DANPACE trial, with data collected on surgery, complications and duration of initial hospitalisation. The model assumed that patients had outpatient follow-up visits at 3 months, 2 years, 4 years and every following year, as per routine practice at Aalborg University Hospital, Denmark. Costs were calculated in Danish Kroner (2012 prices) and then converted to Pound Sterling at a rate of £1 = 8.73 Danish Kroner. The cost of outpatients clinic was £101 (SE £10), with stroke and death costing £13,348 (SE £1,335) and £1,314 (SE £131), respectively.

Summary of results

Cost-effectiveness was reported based on the different approaches used and disaggregated according to risk groups for the adjusted analysis. Probability of cost-effectiveness was calculated across 10,000 simulations at willingness to pay thresholds (WTPs) of £20,000 and £30,000. Table 32 shows a summary of the cost-effectiveness results.

Table 32. Cost-effectiveness results of Oddershede et al.[59]

Population	Incremental cost (£)	Incremental benefit (QALYs)	Net monetary benefit (£) at WTP £20,000 per QALY	Net monetary benefit (£) at WTP £30,000 per QALY	Probability DDDR is cost-effective at WTP £20,000 per QALY	Probability DDDR is cost-effective at WTP £30,000
Adjusted approach						
Risk Group 1	–3,336	–0.022	2,918	2,694	77%	69%
Risk Group 2	–2,570	–0.029	1,996	1,709	60%	55%
Risk Group 3	–5,045	–0.041	4,220	3,442	64%	59%
Adjusted pooled approach						
Risk Group 1	–4,170	–0.103	2,103	1,069	71%	58%
Risk Group 2	–3,856	–0.170	460	–1,238	51%	42%
Risk Group 3	–7,521	–0.218	3,160	980	62%	51%
Unadjusted approach						
All patients	–2,310	0.277	7,847	10,615	88%	86%
Abbreviations used in table: QALY, quality adjusted life year; WTP, willingness to pay.						

Critique

The analysis carried out by Oddershede et al. was clearly reported, with baseline characteristics of patients, utility values and resource cost from DANPACE all presented in the paper. The model seemed reasonable and accounted for clinical heterogeneity in patient populations, which makes the results more robust. A weakness of the pooled analysis is the fact that the combined clinical effectiveness data included a study that compared single atrial pacing to single ventricular pacing.[50] The authors reported that single ventricular pacing was excluded from the analysis, which implies data from a randomised trial was pooled without a comparator arm. This would mean breaking the benefits of randomisation and turning the dataset into observational data. Also, a breakdown of the stroke and death costs would have been useful, particularly with death reported to cost the equivalent of £1,314.

Deniz 2008

Deniz et al.[60] considered the cost-utility, from an Italian government perspective, of dual- versus single-chamber ventricular pacemakers in people with bradycardia as a result of SND or AV block. Costs and benefits (QALYs) were discounted at a rate of 3% per annum over a 5-year time horizon. The authors adapted a discrete event simulation that was originally developed to assess the cost-utility of dual-chamber pacemakers for the management of bradycardia as a result of SND or AV block in the UK (Caro et al.)[52] to consider an Italian government perspective. The model structure used in the analysis reported by Deniz et al.[60] is identical to that described by Caro et al.[52] Similarly, outcome data used in the economic analysis reported by Deniz et al.[60] are identical to those used to inform the economic analysis reported by Caro et al.[52]

Resource use and cost data

The analysis reported by Deniz et al.[60] included the costs associated with devices, initial implantation, device replacement, anticoagulation and stroke. Device costs were obtained from a personal communication from the medical devices company Medtronic Europe. All other included costs were obtained from “regional information published for specific diagnosis-related groups in Italy” via the National Institute of Statistics (Istat) website. The cost associated with stroke was assumed to be equivalent to that associated with a stroke-related hospitalisation. The cost of anticoagulation included warfarin at a dose of 5 mg per day and a physician visit.

Summary of results

Based on 100 replications of 1,000 simulated patients, the ICER estimated for dual- versus single-chamber ventricular pacing was €260 per QALY (equivalent to £215 per QALY [converted on 20/01/2014 by http://markets.ft.com/research/Markets/Currencies]). Univariate sensitivity analysis revealed that the result was sensitive to assumptions regarding the proportion of patients assumed to upgrade to a dual-chamber device following the onset of pacemaker syndrome. That is, under the assumption that 5% of patients (rather than 16.7% as in the base case) experiencing severe pacemaker syndrome upgrade to a dual-chamber device, the ICER rises to €14,233 per QALY; however, this does not take account of any reduction in HRQoL for patients with severe pacemaker syndrome. Multivariate sensitivity analysis based on 1,000 replications, of 1,000 simulated patients, in which parameter uncertainty is included, estimated that dual-chamber devices provided more benefit at a lower cost in 45% of replications.

Critique

Akin to the analysis carried out by Caro et al.,[52] the analysis reported by Deniz et al. is based on a reasonable model of bradycardia in people with SND or AV block; however, consideration of HF as a potential sequelae would have provided greater face validity to the analysis. Similarly, a longer time horizon would have enabled a full comparison of costs and benefits accrued over the lifetime of the devices considered. Further detail on the derivation of stroke costs and QoL weights would have been useful to the critical appraisal of this analysis. Assessment of structural and methodological uncertainty would also have contributed to the robustness of the analysis.

Mahoney 1994

The study reported by Mahoney,[57] compares (without the use of modelling) costs and outcomes associated with single-chamber ventricular (VVI) pacing versus single-chamber atrial (AAI) pacing and versus dual-chamber (DDD) pacing: patient population is not specified. The study purports to assess the long-term costs of care for patients receiving each type of pacing considered. However, the time horizon of the analysis is not stated and no discounting is applied to costs or benefits.

Outcome data

The outcomes considered in the comparison are AV block, AF, congestive heart failure (CHF), pacemaker syndrome, stroke, thromboembolism, and mortality. A meta-analysis of “35 published studies comparing dual and single chamber [pacing] modes” is reported (no reference supplied) as the

source of data on the considered outcomes. Based on the meta-analysis, Mahoney states that compared with VVI pacing, DDD pacing significantly reduces the incidence of AF, pacemaker syndrome, thromboembolism, stroke, and mortality. When compared with VVI pacing, AAI pacing is reported to significantly reduce the incidence of AF, thromboembolism, stroke, CHF and mortality. However, the probability of development of AV block is reported as being greater in people implanted with AAI versus VVI pacemakers.

Resource use and cost data

The "long-term" costs of care for people receiving each considered pacing mode includes device costs (source not stated) and the cost of treating outcomes associated with pacing, for example, AF. The "national average urban Diagnostic Related Group (DRG) payment (e.g., Minneapolis, MN)" is used to inform the costs associated with treatment of outcomes.

Summary of results

The overall cost of VVI is reported to be 24%–27% higher than DDD and 34%–35% higher than AAI. In addition, the cost of treating patients for AF, CHF, stroke and pacemaker syndrome is higher in VVI versus DDD pacing and higher still in VVI versus AAI pacing.

Critique

The study carried out by Mahoney is of poor quality, with an absence of references. Although the outcomes included are reasonable, the lack of referencing prevents validation of the comparative treatment effects. In addition, it is unclear which elements are included in the cost of treating outcomes and the time period over which these costs are considered.

O'Brien 2005

O'Brien et al.[61] carried out an economic evaluation alongside the CTOPP clinical trial. CTOPP considered the effects of physiologic (dual-chamber or single-chamber atrial) pacing versus ventricular pacing in people without chronic AF indicated for initial pacemaker implantation for the management of symptomatic bradycardia.[64] Resource use and cost data were collected from a subset (n = 1,058) of patients enrolled in CTOPP (n = 2,568) and adjusted for censoring using methods described by Lin et al.[84] Life-expectancy and the number of AF episodes by type of pacing (physiological versus ventricular) were estimated from the full trial population of CTOPP.

Summary of results

Cost-effectiveness was assessed per life-year gained and per AF episode avoided, with results further disaggregated into subgroups by intrinsic (unpaced) heart rate ([IHR], IHR ≤ 60 bpm or IHR > 60 bpm). Table 33 summarises the cost-effectiveness results reported by O'Brien et al.

Table 33. Summary of cost-effectiveness results (physiological pacing versus ventricular pacing) presented by O'Brien et al[61]

Patient group	Incremental cost (C$)	Incremental benefit	ICER (C$ [£] per LYG)[a]
All patients	2,976	0.01	297,600 (164,611)
IHR ≤ 60 bpm	4,091	0.25	16,004 (9,040)
IHR > 60 bpm	2,020	–0.11	Physiological pacing dominated by ventricular pacing
Patient group	**Incremental cost (C$)**	**Incremental benefit**	**ICER (C$ [£] per AF episode avoided)[a]**
All patients	2,976	–0.04	74,000 (40,931)
IHR ≤ 60 bpm	4,091	–0.04	102,275 (56,571)
IHR > 60 bpm	2,020	–0.04	40,400 (22,346)

[a] converted on 20/01/2014 using http://markets.ft.com/research/Markets/Currencies.

Abbreviations used in table: AF, atrial fibrillation; bpm, beats per minute; ICER, incremental cost-effectiveness ratio; IHR, intrinsic heart rate; LYG, life-years gained.

Critique

Although of limited relevance to the decision problem that is the focus of this MTA, the economic evaluation carried out by O'Brien et al. is robust with respect to methods of analysis and data used. Furthermore, this economic evaluation may provide a useful external validation of resource use, AF incidence and life-expectancy in people implanted with physiological pacemakers.

Rinfret 2005

Rinfret et al.[58] assessed the cost-utility of dual-chamber (DDDR) versus single-chamber ventricular (VVIR) pacemakers in people paced for SSS. Analyses was carried out from a US societal perspective across a within-trial time horizon (4 years) and a lifetime time horizon, with costs and benefits discounted at 3% per annum.

Model structure and assumptions

Within-trial analysis used Kaplan–Meier survival data to adjust yearly estimates of cost and utility obtained from the MOST trial.[49;70;85] These data were extrapolated over a lifetime time horizon using a Markov model calibrated to trial data. Within the Markov model, individuals were classified according to their current mode of pacing and their history of AF, HF or stroke. State specific costs and utilities were estimated using multiple linear regression models that incorporated the following independent (or predictor) variables:

- initial pacing mode;
- year of trial (year 1 *vs* years 2 to 5);
- crossover in previous year;
- crossover during current year;
- non-fatal event (AF, HF or stroke) during current year;
- 1 prior non-fatal event;
- 2 or more prior non-fatal events;
- death in current year.

Outcome data

Data on the incidence of crossover from VVIR to DDDR pacing as a result of pacemaker syndrome, AF, HF, stroke and event-specific mortality were collected from the MOST trial.[70] These data were supplemented with age and sex adjusted data from US life tables and expert opinion on the requirement for generator replacement. Utility data were elicited directly from patients enrolled in MOST using "a standard TTO instrument".

Resource use and cost data

Detailed data on resource use gathered as part of the MOST trial were used to inform the analyses carried out by Rinfret et al. Table 34 displays the majority of costs considered in the analyses of Rinfret et al. In addition to the costs summarised in Table 34, medication costs, for each class of prescription drugs reported in MOST, were obtained from the 2001 Redbook, and were based on doses considered to be clinically average.

Table 34. Costs used in the analyses carried out by Rinfret et al. (adapted from Table 1; pg 166)[58]

Cost component	DDDR	VVIR	Source
Initial pacemaker implantation			
Device cost	$7,720	$5,277	IMS Hospital supply index
Procedure costs	$1,894	$1,732	Single-centre costs
Post-procedure hospitalisation	$901	$877	Single-centre costs
Physician fees	$688	$679	Medicare physician fee schedule
Follow-up (per annum)			
Year 1	$4,387	$3,825	MOST trial
Subsequent years	$3,328	$2,766	MOST trial
Events (one-off cost)			
Crossover to DDDR	–	$14,451	Single centre costs
First non-fatal event occurring in current year	$4,529	$4,529	MOST trial
Second non-fatal event occurring in current year	$11,261	$11,261	MOST trial
Death occurring in current year	$6,878	$6,878	MOST trial
Generator change	$7,100	$5,737	IMS Hospital supply index
Abbreviation used in table: MOST, the mode selection trial.			

Summary of results

Within-trial cost-utility analysis estimated an ICER of $52,814 per QALY for DDDR versus VVIR pacing over 4 years. Lifetime cost-utility analysis estimated an ICER of $6,800 per QALY for DDDR versus VVIR pacing. Bootstrap analysis (1,000 samples with replacement) estimated that, at a WTP threshold of $50,000 per QALY, DDDR pacing was cost-effective in 91.9% of all samples.

Univariate sensitivity analysis revealed that the model was highly sensitive to the cost associated with implantation of a dual-chamber pacemaker and to assumptions regarding generator lifespan. Cost-effectiveness results were also moderately sensitive to follow-up costs and QoL by pacing mode.

Critique

The analyses carried out by Rinfret et al.[58] are clearly described and are underpinned by high-quality evidence. The use of calibration to ensure consistency between modelled and observed outcomes is a key strength of the Markov based analysis. However, the use of single centre costs somewhat inhibits the generalisability of the results.

Wiegand 2001

Wiegand et al. considered the costs and benefits of single-lead VDD pacemakers compared with DDD pacing in patients with AV block and normal sinus node function. The analysis was carried out based on clinical data gathered in a single-centre prospective study, over an average time horizon of 42 months. No discounting was used and HRQoL was not considered.

Outcome data

Kaplan–Meier data were used to assess the maintenance of AV synchrony and event-free survival in patients paced with a VDD versus a DDD pacemaker, and data were compared with the log rank test.

Resource use and cost data

Resource use was categorised as primary or secondary. Primary resource use was assumed to be any resource associated with initial pacemaker implantation, and included two nights of hospital stay, three doses of the antibiotic cefacolin (Elzogram), one routine pacemaker interrogation, one 24-h Holter-ECG and one chest X-ray.

Resources used in the ongoing management of pacemaker patients were categorised as secondary and included: prolonged stay or re-admission of patients; laboratory examinations; antibiotic therapy; additional chest X-rays, Holter recordings and pacemaker interrogations; operative revision, device explantation and re-implantation; and the treatment of atrial arrhythmias.

The cost associated with devices, leads, single-use operation material and sterilization were estimated from the average cost of each incurred by a single centre. Fees for implanting physicians, nurses and medical technicians were sourced from German standard implantation charges.

Summary of results

No significant differences in the occurrence of AF, cardiac disease or pacemaker-related complications were identified between patients paced with VDD compared with DDD devices.

Similarly, no significant differences in the event-free survival of the two patient groups were observed. However, cumulative costs of DDD pacing were significantly higher when compared with VDD pacing. The authors concluded that this was likely to be a consequence of the higher hardware and initial implantation costs associated with DDD devices, which is further compounded by higher follow-up costs.

Critique

The study by Wiegand et al. is thorough and transparent, with assumptions and potential limitations clearly stated. However, the time horizon considered is unlikely to be sufficient to capture the full cost-benefit of VDD versus DDD devices. With respect to transferability of the study findings to different health care systems, the authors state that the assumptions and standardizations carried out to calculate costs can be reliably transferred. Although application of the assumptions made to different settings may not be entirely feasible given the variation in care across health care centres and countries, the transparency of the study as described by Wiegand et al. may facilitate the comparison of resource use assumptions.

5.1.3 Narrative summary of included costing studies

Ray 1992

The aim of the study carried out by Ray et al.[63] was two-fold, firstly to assess the impact of the 1990 British Pacing and Electrophysiology Group (BPEG) guidelines on clinical practice and to assess the impact of full guideline adherence on cost. An audit of patients undergoing first pacemaker implant for the period of March 1990 to August 1991 was carried out and these data were used to assess changes in clinical practice and average device costs.

Summary of results

The1990 BPEG guideline recommendations by pacing indication are summarised in Table 35. Also presented are the proportion of patients implanted with recommended devices during the study period, the average cost of recommended devices as estimated by Ray et al.[63] and the estimated cost of full guideline adherence. Based on these data, the authors estimated that full adherence to BPEG recommendations would increase the annual budget for pacing hardware by 94% or 61% with respect to optimal or alternative pacing recommendations, respectively.

Table 35. Summary of results presented by Ray et al.[63]

Pacing indication	BPEG recommended pacing mode		Proportion of recommended pacing mode used in study period		Average cost of recommended pacing mode (£)		Cost of full guideline adherence (£)[a]	
	Optimal	Alternative	Optimal	Alternative	Optimal	Alternative	Optimal	Alternative
SND (148 pts)	AAIR	AAI	5.4%	27.0%	1,642	927	243,016	137,196
AV block (329 pts)	DDD	VDD	15.8%	0%	1,811	unknown	595,819	unknown
SND & AV block (6 pts)	DDDR	DDD	16.7%	33.3%	1,992	1,811	11,952	10,866
AV block & AF (52 pts)	VVIR	VVI	13.5%	86.5%	1,773	631	92,196	32,812
CSS/MVVS (15 pts)	DDI		53.3%	–	1,845	–	27,675	–

[a] No. of patients multiplied by average device cost.

Abbreviations used in table: AF, atrial fibrillation; AV, atrioventricular; CSS, carotid sinus syncope; MVVS, malignant vasovagal syncope; pts, patients; SND, sinus node dysfunction.

Critique

The study by Ray et al. provides information on the cost of devices incurred by a single centre in 1991 and is therefore of limited use to inform an up-to-date economic evaluation. However, the study itself seems to have been well conducted, if poorly reported.

5.1.4 Summary and conclusions of available cost-effectiveness evidence

Aside from the work carried out to inform TA88, no economic evaluations considering the cost-effectiveness of dual-chamber versus single-chamber atrial pacemakers in a UK health care setting were identified by the TAG systematic review. Castelnuovo et al. considered the impact of complications, upgrade (as a result of AV block), AF, HF, stroke and death on the cost-utility of dual- versus single-chamber atrial pacemakers. Furthermore, based on the clinical evidence available at the time of TA88, single-chamber atrial pacing was estimated to dominate dual-chamber pacing for

patients with SSS and no AV block. However, new clinical evidence of the relative effectiveness of dual- versus single-chamber atrial pacing has emerged.

In addition to the cost-utility of dual- versus single-chamber atrial pacing, Castelnuovo et al. considered the cost-utility of dual- versus single-chamber ventricular pacing. Similar to the analysis of dual-versus single-chamber atrial pacing, these analyses considered the impact of complications, upgrade (as a result of pacemaker syndrome), AF, HF, stroke and death on estimates of cost-utility.[53]

Subsequent to the publication of TA88, four evaluations of the cost-effectiveness of dual-chamber (or physiological) pacing versus single-chamber ventricular pacing have been published.[52;58;60;61] Of these, two were based on an evidence submission from the Association of British Healthcare Industries (ABHI, carried out by Caro Research) that was submitted as part of TA88.[52;60] These evaluations employed a discrete event simulation considering the impact of implantation-related complications, pacemaker syndrome (potentially resulting in an upgrade procedure), AF, stroke and death on the cost-utility of dual- versus single-chamber ventricular pacemakers. Of the two remaining cost-effectiveness analyses, one was carried out alongside the CTOPP clinical trial[61] and considered costs in relation to the relative extension of life or prevention of AF in patients paced with dual-versus single-chamber ventricular pacemakers. The remaining study assessed the impact of complications, upgrade as a result of pacemaker syndrome, AF, HF, stroke and death on the cost-utility of dual-versus single-chamber ventricular pacemakers.[58]

In the updated search conducted by the TAG, a cost-effectiveness analysis that included the DANPACE trial was identified.[59] The main strength of this evaluation was that it was informed by individual patient-level data. However, it was conducted from the perspective of the Danish health care system and principally focused on the occurrence of stroke or death as the clinical outcomes of interest in the model.

Therefore, based on review of the current economic literature, the TAG considered there to be a need for a *de novo* economic analysis of dual- versus single-chamber atrial pacing in people with bradycardia as a result of SSS and with no AV block. Furthermore, review of the economic literature around pacing revealed common consideration of the following pacemaker sequelae:

- peri- and post-operative complications;
- the potential for upgrade requirements in people paced with single-chamber devices;

- onset of AF;
- HF;
- stroke;
- cardiovascular mortality;
- all-cause mortality.

Consequently, following consultation with clinical experts, these outcomes were incorporated into the economic evaluation developed by the TAG (Section 5.2).

5.2 Independent economic assessment

5.2.1 Overview

The TAG constructed a *de novo* economic model in Microsoft Excel to estimate the cost-effectiveness of dual-chamber versus single-chamber atrial pacemakers in a population of patients with bradycardia as a result of SSS without AV block. A Markov model was utilised with monthly cycle length to carry out the analysis. The perspective used in the economic model is that of the NHS and Personal Social Services (PSS). Costs and benefits are discounted at 3.5% per annum and the model uses a monthly cycle length. Full details of the population modelled, model structure used, inputs, outputs and sensitivity analyses are presented in the sections that follow.

5.2.2 Comparison to scope

The final scope issued by NICE for this MTA is summarised in Table 36, alongside a commentary detailing to what extent the TAG economic analysis adheres to the scope.

Table 36. Comparison of the Technology Assessment Group analysis with the NICE scope

NICE scope		**TAG *de novo* analysis**
Intervention	Permanent implantable dual-chamber pacemakers	Yes
Population(s)	People with symptomatic bradyarrythmias due to sick sinus syndrome without atrioventricular block.	Yes
Comparator	Single-chamber atrial pacemakers	Yes
Outcomes	The outcome measures to be considered	Partially

	include: • mortality • morbidity (including incidence of heart failure, atrial fibrillation and stroke) • exercise capacity • cognitive function • requirement for further surgery • adverse effects of treatment (including peri- and post-operative complications, atrial fibrillation and device replacement) • health related quality of life.	Clinical, but not economic, assessment of the relative difference in the outcomes of exercise capacity and cognitive function were carried out.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	Yes, incremental cost per quality-adjusted life year assessed, time horizon is 10 years (to capture expected lifetime of devices), only costs relevant to an NHS and PSS perspective are included.
Other considerations	Guidance will only be issued in accordance with the CE marking.	NICE has formally requested information on CE marking from manufacturers but it has not been made available in time for inclusion in this MTA.
Abbreviations used in table: CE, Conformité Européenne; NICE, National Institute for Health and Care Excellence; MTA, Multiple Technology Appraisal; PSS, Personal Social Service; TAG, Technology Assessment Group.		

5.2.3 Population

The population that is the focus of this MTA is people with symptomatic bradyarrythmias as a consequence of SSS with, after full evaluation, no evidence of impaired AV conduction. As discussed in Section 4.2.2, from the trials identified in the TAG review of the clinical effectiveness literature, pooled estimates of clinical outcomes were available for:

- stroke (DANPACE 2011 and Nielsen 2003);
- change in pacing mode (Albertsen 2008, DANPACE 2011 and Nielsen 2003).

Although the review of the clinical effectiveness literature identified 6 relevant studies, disparity across the trials in definition of and reporting of clinical outcomes precluded meta-analysis for several outcomes. Thus, estimates of the relative effect of dual-chamber versus single-chamber atrial pacemakers are not available for all clinical outcomes considered in the economic model. Furthermore, the data from which pooled estimates of stroke and change in pacing mode are derived differ by outcome. Based on this and on clinical expert opinion of the reliability of the DANPACE trial, the TAG used data from DANPACE, rather than pooled estimates, to inform the base case economic model. The impact of incorporating pooled estimates on the cost-effectiveness of dual chamber pacemakers versus single-chamber atrial pacemakers, where possible, is explored in sensitivity analysis (Section 5.2.12).

The age and sex proportions of patients considered in the TAG's *de novo* economic evaluation mirror the baseline age (73 years) and sex proportion (35% male) of patients enrolled in the DANPACE trial. However, the proportions of patients with a history of AF (DANPACE: 44%), stroke (DANPACE: 8%) or HF (DANPACE: 12%) is assumed to be zero on entry into the economic model. This is a simplifying assumption (to avoid the need for multiple health states within the economic model) based on the use of measures of treatment effect (HRs) that are adjusted for potentially confounding factors, such as a history of AF, stroke or HF (see Section 5.2.7).

5.2.4 Interventions and comparators

The interventions and comparators of interest in this MTA are dual-chamber pacemakers versus single-chamber atrial pacemakers. As discussed in Section 2.3, pacemakers may or may not be rate-responsive; that is, have the functionality to sense and increase the heart rate in response to physical, mental or emotional activity. A variety of pacing modes are available in dual-chamber and single-chamber atrial pacemakers, for example:

- DDDR-s dual-chamber pacing with short AV delay (< 150 ms);
- DDDR-l, dual chamber pacing with a fixed long AV delay (300 ms);

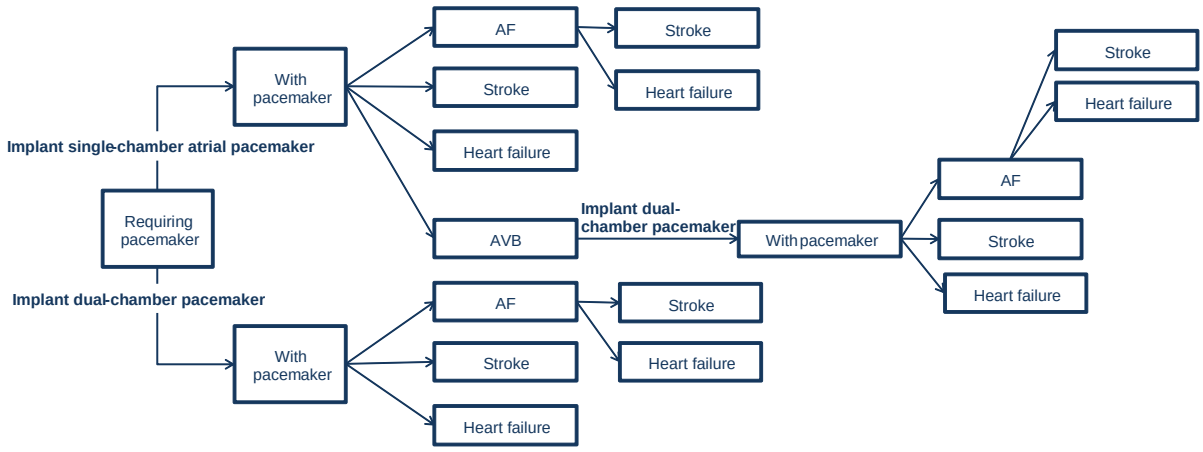
The DANPACE trial, and therefore the TAG economic evaluation, considers DDDR (dual-chamber pacing with rate control) versus AAIR (single-chamber atrial pacing with rate control) pacemakers.

5.2.5 Model structure

The TAG economic model is a Markov cohort model consistent with that used in TA88, of which this MTA is, in part, an update. Furthermore, to facilitate a comparison of the cost-effectiveness of dual-chamber pacemakers versus single-chamber atrial pacemakers, the model structure employed by the TAG is derived from that used in TA88 to assess the cost-effectiveness of these interventions in people with SSS and no AV block (Figure 9). The cycle length of the model is 1 month, as, according to clinical experts, 1 month is sufficient for patients to feel the benefit of pacemaker implantation.

Patients enter the model requiring a pacemaker and are assigned to receive either a dual-chamber pacemaker ("Implant dual-chamber pacemaker"; n = 1,000) or a single-chamber atrial pacemaker ("Implant single-chamber atrial pacemaker"; n = 1,000). After implantation of the respective pacing devices, patients transition into the "With pacemaker" health states; that is, the "With dual-chamber pacemaker" and "With single-chamber atrial pacemaker" health states.

Figure 9. Overview of TAG economic model structure



The risk of reoperation is only possible for patients initially implanted with a single-chamber device (see Section 5.2.7). Based on a subgroup analysis of reoperation data from DANPACE, all patients requiring reoperation are assumed to receive a dual-chamber device. Analysis of reasons for reoperation in DANPACE indicated that a statistically significantly larger proportion of people who initially received a single-chamber pacemaker required reoperation to change pacing mode compared with those who received a dual chamber pacemaker (Table 37): all other reasons for reoperation were found to be not statistically significant.

For people implanted with single-chamber atrial devices, the need to change pacing mode is predominantly a result of the development of AV block requiring upgrade to a dual-chamber device. Therefore, to capture this statistically significant difference in the need for reoperation between the two pacemaker types, the cost and QoL of patients requiring a reoperation was based on the difference in event rates between the two arms and was applied in the model solely to patients receiving a single-chamber atrial device. This simplification in the model was tested in a structural sensitivity analysis (see Section 5.2.12).

Furthermore, to maintain the focus of the model on the statistically significant difference between the device arms attributed solely to reoperation to change pacing mode, only one instance of reoperation was permitted within the model time horizon.

Table 37. Reasons for reoperation in patients enrolled in DANPACE (adapted from Table 3 of Nielsen et al[42]

Reason for re-operation	**Treatment arm**		**p-value**
	AAIR, n (%)	**DDDR, n (%)**	
Battery depletion	59 (8.3)	42 (5.9)	0.09
Change of mode of pacing	66 (9.3)	4 (0.6)	< 0.001
Lead complications	37 (5.2)	30 (4.2)	0.42
Surgical or mechanical complications	10 (1.4)	7 (1.0)	0.52
Infection	3 (0.4)	3 (0.4)	0.98
Skin erosion	1 (0.1)	3 (0.4)	0.31
Device failure	2 (0.3)	2 (0.3)	0.99
Abbreviations used in table: AAIR, single-chamber atrial pacing with rate control; DDDR, dual-chamber pacing with rate control.			

Patients residing in the “With pacemaker” health states are at risk of developing the sequelae of AF, stroke or HF, and patients who develop HF or stroke remain at risk of reoperation; however, in the event of reoperation, patients do not transition from the “HF” or “Stroke” health states, but instead simply incur the cost of reoperation. Patients who develop AF are at risk of the further sequelae of HF or stroke. However, once patients develop AF they are at no further risk of reoperation, as, after consultation with clinical experts, it has been assumed that, on development of AF, pacing will either cease or patients will be given a ventricular pacing device.

All patients are at risk of death, regardless of health state (Section 5.2.8).

5.2.6 Overview of model parameters, sources and assumptions

Table 38. Summary of parameters and accompanying distributions used to inform the TAG economic model.

Parameter	Mean Value	Variance	Source	Section
Baseline characteristics				
Age	73	Estimated 95% CI: 50.85 to 95.15	Assumption	5.2.3
Probabilities Dual Chamber pacemakers				
Paroxysmal AF	0.23	95% CI: 0.16 to 0.35[a]	Nielsen 2011[42] (163 events, 708 patients).	5.2.7
Chronic AF	0.11	95% CI: 0.08 to 0.7[a]	Nielsen et al 2011[42] (76 events, 708 patients).	5.2.7
Heart failure	0.24	95% CI: 0.17 to 0.36[a]	Nielsen 2011[42] (169 events, 708 patients).	5.2.7
Stroke	0.05	95% CI: 0.03 to 0.07[a]	Nielsen et al 2011[42] (34 events, 708 patients).	5.2.7
Hazard ratios; clinical sequelae for single-atrial chamber pacemakers compared to dual chamber pace makers				
Paroxysmal AF	HR 1.24	95% CI: 1.01 to 1.52	Nielsen 2011 [42]	5.2.7
Chronic AF	HR 1.01	95% CI: 0.74 to 1.39	Nielsen 2011[42]	5.2.7
Heart failure	HR 1.09	95% CI: 0.88 to 1.35	Riahi 2012 [45]	5.2.7
Stroke	HR 1.11	95% CI: 0.70 to 1.77	Nielsen 2011 [42]	5.2.7
Mortality				
Implantation health states	Age specific rate of all-cause mortality from UK	N/A	ONS[86]	5.2.8
With pacemaker				

health states	general population; weighted by the proportion of male and female patients modelled.			
Hazard ratios; mortality				
AF (versus general population)	2.08	95% CI: 2.01 to 2.16	Miyasaka 2007[87]	5.2.8
Stroke-males (versus general population)	3.59	95% CI: 2.38 to 5.42[b]	Carter 2007[88]	5.2.8
Stroke-females (versus general population)	3.14	95% CI: 2.26 to 4.38	Carter 2007[88]	5.2.8
Heart failure (versus general population)	1.32	Estimated 95% CI: 1.17 to 1.48	Pocock 2006[89]	5.2.8
AF & stroke (versus stroke population)	1.33	95% CI: 1.01 to 1.76	Carter 2007[88]	5.2.8
AF & Heart failure (versus HF population)	1.11	95% CI: 1.00 to 1.23	Pocock 2006[89]	5.2.8
Health state utility values				
Implant pacemaker	0.73	–	Fleischmann 2006[90]	5.2.10
With pacemaker	0.83	–	Fleischmann 2006[90]	5.2.10
Stroke	(month 1) 0.64	95% CI: 0.15 to 1.00	Luengo-Fernandez 2013[91]	5.2.10
	(after 1 month) 0.70	95% CI: 0.28 to 1.00		
Change from 'with pacemaker to atrial fibrillation'	0.02	95% CI: 0.01 to 0.03	Fleischmann 2009[92]	5.2.10
AF& Stroke	(month 1) 0.64 (after 1 month)	95% CI: 0.15 to 1.00 95% CI: 0.28 to	Assumption that values are the same as stroke without AF[91]	5.2.10

	0.70	1.00		
Heart failure	0.64	95% CI: 0.44 to 0.91	Lopez-Jimenez 2002[11]	5.2.10
AF & Heart failure	0.64	95% CI: 0.44 to 0.91	That values are the same as heart failure without AF[11]	5.2.10
Death	0	N/A	Assumption	5.2.10
Costs				
Unit costs				
Single chamber atrial pacing	£1,875	Estimated 95% CI: £1,191 to £2,366	Weighted average calculated from NHS Reference Costs 2012- 2013[93]	5.2.11
Dual chamber pacing	£2,438	Estimated 95% CI: £1,642, £3,040	Weighted average calculated from NHS Reference Costs 2012- 2013[93]	5.2.11
Heart failure episode	£1,228	Estimated 95% CI: £1,004 to £1,541	Weighted average calculated from NHS Reference Costs 2012- 2013[93]	5.2.11
Stroke episode	£1,427	Estimated 95% CI: £988 to £1,616	Weighted average cost calculated from NHS Reference Costs 2012- 2013[93]	5.2.11
Cardiologist Non-Admitted Non-Face to Face Attendance, Follow-up	£86	Estimated 95% CI: £40 to £107	NHS Reference Costs 2012-2013[93]	5.2.11
Total UK direct healthcare cost of CVD	£8,680,892	95% CI: £6,267,529 to £13,422,948[a]	Townsend 2012[94]	5.2.11
Average annual post-stroke hospitalisation cost	£1,444	95% CI: £1,043 to £2,234[a]	Calculated from average of post-first year hospitalization costs (2009 cost year US$ converted to UK£ according to conversion rate reported in study [$1 = £0.64]),Luengo-Fernandez 2012[95]	5.2.11
Total annual UK stroke medication costs	£86,172	95% CI: £62,215 to £133,245[a]	Townsend 2012[94]	5.2.11

Total UK stroke primary care costs	£40,034	95% CI: £28,904 to £61,903[a]	Townsend 2012 [94]	5.2.11
Episode cost of stroke in people with AF	£10,413	£95% CI: £215 to £53,539	Luengo-Fernandez 2013[96]	5.2.11
Average annual post-stroke hospitalisation cost in people with AF	£3,370	95% CI: £0.85 to £24,371	Annual costs for people surviving past the 90-day acute period, Luengo-Fernandez et al[96]	5.2.11
Cost of GP referrals for AF	£49,800	95% CI: £35,955 to £77,004[a]	Stewart 2004[97]	5.2.11
Cost of hospital outpatient referrals for AF	£36,400	95% CI: £26,280 to £56,284[a]	Stewart 2004[97]	5.2.11
Cost of hospital admissions with principal diagnosis of AF	£271,600	95% CI: £196,093 to £419,965[a]	Stewart 2004[97]	5.2.11
Cost of post-discharge outpatient visits	£31,700	95% CI: £22,887 to £49,017[a]	Stewart 2004[97]	5.2.11
Cost of anticoagualation in AF patients: - Apixaban - Dabigatran - Rivaroxaban - Warfarin	 £1.10 £1.10 £2.20 £6.08	N/A	 BNF 67(98) BNF 67(98) BNF 67(98) eMIT(99)	5.2.11

[a] As no measure of uncertainty was reported, a standard error of 0.25 was assumed.

Abbreviations used in table: AF, atrial fibrillation; AV, atrioventricular; BNF, British National Formulary; eMIT, electronic market information tool; HR, hazard ratio; NHS, National Health Service; ONS, Office of National statistics.

5.2.7 Treatment effectiveness

The effect of dual-chamber versus single-chamber atrial device implantation on the clinical outcomes considered in the TAG economic model were predominantly informed by the results reported from the DANPACE trial. In particular, the risk of reoperation due to change of mode of pacing was

estimated from summary statistics reported by Nielsen et al.[42] Similarly, the risks of developing AF or stroke were based on summary statistics reported by Nielsen et al. and the risks of HF based on summary statistics reported by Raihi et al.[42;45] Targeted literature searches were carried out in Google Scholar to identify up-to-date published sources of the risks of stroke and HF in people with AF.

Probabilities of reoperation

Nielsen et al. reports the number of patients requiring reoperation for various indications, including battery depletion, need for surgical change of mode of pacing, lead complications, surgical or mechanical complications, infection, skin erosion and device failure. Overall, reoperation is statistically significantly (adjusted HR [single-chamber atrial versus dual-chamber pacing]: 2.00, 95% CI: 1.54 to 2.61, $p < 0.001$)[42] different between treatment arms, with a higher rate of reoperation in people receiving a single-chamber atrial pacemaker (Section 5.2.5).

As discussed in Section 5.2.5, of conditions requiring reoperation, a statistically significant difference between pacemaker types was identified only for surgical change of mode of pacing, with a significantly larger proportion of people in the AAIR treatment arm requiring reoperation compared with the DDDR treatment arm (9.3% AAIR *vs* 0.6% DDDR, $p < 0.001$) over an average follow-up period of 5.4 years.

For people implanted with single-chamber atrial devices, the need to change pacing mode is predominantly a result of the development of AV block, which requires an upgrade to a dual-chamber device. For the model, the difference in event rates for reoperation was used to estimate the risk of patients with a single-chamber atrial device developing AV block per patient per month, and this was applied as a constant risk for the time horizon covered by the model.

To derive the probabilities required for the economic model, the difference in monthly event rates in the single- and dual-chambers arms was calculated using:

$$r = \frac{-Ln\left(1 - \left(\frac{n_s}{N_s} - \frac{n_d}{N_d}\right)\right)}{5.4 * 12}$$

Where r = event rate, n_s = number of events in the single-chamber atrial pacemaker arm, N_s = number of patients receiving a single- chamber atrial pacemaker, n_d = number of events in the dual-chamber pacemaker arm, N_d = number of patients receiving a dual-chamber pacemaker:

This monthly rate was then converted into a monthly probability, using standard formulae:

$$p = 1 - \exp(-rt)$$

Where p = monthly probability, r = event rate and t = time (months).

This resulted in a monthly rate of 0.142% and a monthly probability of 0.142%.

The decision to use this approach was based on the need to capture the uncertainty associated with reoperation for one-way sensitivity analysis and probabilistic sensitivity analysis (see Section 5.2.12). However, as the Kaplan–Meier plot presented by Nielsen et al.[42] suggests a non-linear decline in reoperation, as opposed to a constant rate, an alternative approach using reoperation as a time-dependent parameter was explored as a structural sensitivity analysis (see Section 5.2.12).

At 96 months post-implantation, based on an 8-year battery life, all patients who had not yet experienced reoperation or developed AF were assumed to receive a replacement dual-chamber device.

Probabilities of atrial fibrillation, heart failure and stroke

Nielsen et al. and Riahi et al. report the number of cases of AF, stroke and HF observed per arm, together with HRs of single-chamber atrial pacemakers versus dual-chamber pacemakers over an average follow-up period of 5.4 years.[42;45] Therefore, to derive the probabilities required for the economic model, the event rates in the dual-chamber arm were calculated using:

$$r = \frac{-Ln(1 - \frac{n}{N})}{5.4*12}$$

Where r = event rate, n = number of events and N = number of patients receiving a dual-chamber pacemaker.

The event rates in the single-chamber atrial pacemaker arm were calculated by applying the event specific HR to the event rate in the dual-chamber arm.

These rates were then converted into monthly probabilities, using standard formulae:

$$p = 1 - \exp(-rt)$$

Where p = monthly probability, r = event rate and t = time (months),

Table 39 summarises the monthly probabilities used to estimate the number of people implanted with a single-chamber atrial or dual-chamber device who go on to experience AF, HF or stroke.

Table 39. Probability of clinical sequelae derived from DANPACE[42]

Outcome	Single-chamber atrial pacemaker arm			Dual-chamber pacemaker arm	
	HR	Monthly Rate	Monthly Probability	Monthly Rate	Monthly Probability
Paroxysmal AF	1.24	0.50%	0.68%	0.40%	0.58%
Chronic AF	1.01	0.18%		0.18%	
Heart failure	1.09	0.46%	0.46%	0.42%	0.42%
Stroke	1.11	0.08%	0.08%	0.08%	0.08%
Abbreviations used in table: AF, atrial fibrillation; HR, hazard ratio.					

Probabilities of heart failure and stroke in people with AF

As discussed in Section 5.2.5, patients who develop AF are at risk of the further sequelae of HF or stroke. HF and AF are often co-morbid conditions and AF is a well-known risk factor for stroke, in particular ischaemic stroke.[71] Therefore, targeted searches of the literature were carried out in Google Scholar to identify recent publications estimating the risk of HF and of stroke in people with AF. No studies were identified in which the risk of HF in people with AF was estimated; therefore, it was assumed within the economic analysis that the risk of HF was the same in people with and without AF.

With respect to the risk of stroke in people with AF, a recent publication by Gallagher et al. was identified in targeted searches.[100] Gallagher et al. report the results of a population-based cohort study of people with AF. Incidence rates of stroke, adjusted for covariates such as $CHADS_2$ score, age, and smoking status, were presented for:

- all patients (2.3 per 100 person years);
- patients currently exposed to warfarin therapy (0.9 per 100 person years);
- patients recently exposed to warfarin therapy (2.2 per 100 person years);
- patients with a history of warfarin therapy (2.4 per 100 person years);
- patients with no history of warfarin therapy (3.4 per 100 person years).

Current guidelines recommend effective anticoagulation therapy for stroke prevention in people with paroxysmal and persistent AF.[101] Therefore, the incidence rate of stroke in people currently exposed to warfarin therapy (0.9 per 100 person years) was considered the most suitable to inform the risk of stroke in people with AF. The TAG notes that this is close to the monthly rate of stroke (0.08%) identified in DANPACE.

5.2.8 Mortality

Within the TAG economic model, patients are at risk of death following entry into the model until transition into the absorbing state of "Death". Based on pooled estimates of all-cause and cardiovascular mortality identified in the clinical literature review, the risk of death is assumed to be consistent across treatment arms. However, the level of mortality risk to which patients are exposed varies with respect to age and the health state in which they reside. Table 40 summarises the risk of all-cause mortality, by health state, along with the sources of these data (identified in targeted searches of the literature).

As no evidence of inflated mortality risks for people requiring a pacemaker or people implanted with a pacemaker were identified, patients residing in the "Implantation" and "With pacemaker" health states were assumed to be at the same risk of death as the age- and gender-matched UK general population.

Table 40. All-cause mortality data used in the TAG economic model

Health state	Rate of all-cause mortality[a]	Source (Country)
Implantation health states	Age specific rate of all-cause mortality from UK general population;	ONS 2012 (UK)[86]

With pacemaker health states	weighted by the proportion of male and female patients modelled.	
AF	HR of 2.08 versus the general population all-cause mortality rate	Miyasaka 2007, a 21 year community-based study analysing the all-cause mortality risk of people with AF versus an age and gender matched general population (US). [87]
Stroke	HRs of 3.59 and of 3.14 versus the general population for males and females, respectively.	Carter 2007, a hospital-based cohort study to determine all-cause mortality with ischemic stroke compared with an age-matched healthy cohort (UK). [88]
AF and stroke	HR of 1.33 versus people with stroke and no AF	
Heart failure	HR of 1.32, calculated from a weighted average of HR for people with NYHA Class III (1.30, n = 3,985) and NYHA Class IV (1.68, n = 197).	Pocock 2006, an analysis of data from the CHARM programme to develop predictive models of all-cause mortality (International) [89]
AF and heart failure	HR of 1.11 versus people with heart failure and no AF	
[a] Converted into monthly probabilities for use in the model; prob=1-exp(-rate*time). Abbreviations used in table: AF, atrial fibrillation; CHARM, Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity; HR, hazard ratio; NYHA, New York Heart Association; ONS, Office of National statistics; SMR, standardised mortality rate; TAG, Technology Assessment Group.		

Based on publications identified by Miyasaka et al.,[87] Carter et al.[88] and Pocock et al.[89] people with AF, stroke, or HF are assumed to be at increased risk of all-cause mortality versus the UK general population. Furthermore, people with AF and stroke and people with AF and HF are assumed to be at further risk of death as a result of the concomitant conditions.

In addition to all-cause mortality, patients experiencing events such as stroke and HF are at risk of death as a direct result of the event experienced. Case fatality as a result of stroke was calculated from data presented by Carter et al.[88] Carter et al. report the number of people dying within 30 days of an acute stroke event (n = 32/545) and, of these, the number with concomitant AF (n = 14). Table 41 summarises the calculation of the probability of stroke case fatality in people with and without AF.

Table 41. Probability of fatal stroke based on data presented by Carter et al.[88]

AF (N)	Fatal stroke (n)	Probability of fatal stroke
Yes (103)	14	13.59%
No (442)	18	4.07%
Abbreviation used in table: AF, atrial fibrillation.		

Case fatality after development of HF is derived from information presented by Cowie et al.[102] and Mosterd et al.[103] for people without and with AF, respectively. Cowie et al. report the results of a population based observational study (West London, UK) of patients with a new diagnosis of HF; 81% of patients were reported as being alive 1 month after developing HF. Therefore, in the TAG economic model, 19% of new HF cases were assumed to be fatal. Mosterd et al. report the results of prognostic analyses of a population based cohort study (Rotterdam, the Netherlands) in patients with HF; cardiac death in people with AF was associated with a HR of 2.08, which was applied to the 19% risk of fatal HF in people to calculate the risk of fatal HF in people with AF. Table 42 summarises the probability of death following event sequelae used in the base case economic analysis. All the probabilities used to inform mortality in the economic model are tested in one-way and probabilistic sensitivity analyses (see Section 5.2.12).

Table 42. Probability of fatal event used in TAG base case economic evaluation

Event	Probability of fatal event	Source
Stroke	4.07%	Carter 2007[88]
Stroke (and AF)	13.59%	
Heart failure	19.00%	Cowie 2000[102]
Heart failure (and AF)	34.80%	Mosterd 2001 [103]
Abbreviation used in table: AF, atrial fibrillation.		

5.2.9 Adverse events

Review of the clinical effectiveness and safety evidence for single-chamber atrial pacemakers versus dual-chamber pacemakers identified information on the following adverse events:

- lead displacement;
- infection;

- haematoma;
- pacemaker-mediated tachycardia;
- oversensing;
- loss of pacing capture;
- pacing system explantation;
- atrial arrhythmia;
- ventricular arrhythmia;
- syncope;
- skin erosion;
- device failure.

No statistically significant differences in the rates of these adverse events were identified between treatment arms. Therefore, with the exception of adverse events leading to reoperation, which are captured within the reoperation data from DANPACE (Section 5.2.7), no adverse events were included in the base case economic model.

5.2.10 Health-related quality of life data

A systematic review was carried out in December 2013 to identify published HRQoL evidence relevant to the decision problem that is the focus of this MTA. That is, dual chamber pacemakers versus single chamber atrial pacemakers in patients with bradycardia as a result of SSS without AV block. The following databases were searched:

- MEDLINE (Ovid);
- EMBASE (Ovid);
- HTA database (HTA, Cochrane Library);
- NHS EED (Cochrane Library).

To facilitate the identification of all potentially relevant information, the MEDLINE and EMBASE search strategies used terms capturing population (pacing), interventions (dual-chamber pacemakers) and HRQoL studies combined with terms designed to capture a broader range of comparators than

those specified in the final scope: HRQoL evidence in patients receiving single chamber ventricular pacing was considered likely to be transferable to the patient population that is the focus of this MTA.

The search strategy for HTA and NHS EED combined terms for the target condition (AV block, SSS), terms for the intervention (pacemaker) and terms for HRQoL (quality of life, QoL and QALY). All databases were searched from inception, full details of the search terms are presented in Appendix 1 Literature search strategies. In addition to database searching, the reference lists of identified studies were reviewed for any potentially relevant studies.

No restrictions on language or setting were applied to any of the searches. The titles and abstracts of papers identified through the searches were independently assessed for inclusion by two health economists using the criteria outlined in Table 43.

The systematic review was updated in June 2014. The search strategy remained the same as outlined above; however, results were limited from 17 December 2013 to 6 June 2014 in order to identify only additional relevant studies.

Table 43. Inclusion and exclusion criteria for the systematic review of health related quality of life evidence

Inclusion criteria	Exclusion criteria
Q1: possible generic, preference based measure of HRQoL (e.g., EQ-5D, SF-6D, HUI) or standard gamble/time trade-off studies any setting (to be as inclusive as possible) Q2: possible generic, non-preference based measure of HRQoL (e.g., SF-36) Q3: possible condition specific measure of HRQoL	• abstracts with insufficient methodological details • systematic reviews • intervention is not pacing • disease area is not AV block or SSS • publications in languages other than English
Abbreviations used in table: AV, atrioventricular; SSS, sick sinus syndrome.	

A total of 501 papers was identified from the December 2013 search (Figure 10). Of these papers, 425 were excluded following review of the title and abstract. Therefore, a total of 76 papers were identified as potentially relevant. Of these papers, 13 were identified, from the abstract, as reporting condition specific measures of HRQoL and 12 as reporting generic non-preference-based measures of HRQoL (mostly SF-36), with 51 papers identified as potentially reporting generic, preference-based measures of HRQoL (Q1, Table 43). To be as inclusive as possible, studies for which it was unclear

from the abstract which type of HRQoL measure was used were labelled as potentially reporting a generic, preference-based measure of HRQoL.

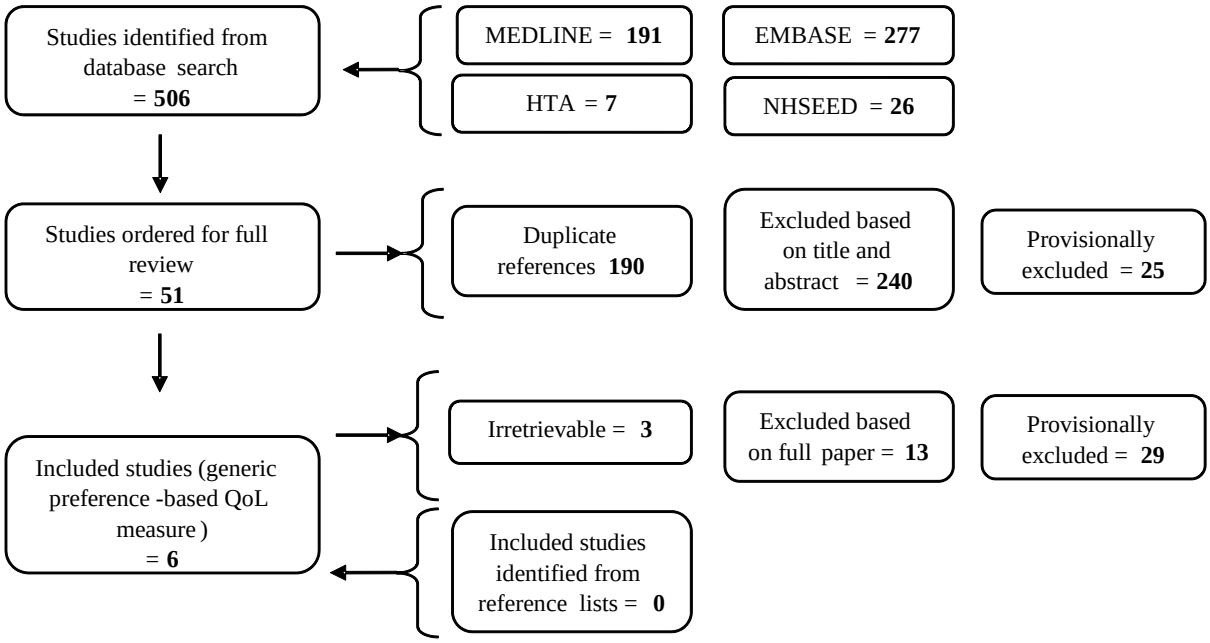
Papers identified as reporting either condition-specific measures of HRQoL or generic non-preference-based measures of HRQoL during the December 2013 search were provisionally excluded. That is, these studies were reserved for inclusion, and the full-text reviewed only if no suitable generic, preference-based measures of HRQoL were identified: this is because, as specified in the NICE reference case,[104] generic, preference-based measures of HRQoL, such as the EQ-5D, are preferred for the purposes of economic evaluation.

Review of the 51 papers potentially reporting generic, preference-based QoL studies identified 6 studies as relevant, and these studies were listed for final inclusion. The remaining 45 studies were excluded (or provisionally excluded) for the following reasons (full details provided in Appendix 4 Table of excluded studies):

- 14 reported generic non-preference-based measures of QoL;
- 10 did not report any QoL data;
- 9 reported condition-specific measures of QoL;
- 6 were published in a language other than English;
- 3 were irretrievable;
- 2 were reviews;
- 1 study did not consider pacing.

As HRQoL data from the UK were considered to be the most relevant to the decision problem that is the focus of this MTA, papers published in languages other than Englosh were provisionally excluded at this stage. Five papers were identified from the updated search in June 2014. However, after reviewing the title and abstract none was identified as reporting HRQoL data relevant to the scope of this review.

Figure 10. Identified HRQoL studies, December 2013 and June 2014 searches



Six studies were identified as reporting generic, preference-based HRQoL data. Full details of the populations and health states considered and instruments and utility values reported in these studies are presented in Appendix 2 Data abstraction; a summary of these data is presented in Table 44.

Table 44. Summary of included HRQoL studies

Included study	Country	Population[a]	Health states	Instrument
Fleishmann 2009	USA	Patients enrolled in MOST[70]	No AF, developing PAF, CAF	TTO
Fleishmann 2006	USA	Patients enrolled in MOST[70]	DDDR pacing, VVIR pacing	TTO
Shukla 2005	USA	Patients enrolled in MOST[70]	Pacemaker sensing mode (accelerometer, piezoelectric crystal or blended)	TTO
Link 2004	USA	Patients enrolled in MOST, [70] who were randomised to VVIR pacing mode and went on to develop pacemaker syndrome	Baseline, pre-crossover, post-crossover	TTO
Lamas 2002	USA	Patients enrolled in MOST[70]	DDDR pacing, VVIR pacing	TTO
Lopez-Jimenez	USA	Patients enrolled in PASE	Baseline and 3 months, 9	TTO

2002		Lopez-Jimenez [11]	months and 18 months after implantation	

[a] Patients enrolled in MOST and PASE received dual-chamber pacing systems and were randomised to be paced in VVIR or DDDR pacing modes.

Abbreviations used in table: AF, atrial fibrillation; CAF, chronic atrial fibrillation; HRQoL, health-related quality of life; PAF, paroxysmal atrial fibrillation; SSS, sick sinus syndrome; TTO, time trade off.

All the HRQoL studies identified for inclusion, report time trade off (TTO) utility data collected directly from patients (i.e., patient measurement and valuation). Of these, five[70;90;92;105;106] report the results of QoL analyses carried out with patients enrolled in the MOST clinical trial.[70] The remaining study[11] reports utility data collected from patients enrolled in the PASE trial.[73] These studies are described in further detail in Appendix 2 Data abstraction.

Narrative summary of included HRQoL studies

Fleischmann 2009

Fleischmann *et al*[92] assess the impact of AF on the QoL and functional status of patients enrolled in the MOST clinical trial.[70] Patients enrolled in MOST had SSS and were randomised to either DDDR or VVIR pacing. The average age of patients was 73 years, 52% were male, approximately 45% had paroxysmal AF and 20% had some form of AV block. HRQoL was assessed using the Medical Outcomes Study 36-item Short Form (SF-36) General Health Survey, and utilities were elicited using standard TTO methodology. Functional status was assessed using the Specific Activity Scale (SAS). Measurements were collected at baseline, 3 months and 12 months post-implantation in 1,841 patients, who were sub-divided into:

- those without AF (n = 1,737);
- those who developed paroxysmal AF but not chronic AF (n = 75);
- those with chronic AF (n = 29).

The changes observed in each measure (SF-36, TTO and SAS) between baseline and 12 months and between 3 months and 12 months of follow-up were analysed, with adjustments for age, gender, history of AF, history of HF, treatment arm, and baseline QoL score. In addition, to avoid confounding as a result of crossover, the last observed scores of patients who crossed over from VVIR to DDDR pacing were carried forward for the remainder of the analytical time frame. A summary of

the results reported by Fleischmann et al. is presented in Table 45, statistically significant differences in utility, as assessed using TTO methodology, were identified.

Table 45. Summary of results reported by Fleischmann et al.[92]

Measure	No AF	Paroxysmal AF	Chronic AF	p-value[a]
Baseline to 12 months post-implantation				
PCS MC(SEM)	2.50 (0.44)	0.90 (0.77)	–0.30 (1.62)	0.04
SAS MC (SEM)	0.03 (0.03)	0.15 (0.06)	0.21 (0.12)	0.05
TTO	0.07	0.06	0.11	> 0.05
3 months to 12 months post-implantation				
SAS MC (SEM)	0.05 (0.03)	0.12 (0.10)	0.44 (0.14)	0.02
TTO	0.00	–0.02	0.03	> 0.05

[a] Comparison between AF (paroxysmal AF and chronic AF) and no AF.

Abbreviations used in table: AF, atrial fibrillation; MC, mean change; PAC, physical component (of SF-36) score; SAS, Specific Activity Scale; SEM, standard error of the mean; TTO, time-trade off.

Based on the analyses conducted, the authors concluded that "AF was not a major determinant of most QoL measures". However, statistically significant changes in the physical component of the SF-36 score and in the SAS measure of functional capacity indicate that the presence of AF may impair the physical improvement associated with pacemaker implantation.

Fleischmann 2006

In this analysis of serial QoL measures elicited from people enrolled in the MOST clinical trial,[70] Fleischmann et al.[90] consider the impact of pacemaker implantation and pacemaker mode (DDDR versus VVIR) on QoL. SF-36, SAS and TTO measures were used to assess QoL at baseline, and after 3 months and 12 months of follow-up, followed by yearly estimates: last observations were carried forward in people who crossed over from VVIR to DDDR pacing. Table 46 displays the TTO utilities, adjusted for age and gender, by pacing mode as presented by Fleischman et al.[90]

The authors conclude that irrespective of sex, the presence of HF or level of co-morbidity, pacemaker implantation was associated with statistically significant improvements in QoL. Furthermore, although a small but measurable effect of pacemaker mode was noted with the SF-36, no significant differences were observed in TTO utility estimates.

Table 46. Age and sex adjusted time trade off utilities presented by Fleischmann et al.[90] by pacing mode

Time point	DDDR	VVIR
Baseline (n = 1,935)	0.72	0.73
3 months (n = 1,736)	0.83	0.82
12 months (n = 1,639)	0.83	0.82
24 months (n = 1,208)	0.83	0.81
36 months (n = 748)	0.86	0.83
48 months (n = 392)	0.83	0.87

Shukla 2005

Shukla et al.[106] assessed the impact of pacemaker sensor type (accelerometer, piezoelectric or blended) on the QoL of patients enrolled in MOST.[70] The SF-36, SAS, 0–100 scale and TTO measures were used to elicit QoL and, in the case of TTO, to value QoL. Measures were taken at baseline, 3 months post-transplant and yearly thereafter: adjustments were made for age, gender, pacing mode (DDDR vs VVIR), follow-up time and baseline QoL. Patients implanted with a blended sensor device reported statistically significantly worse physical function at (physical function, $p = 0.009$; physical summary score, $p = 0.039$ and physical role function, $p = 0.08$) than patients with accelerometer or piezoelectric sensors. However, no other statistically significant differences in QoL were identified.

The authors concluded that patients implanted with blended sensor devices had lower physical function and absolute QoL scores. However, the authors considered that these observations may be a result of "clinical selection of the most sophisticated sensor for the most ill patient".

Link 2005

A subset (18.3%) of patients enrolled in MOST[70] and randomised to VVIR pacing went on to develop pacemaker syndrome according to pre-specified criteria. That is, developed "either congestive signs and symptoms associated with retrograde conduction during VVIR pacing or a ≥ 20 mm Hg reduction of systolic blood pressure during VVIR pacing, associated with reproducible symptoms of weakness, lightheadedness, or syncope".[105] Link et al. report the QoL (SF-36, SAS, TTO and 0–100 score) measured in these patients at baseline, prior to crossover and after crossover. Significant decrements in QoL were observed in six of the 10 SF-36 scales from baseline (i.e., pre-

implantation) to pre-crossover (Table 47). Utility was also lower than at baseline, but the difference was not statistically significant. After crossover, statistically significant improvements were seen in all measures of QoL (Table 47).

Table 47. Baseline, pre-crossover and post-crossover utility data presented by Link et al.[105]

QoL measure	Baseline score (SD) n = 153	Pre-crossover score (SD) n = 80[a]	Post-crossover score (SD) n = 136[b]
SF-36:			
Physical–composite	35.8 (10.7)	33.3 (10.1)	**38.0 (11.6)**
Mental–composite	51.5 (9.5)	49.8 (10.9)	**52.7 (11.6)**
Physical–function	56.4 (27.6)	**39.8 (28.1)**	**55.0 (29.7)**
Role–physical	28.4 (38.7)	28.4 (39.3)	**50.6 (43.0)**
Pain	66.8 (29.1)	70.9 (24.7)	69.5 (26.3)
Health perception	57.2 (21.1)	**52.4 (20.7)**	56.5 (21.5)
Energy	39.6 (23.2)	**32.1 (21.4)**	**49.9 (24.5)**
Social–function	67.7 (24.7)	**62.2 (26.5)**	**71.1 (24.1)**
Role–emotional	80.4 (34.7)	**75.4 (39.2)**	83.6 (32.9)
Mental health	77.4 (17.2)	**73.5 (19.6)**	**77.5 (17.8)**
SAS	2.09 (0.93)	**2.50 (0.91)**	**2.07 (0.94)**
TTO	0.75 (0.34)	0.73 (0.35)	**0.82 (0.31)**

[a] significant changes compared with baseline are in **bold.**

[b] significant changes from pre-crossover highlighted in **bold.**

Abbreviations used in table: QoL, quality of life; SAS, specific activities scale; SD, standard deviation; SF-36, short form 36 health survey; TTO, time trade off.

The authors concluded that "quality of life, as assessed by a variety of metrics, decreased at the time of diagnosis of pacemaker syndrome and improved after the pacemaker was reprogrammed to a physiologic mode. (However, a placebo effect cannot be truly ruled out, because neither patients nor physicians were blinded to the crossover status.)"[105]

Lamas 2002

Lamas et al. report the results, including HRQoL, of the MOST clinical trial.[70] QoL was assessed with the SF-36, SAS and TTO measures. Table 48 presents the changes in QoL measures from baseline as reported by Lamas et al.[70]

Table 48. Change in measures of quality of life observed in MOST[70]

Quality of life measure	Baseline		48 months		Change from baseline	p-value (dual versus ventricular)
	Dual	Ventricular	Dual	Ventricular		
SF-36						
Physical function	58.8	58.9	–3.2	–0.1	1.9	0.04
Physical role	35.7	34.6	18	26.7	8.6	< 0.01
Social function	63.5	62.6	6.4	9.8	2.5	< 0.01
Energy	41.9	42.6	3.6	5.2	4.1	< 0.01
Mental health	72	72	4.7	4.6	1.2	0.05
Emotional role	74	74	4.8	12.3	3.6	< 0.01
Pain	67.5	67	6.9	5.1	0.5	0.57
Health perception	60	60.2	–3.5	–2.5	1.1	0.09
Mental-component summary	48.4	48.4	2.4	3.5	1.1	< 0.01
Physical-component summary	38.5	38.4	1	2.2	1.2	< 0.01
Specific Activity Scale	2.01	1.97	0.16	0.13	0.002	0.94
Time-trade off utility (%)	73	72	6	6	2	0.06
Abbreviations used in table: SF-36, short form 36 health survey.						

Similar to the conclusions of Fleischmann et al.,[90] the authors noted that, compared with ventricular pacing, dual-chamber pacing provided significant improvements in six of the 10 SF-36 subscales, including the physical and mental component summary. However, no significant differences in utility as assessed by TTO were observed by pacing mode.

Lopez-Jimenez 2002

Lopez-Jimenez et al. report the results of the Pacemaker Selection in the Elderly (PASE) study, which is an RCT with the primary endpoint of HRQoL. Patients enrolled in PASE were in sinus rhythm and indicated for permanent pacing as a result of bradycardia, and were randomised to VVIR or DDDR pacing mode. The average age of patients was 76 years, 59% were male, 57% had AV block and 28% had NYHA Class III or IV HF. HRQoL was assessed using the TTO, SF-36 and 0–100 scoring systems. In addition to HRQoL, patients' functional status was assessed with SAS. Measurements were collected at baseline, 3 months, 9 months and 18 months after enrolment Table 49 summarises the estimates of HRQoL over time obtained by Lopez-Jimenez et al.[11]

Table 49. Summary of HRQoL estimates presented by Lopez-Jimenez et al.[11]

QoL measure	Baseline (n = 398)	3 months[a] (n = 284)	9 months[b] (n = 291)	18 months (n = 250)
TTO	0.74	**0.91**	0.87	0.87
SAS	2.0	1.89	**1.7**	–
0–100	64.1	**71.0**	**68.8**	–
SF-36				–
Physical function	53.9	57.5	57.0	
Social function	63.0	**76.7**	**70.2**	
Physical role	34.7	**62.4**	**57.0**	
Emotional role	68.6	**89.5**	**82.3**	
Mental health	72.7	**78.2**	78.3	
Energy	43.3	**55.3**	**52.2**	
Pain	66.7	70.2	71.3	
Health perception	60.5	62.6	**59.9**	

[a] Significant changes compared with baseline are in **bold.**

[b] Significant changes from 3 months follow-up highlighted in **bold.**

Abbreviations used in table: QoL, quality of life; SAS, Specific Activity Scale; TTO, time trade off.

In order to assess the validity of the TTO measure, the authors carried out "known group validity tests" in patients with and without CHF and in patients with and without stable angina. As expected, people with a history of CHF had a significantly lower utility than people with no history of CHF (0.64 vs 0.78, $p < 0.001$). Furthermore, people with NYHA classification of III or IV had a significantly lower utility than people with a NYHA classification of I or II (0.62 vs 0.80, $p = 0.0001$).

Utility estimates were not adjusted for potential covariates such as age or gender. However, subgroup analyses suggest that improvements in utility following pacemaker implantation were consistent regardless of implantation diagnosis, pacing mode, gender, age, employment status or history of angina.

The authors concluded that pacemaker implantation improves HRQoL to a mean level close to that of the general population.

Quality of life data selected for the economic model

The TAG economic model has the following health states, for which estimates of utility are required to facilitate the use of QALYs as the measure of benefit:

- implant single-chamber atrial pacemaker;
- implant dual-chamber pacemaker;
- with single-chamber atrial pacemaker;
- with dual-chamber pacemaker;
- AF;
- stroke;
- HF;
- AF and stroke;
- AF and HF;
- death.

Table 50 summarises the utility values used, along with the source of these data and the rationale for selecting these data to inform the base case model. The analyses carried out by Fleishmann et al.[90;92] and Lopez-Jimenez et al.[11] were identified in the TAG systematic review of the HRQoL literature. A targeted search for utility associated with stroke (with or without AF) was carried out identified a study by Luengo-Fernandez et al. that evaluated QoL after transient ischaemic attack and stroke.[91]

Table 50. Health state utility values used in the base case model

Health state	Utility	Source	Rationale for use in base case model
Implant single-chamber atrial pacemaker	0.725[a]	Fleischmann et al.[90]	• Largest and most homogeneous HSUV study identified in people with SSS; • Based on age and gender adjusted analysis.
Implant dual-chamber pacemaker			
With single-chamber atrial pacemaker	0.825[a]		
With dual-chamber pacemaker			

AF	0.805	Fleischmann et al.[92]	Only HSUV study of the impact of AF in people paced for bradycardia.
Stroke	0.640 (month 1), 0.70 thereafter	Luengo-Fernandez et al.[91]	Most recent and robust study identified by targeted search.
Heart failure	0.640	Lopez-Jimenez et al.[11]	Only HSUV study identified which reporting utility data for bradycardia patients with heart failure.
AF and stroke	0.640 (month 1), 0.70 thereafter	Luengo-Fernandez et al.[91]	Assumption
AF and heart failure	0.640	Lopez-Jimenez et al.[11]	Assumption
Death	0	Assumption	

[a] Average of value for people implanted with dual or single-chamber device.

Abbreviations used in table: AF, atrial fibrillation; AV, atrioventricular; HSUV, health state utility value; QoL, quality of life; SSS, sick sinus syndrome.

Clinical expert opinion suggests that the QoL of patients suffering a stroke in the presence of AF is lower than that of people suffering a stroke in the absence of AF. However, no utility data for AF patients suffering a stroke were identified from the literature. Therefore, the base case model assumes that the utility of stroke is the same regardless of the patient's AF status. Death is assumed to be associated with a utility of 0.

5.2.11 Costs

The costs accounted for within the TAG economic model, are categorised as follows:

- device and implantation costs;
- monitoring costs;
- episode costs;
- long-term costs.

No currently relevant UK costing studies were identified in the TAG's systematic review of the economic literature. Therefore, where possible, standard UK sources (NHS Reference costs 2012-

2013, NHS Generic Pharmaceuticals electronic Market Information Tool [eMIT] or the British National Formulary [BNF]) were used to inform the unit costs applied within the TAG economic model; these are described in more detail in the following sections. In addition, targeted searches for UK-specific resource use and costing studies of AF, HF and stroke were carried out in Google Scholar by trying different combinations of the terms; "costs", "NHS", "UK", with the various conditions "atrial fibrillation", "heart failure", "stroke" and "cardiovascular disease". Of these, the following publications were selected to provide base case model inputs:

- Townsend et al. British Heart Foundation (BHF) Coronary heart disease statistics. A compendium of health statistics. 2012 edition;[94]
- Luengo-Fernandez et al. Hospitalization resource use and costs before and after TIA and stroke: results from a population-based cohort study (OXVASC);[107]
- Luengo-Fernandez et al. Population-based study of acute and long-term care costs after stroke in patients with AF.[96]

Device and implantation costs

The procedure costs (including hardware cost) associated with implantation of a single- or dual-chamber device were obtained from a weighted average of episode costs associated with relevant HRG codes (NHS Reference costs 2012–2013[93]). Table 51 summarises the HRG codes used to inform each procedure cost used within the TAG economic model. Upgrade procedures were assumed to cost the same as an initial implantation of a dual-chamber device. Spell level (rather than episode level) data for each HRG code were used in sensitivity analysis (see Section 5.2.12).

Table 51. Summary of unit costs used to inform procedure costs within the TAG economic model

Procedure	Unit costs (HRG code)	Activity	Total cost[a]
Implantation of a single-chamber device	• £2,937 (EA03A, Pace 1: Single Chamber or Implantable Diagnostic Device, with CC Score 11+); • £2,277 (EA03B, Pace 1: Single Chamber or Implantable Diagnostic Device, with CC Score 8-10); • £2,085 (EA03C, Pace 1: Single Chamber or Implantable Diagnostic Device, with CC Score 5-7); • £2,083 (EA03D, Pace 1: Single Chamber or	• 2,233 • 2,711 • 5,291 • 11,768 • 19,218	£1,875

	Implantable Diagnostic Device, with CC Score 2-4); • £1,509 (EA03E, Pace 1: Single Chamber or Implantable Diagnostic Device, with CC Score 0-1).		
Implantation of a dual-chamber device	• £3,367 (EA05A, Pace 2: Dual Chamber, with CC Score 9+); • £2,630 (EA05B, Pace 2: Dual Chamber, with CC Score 5-8); • £2,466 (EA05C, Pace 2: Dual Chamber, with CC Score 2-4); • £2,146 (EA05D, Pace 2: Dual Chamber, with CC Score 0-1).	• 1,904 • 4,504 • 9,328 • 9,898.	£2,438
[a] Weighted average of unit costs; weighted by activity. Abbreviations used in table: CC, critical care; HRG, Healthcare Resource group.			

Device and implantation costs are applied at two points in the model: at first implantation and at upgrade, that is, to patients in the "Implant single-chamber atrial pacemaker" or "Implant dual-chamber pacemaker" health states.

Monitoring costs

Following pacemaker implantation, patients receive follow-up checks from a cardiologist (WF01C, Cardiologist Non-Admitted Non-Face to Face Attendance, Follow-up, £86).[93] Based on expert clinical opinion, initial follow-up is assumed to be 1 week after implant, with a second follow-up carried out at 2 months post-implantation and subsequent annual visits.[108] Therefore, within the model, the cost of a follow up visit is applied on entry into the "Implant single-chamber atrial pacemaker", "Implant dual-chamber pacemaker", "With single-chamber atrial pacemaker" and "With dual-chamber pacemaker" health states. The cost of a follow-up visit is also applied annually to all patients in the "With single-chamber atrial pacemaker" and "With dual-chamber pacemaker" health states.

Episode costs

Over the course of the TAG economic model, patients are exposed to the risk of HF and stroke, with or without the presence of AF. In the absence of AF, the occurrence of HF or stroke is associated with a cost that is based on a weighted average of episode level costs (spell level costs are used in sensitivity analysis, see Section 5.2.12) associated with relevant HRG codes (Table 52). In the presence of AF, however, the episode cost of stroke is assumed to be £11,275 based on evidence from

the OXVASC population-based cohort study reported by Luengo-Fernandez et al.[96] No evidence was identified indicating that the episode cost of HF would differ in the presence of AF.

The episode cost of HF is applied to patients entering the "Heart failure" and "AF & heart failure" health states. The episode cost of stroke is applied to patients entering the "Stroke" health state and the episode cost of stroke following AF is applied to patients entering the "AF & stroke" health state.

In people with dual-chamber pacemakers, the onset of AF may be associated with a need for reprogramming the device to act as a ventricular pacemaker. In line with clinical expert opinion and assumptions made in TA88, this cost comprises a cardiological consultation (WF01C, Cardiologist Non-Admitted Non-Face to Face Attendance, Follow-up, £86), and an ECG (DIAGIMDA, Simple Echocardiogram, 19 years and over, £41). People with single-chamber atrial pacemakers who develop AF may also require ventricular pacing, in which case the single-chamber atrial device will need to be replaced with a single-chamber ventricular device. The cost associated with device replacement is assumed to be equivalent to that of initial single-chamber implantation (£1,875).

Based on expert clinical opinion, the cost of reprogramming and of device replacement is applied to one third of people developing AF from the "With dual-chamber pacemaker" and "With single-chamber atrial pacemaker" health states. The impact of this assumption was tested in sensitivity analysis.

Table 52. Summary of unit costs used to inform heart failure and stroke episode costs within the TAG economic model

Episode	Unit costs (HRG code)	Activity	Total cost[a]
Heart failure	• £2,398 (EB03A, Heart Failure or Shock with CC Score 14+); • £1,919 (EB03B, Heart Failure or Shock with CC Score 11-13); • £1,389 (EB03C, Heart Failure or Shock with CC Score 8-10); • £1,034 (EB03D, Heart Failure or Shock with CC Score 4-7); • £799 (EB03E, Heart Failure or Shock with CC Score 0-3);	• 5,832 • 26,264 • 47,488 • 81,459 • 23,133;	£1,228
Stroke	• £5,497 (AA35A, Stroke with CC Score 16+);	• 3,263	£1,427

	• £4,428 (AA35B, Stroke with CC Score 13-15); • £2,433 (AA35C, Stroke with CC Score 10-12); • £1,575 (AA35D, Stroke with CC Score 7-9); • £1,060 (AA35E, Stroke with CC Score 4-6); • £1,023 (AA35F, Stroke with CC Score 0-3).	• 9,563 • 28,388 • 58,580 • 114,664 • 92,215	
Stroke following AF[b]		–	£11,275

[a] Weighted average of unit costs; weighted by activity.

[b] Based on 2008/09 cost of £10,413 reported by Luengo-Fernandez et al.[96] inflated to 2013 prices.[109]

Abbreviations used in table: CC, critical care; HRG, Healthcare Resource Group.

Long-term costs

Following the onset of HF, stroke or AF, patients are assumed to accrue costs over the long term, for example, medication, hospitalisation and primary care costs. For people with HF, these costs were determined from national prevalence and cost statistics reported in the 2012 BHF, Coronary heart disease statistics publication.[94] The following data were extracted from the BHF statistics report:

- 2009 total UK direct healthcare costs of cardiovascular disease (CVD): £8,680,892,000;
- 2011 UK prevalence of HF: 0.90% in men and 0.70% in women, total 160,719 cases;
- 2007–2010 UK prevalence of CVD (Table 53).

Table 53. Prevalence of cardiovascular disease, by sex and age, UK 2007 to 2010 (adapted from Table 2.20, Townsend et al[94]

Year	Men	Women
2007	10.9%	9.7%
2008	11.1%	9.4%
2009	11.4%	9.5%
2010	11.7%	10.1%

Based on the prevalence data presented in Table 53 above, the relative prevalence of HF as a percentage of CVD was calculated (7.53% for men and 6.39% for women, average 6.96%). Thereafter, the 2011 UK direct healthcare costs of CVD (£9,086,227,882) and of HF (£632,586,584) were estimated. Resulting in a per person cost of HF of £4,112 per annum (£343 per cycle) at 2013 prices. Full calculation details are available in Appendix 6 Calculation of long-term care costs associated with heart failure. The long-term costs associated with people with HF were applied monthly to people residing in the “Heart failure” and “AF & heart failure” health states.

For people experiencing stroke, the cost of hospitalisation estimated from the OXVASC population-based cohort study reported by Luengo-Fernandez et al.[96;107] were used. The cost of medication and primary care reported by Townsend et al.[94] were used to inform the base case. Table 54 summarises the unit costs used to inform long-term costs for people experiencing stroke.

Table 54. Summary of unit costs used to inform long-term costs of stroke used within the TAG economic model

Cost component	Annual cost	Source
Post-stroke hospitalisation cost	£1,564	Average of post-first year hospitalization costs (2009 cost year US$ converted to UK£ according to conversion rate reported in study [$1 = £0.64]), Luengo-Fernandez et al.[95] inflated to 2013 prices.
Post-stroke hospitalisation cost (in people with AF)	£3,649	Annual costs for people surviving past the 90-day acute period Luengo-Fernandez et al.[96] inflated to 2013 prices.
Medication costs	£81	Calculated from the 2009 stroke medication costs reported by Townsend et al.[94] (inflated to 2010/11 costs) divided by the 2010–2011 stroke prevalence also reported by Townsend et al.[94] inflated to 2013 prices.
Primary care costs	£38	Calculated from the 2009 stroke primary care costs reported by Townsend et al.[94] (inflated to 2010–2011 costs) divided by the 2010–2011 stroke prevalence also reported by Townsend et al.[94] inflated to 2013 prices.
Total cost per cycle "Stroke" health state		**£140**
Total cost per cycle "Stroke & AF" health state		**£400**
Abbreviations used in table: AF, atrial fibrillation.		

The long-term costs associated with people with stroke and people with AF and stroke were applied monthly to people residing in the "Stroke" and "AF & stroke" health states, respectively.

In people with AF, long-term costs of primary care and hospitalisation were identified from a predictive study carried out by Stewart et al.[97] Stewart et al. evaluated the UK health and social services cost of AF in 1995, and projected costs to 2000 based on epidemiological trends. Table 55 summarises the calculation of per person primary care and hospitalisation costs, based on information presented by Stewart et al.[97]

Table 55. Calculation of per person cost of primary care and hospitalisation for people with AF based on costs reported by Stewart et al.[97]

Year	Information	Data
2000	Total number of AF cases	601,149
	Cost of GP referrals	£49,800,000
	Cost of hospital outpatient referrals	£36,400,000
	Cost of hospital admissions with principal diagnosis of AF	£271,600,000
	Cost of post-discharge outpatient visits	£31,700,000
	Total non-medication and non-secondary hospital admission cost of AF	£390,101,149
	Annual per person cost of AF[a]	£649
2013	Annual per person cost of AF[b]	£955

[a] Calculated as sum of cost components divided by total number of AF cases.

[b] Uplifted to 2013 prices using HCHS inflation indices.[109]

In addition to the costs of primary and hospital care, people with AF are assumed, in line with current clinical guidance,[110] to receive effective anticoagulation therapy with apixaban, dabigatran etexilate (hereafter referred to as dabigatran), rivaroxaban or warfarin. Analysis of 2013 prescribing data indicate that, in primary care, the current market shares of apixaban, dabigatran, rivaroxaban and warfarin are 0.0004%, 0.47%, 0.15% and 99.38%, respectively.[111] However, data from the Hospital Prescribing Audit Index (HPAI) database indicate 179873.2%, 132.4% and –21.5% changes since 2012 in the use of apixaban, dabigatran and rivaroxaban, respectively.[112] Given the recent recommendation of these therapies for use in the prevention of stroke and systemic embolism in people with non-valvular AF, it is likely that market share will continue to change over the coming years. Therefore, while current market share estimates are used in the base case, the model is set up to have market share as a user input and different market share scenarios are assessed in sensitivity analyses (see Section 5.2.12). Table 56 summarises the calculation of a per person monthly cost of oral anticoagulation used in the TAG's base case model.

Table 56. Calculation of monthly cost of oral anticoagulation used in the base case model

Treatment	Market share	Unit Costs	Daily dose
Apixaban	0.0004%	£1.10[a]	Twice daily
Dabigatran	0.47%	£1.10[a]	Twice daily
Rivaroxaban	0.15%	£2.20[a]	Once daily

Warfarin	99.38%	£6.08[b]	Once daily
Monthly cost of oral anticoagulation[c]			**£6.45**

[a] Unit cost from BNF67.[98]

[b] Calculated from a weighted average of quantity and average price, reported in eMiT.[99]

[c] Weighted average of cost, weighted by market share.

The long-term cost associated with people with AF and stroke was applied monthly to people residing in the "AF", "AF & stroke" "AF & heart failure" and health states.

5.2.12 Approach to uncertainty

Assessment of uncertainty associated with the TAG economic model is carried out probabilistically (with mean estimates of costs and QALYs used to calculate the base case results), deterministically (one-way sensitivity analysis) and through structural and scenario analyses.

Probabilistic

The TAG economic model has been constructed probabilistically; that is, to simultaneously account for the impact of parameter uncertainty on the cost-effectiveness results. Probability distributions were assigned to parameters used within the model, from which values have been simultaneously sampled 1,000 times. Table 57 summarises the type of distribution, and rationale for selection of the distribution, used to inform each group of parameters; full details of distributional specifications are provided in Table 38.

Table 57. Probability distributions used for model parameters

Parameter type	Parameter description	Distribution(s) used	Rationale
Probabilities	Probabilities of clinical outcomes with dual-chamber pacemaker and probability of re-operation due to AV block	Beta	Probabilities that are based on the proportion of observed outcomes (i.e., probability of event is 1 – probability of non-event) may be assumed to follow a binomial distribution. Therefore, the beta distribution was used as it is the conjugate of the binomial distribution and is bounded by 0 and 1.[113]
Hazard ratios	Hazard ratios of clinical outcomes	LogNormal	Lognormal distribution was used in order to replicate the "real-world" confidence

	with single versus dual-chamber pacemaker		intervals.[113]
Costs	Unit costs	Gamma	Gamma distribution was chosen for all cost data.[113]
Utilities	Health state utility values	Beta	Beta distribution was chosen based on the (0,1) boundary imposed by this distribution.[113]
Note: where 95% confidence intervals or standard errors were not available from the literature a standard error of 0.25 was assumed.			

Deterministic

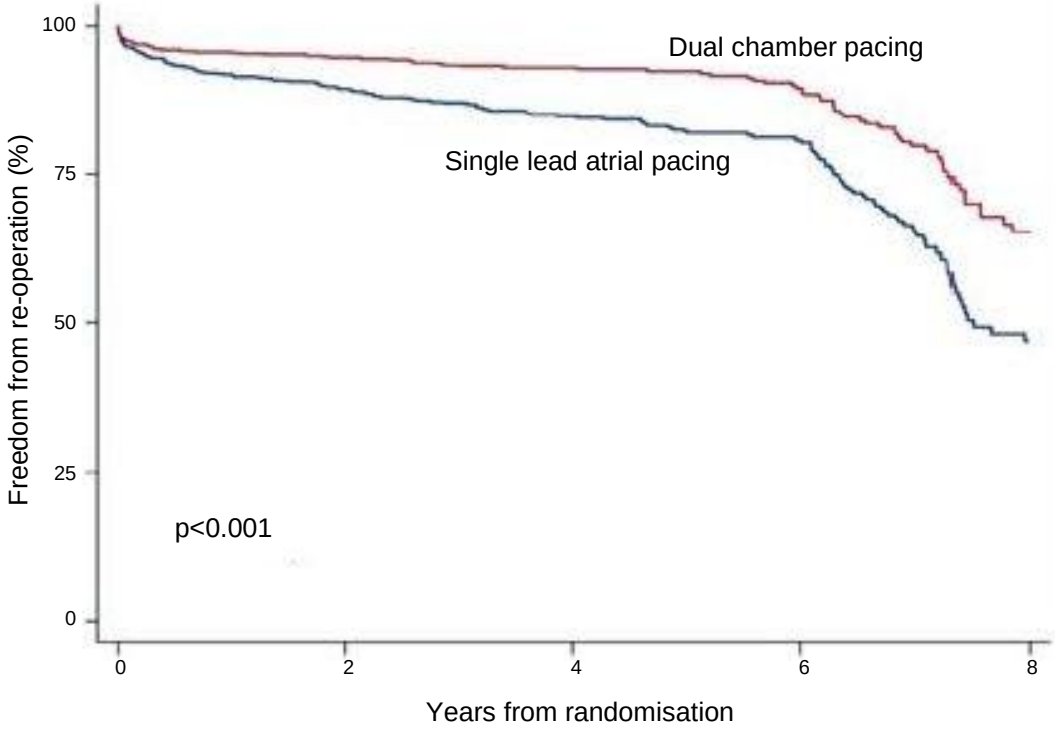
A series of one-way sensitivity analyses (OWSAs) was carried out by using the lower and upper limits of the 95% CIs of the following parameters to assess their the impact on the ICER: age; efficacy values; utility values; costs; all-cause mortality; and HF hospitalisation. The estimates for the upper and lower 95% CIs are displayed in Table 38. Each key parameter was alternately assigned a low and high value and the deterministic cost-effectiveness results using this value were recorded.

Structural sensitivity analysis

The base case analysis assumes a time horizon of 10 years, which requires an extrapolation of the data available from the pivotal RCT, DANPACE, beyond the typical duration that patients were followed up within the trial (5.4 years).[21] As a structural sensitivity analysis, the time horizon was reduced to 5 years to assess the degree of impact this extrapolation may have had on the base case results.

Also, as discussed in Section 5.2.7, the risk of reoperation due to AV block was based on reoperation due to need for surgical change of mode of pacing, where it was found to be significantly higher in the AAIR treatment arm compared with the DDR treatment arm (9.3% AAIR *vs* 0.6% DDDR, $p < 0.001$) over an average follow-up period of 5.4 years. However, the Kaplan–Meier plot (Figure 11) suggests a non-linear decline in reoperation, as opposed to a constant rate. In order to test the assumption of reoperation as a constant risk in the base case, a structural sensitivity analysis was undertaken based on the Kaplan–Meier data.

Figure 11. Time-to-event curve for freedom from reoperation from DANPACE.[42]Unadjusted p-value (log-rank test) shown



In the structural sensitivity analysis, while residing in the "With dual-chamber pacemaker" and "With single-chamber atrial pacemaker" health states, patients are at risk of experiencing complications that require a reoperation, such as lead displacement or device failure. The risk of reoperation is time-dependent and all patients requiring reoperation are assumed to be implanted with a dual-chamber device, regardless of the reason for reoperation or which pacemaker was originally implanted. The assumption that all patients requiring reoperation receive a dual-chamber device is based on reoperation data collected in DANPACE. As in the base cae, only one instance of reoperation was permitted within the model time horizon.

The monthly probability of reoperation, by treatment arm, estimated from Kaplan–Meier data presented by Nielsen et al.[42] can be found in Appendix 7 Monthly probability of re-operation by treatment arm. These probabilities were estimated through digitisation of the Kaplan–Meier plot using the freely available online software WebPlotDigitizer (http://arohatgi.info/WebPlotDigitizer/). The

digitisation process provided monthly estimates of the "survival" function S(t), from which the monthly probabilities of reoperation were calculated using the following formula:

$$p(re-operation)_t = 1 - \frac{S(t)}{S(t-1)}$$

Where t = time (months) and $p(\text{re-operation})_t$ = probability of re-operation at time t.

Scenario analysis

Various assumptions have been made in the construction of the TAG's base case model. Where possible these have been tested in scenario analysis. Table 58 lists the scenario analyses carried out by the TAG, the parameters used to inform these scenarios, and the rationale for each analysis.

Table 58. Scenario analyses carried out by the TAG

Scenario analysis	Parameter definition	Rationale
Cost scenarios		
Cost of pacemaker implant/implantation	Spell costs of single-chamber pacemaker £3,362.18 Spell costs of dual-chamber pacemaker £4,142.11	To assess the impact of utilising an alternative source of cost of pacemaker implant/implantation
Cost per cycle for heart failure	£205.63 uplifted from TA88[53]	To assess the impact of utilising an alternative source for cost of heart failure
Cost per cycle for stroke	£1,104 uplifted from TA88 [53]	To assess the impact of utilising an alternative source for cost of stroke
Cost per cycle for stroke	£343 uplifted from Saka 2009[114]	To assess the impact of utilising an alternative source for cost of stroke
Cost of reprogramming and of device replacement in people developing AF	Applied to 0% and 100% of people developing AF	To test the impact of using extreme values for reprogramming/device replacement in people developing AF

Other		
Alternative discount rates for costs and benefits	Discount rate for costs and benefits assumed to be 1% or 6%	As per NICE methods guides[104]
Market share change for apixaban, dabigatran, rivaroxaban, and warfarin	Assumed 15% receive each of apixaban, dabigatran, and rivaroxaban and 55% receive warfarin	To assess the potential impact of future increased uptake of apixaban, dabigatran, rivaroxaban
Abbreviations used in table: AF, atrial fibrillation; HR, hazard ratio; NICE, National Institute for Health and Care Excellence; TA, Technology Appraisal.		

5.2.13 Base-case results

Incremental deterministic and probabilistic results are presented in Table 59. In the deterministic analysis, the mean costs associated with dual-chamber pacemakers were £6.023.21, whereas single-chamber atrial pacemakers had a mean cost of £5,566.11, resulting in an incremental cost of £457.10. Mean QALYs were 5.56 and 5.51 for dual-chamber pacemakers and single-chamber atrial pacemakers respectively, with a resultant ICER of £10,288 per QALY.

When accounting for uncertainty surrounding parameters, the mean costs associated with dual-chamber pacemakers were £8,991.02 across 1,000 simulations, whereas single-chamber atrial pacemakers accrued a mean cost of £8,720.68, thus yielding an incremental cost of £270.34. Mean QALYs were 5.29 and 5.25 for dual-chamber pacemakers and single-chamber atrial pacemakers respectively, with a resultant ICER of £5,989 per QALY.

Table 59. Base case results

Intervention	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (cost per QALY)
Deterministic results					
Single-chamber atrial pacemakers	£5,566.11	5.51	–	–	–
Dual-chamber pacemakers	£6,023.21	5.56	£457.10	0.04	£10,288
Probabilistic results					
Single-chamber atrial pacemakers	£8,720.68	5.25	–	–	–
Dual-chamber pacemakers	£8,991.02	5.29	£270.34	0.05	£5,989
Abbreviations used in table: QALY, quality adjusted life year.					

5.2.14 Results of the sensitivity analysis

Probabilistic sensitivity analysis

Using a time horizon of 10 years, the results of the probabilistic analysis are presented below in Figure 12 and Figure 13. Probabilistic sensitivity analysis revealed that, in the majority (63.40%) of cases, implanting patients with dual-chamber pacemakers resulted in greater costs and greater QALYs than implanting single-chamber atrial pacemakers. Furthermore, dual-chamber pacemakers produced more QALYs at a lower cost in 25.8% of cases and were dominated by single-chamber atrial pacemakers in 10% of cases. At a WTP threshold of £20,000, the probability of dual-chamber pacemakers being cost-effective is 72.3%, which increases to 76.6% at a WTP threshold of £30,000.

Figure 12. Scatter plot of cost-effectiveness results for dual-chamber pacemakers versus single-chamber atrial pacemakers using a time horizon of 10 years (dark blue line indicates threshold of £20,000 per additional QALY, light blue line indicates threshold of £30,000 per additional QALY)

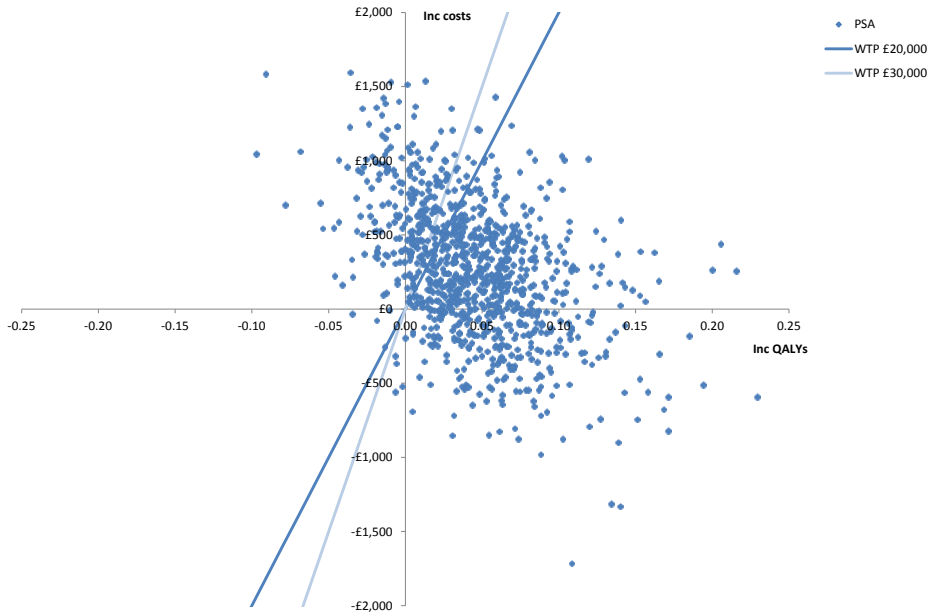
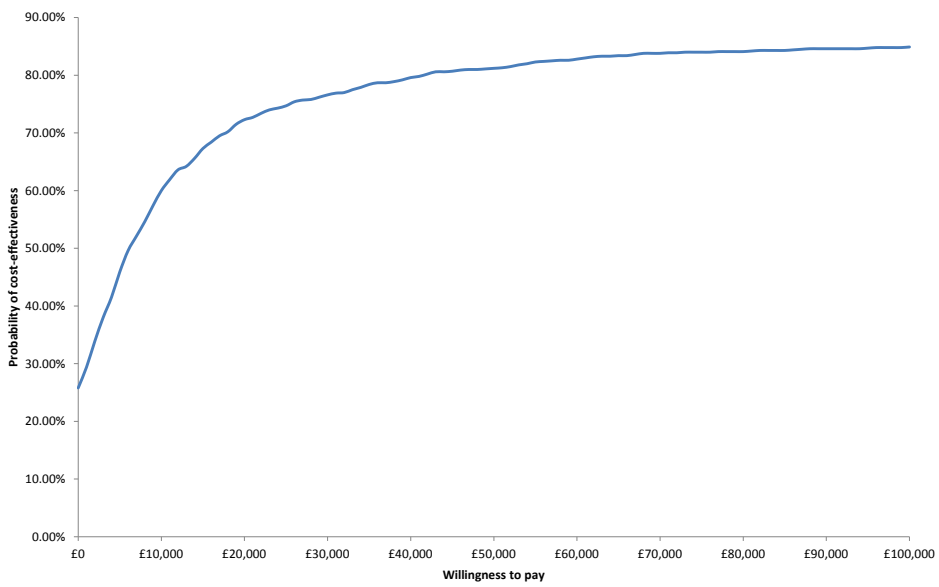


Figure 13. Cost-effectiveness acceptability curve for dual-chamber pacemakers versus single-chamber atrial pacemakers using a time horizon of 10 years



Structural sensitivity analysis

Table 60 presents the results of the structural sensitivity analysis, where the time horizon was reduced from 10 years to 5 years. The difference in costs in the deterministic results falls to £307.79 with a reduction in QALYs accrued to 0.02. This results in an increase in the deterministic ICER for the base case from £10,288 to £19,549. Similarly, the probabilistic results demonstrate a fall in the incremental costs to £236.80 and a reduction in the incremental QALYs gained to 0.02, resulting in an increased ICER to £14,002. These results are perhaps to be expected, a halving of the time horizon results in a roughly halving of the difference in incremental QALYs and roughly a doubling of the resulting ICER.

The results of the probabilistic sensitivity analysis when the time horizon is reduced to 5 years are presented below in Figure 14 and Figure 15. At a WTP threshold of £20,000 the probability of dual-chamber pacemakers being cost-effective is 54.2%, which increases to 63.2% at a WTP threshold of £30,000.

Table 60. Structural sensitivity analysis using a 5-year time horizon

Intervention	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (cost per QALY)
Deterministic results					
Single-chamber atrial pacemakers	£3,544.22	3.48	–	–	–
Dual-chamber pacemakers	£3,852.01	3.49	£307.79	0.02	£19,549
Probabilistic results					
Single-chamber atrial pacemakers	£4,756.14	3.34	–	–	–
Dual-chamber pacemakers	£4,992.94	3.36	£236.80	0.02	£14,002
Abbreviations used in table: QALY, quality adjusted life year.					

Figure 14. Scatter plot of cost-effectiveness results for dual-chamber pacemakers versus single-chamber atrial pacemakers using a time horizon of 5 years (dark blue line indicates threshold of £20,000 per additional QALY, light blue line indicates threshold of £30,000 per additional QALY)

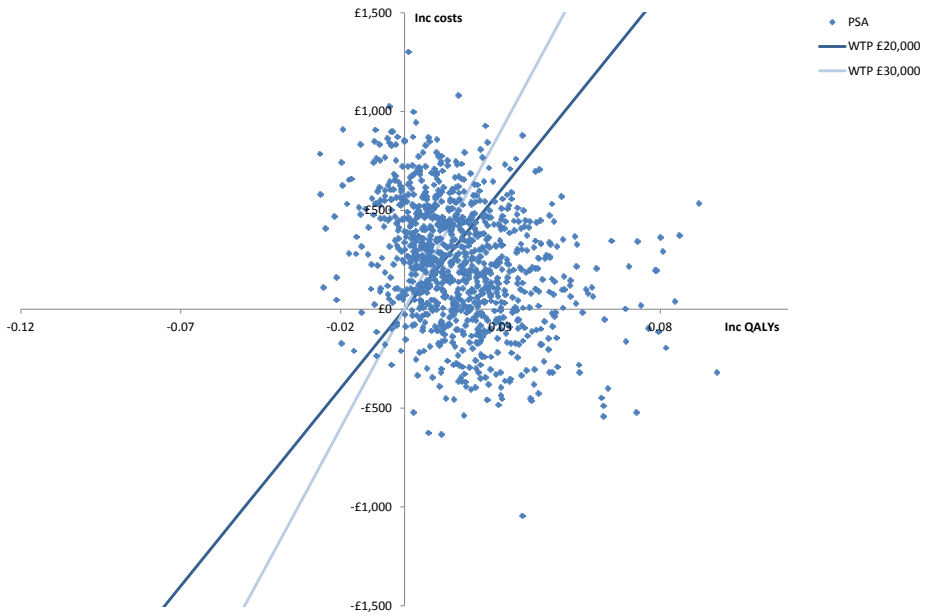


Figure 15. Cost-effectiveness acceptability curve for dual-chamber pacemakers versus single-chamber atrial pacemakers using a time horizon of 5 years

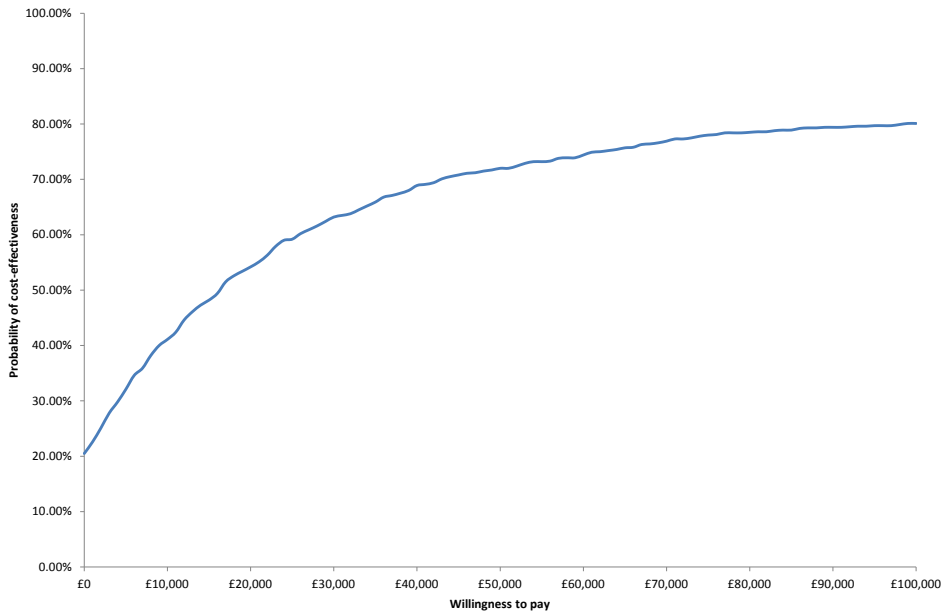


Table 61 shows the results of the structural sensitivity analysis when risk of reoperation was taken from Kaplan–Meier data instead of using a constant risk. The incremental costs of dual-chamber pacemakers decreased to £306.37 while QALYs remained the same compared with the deterministic base case. This caused the ICER to decrease to £7,691 per QALY.

Table 61. Structural sensitivity analysis using Kaplan–Meier data as the basis for reoperation

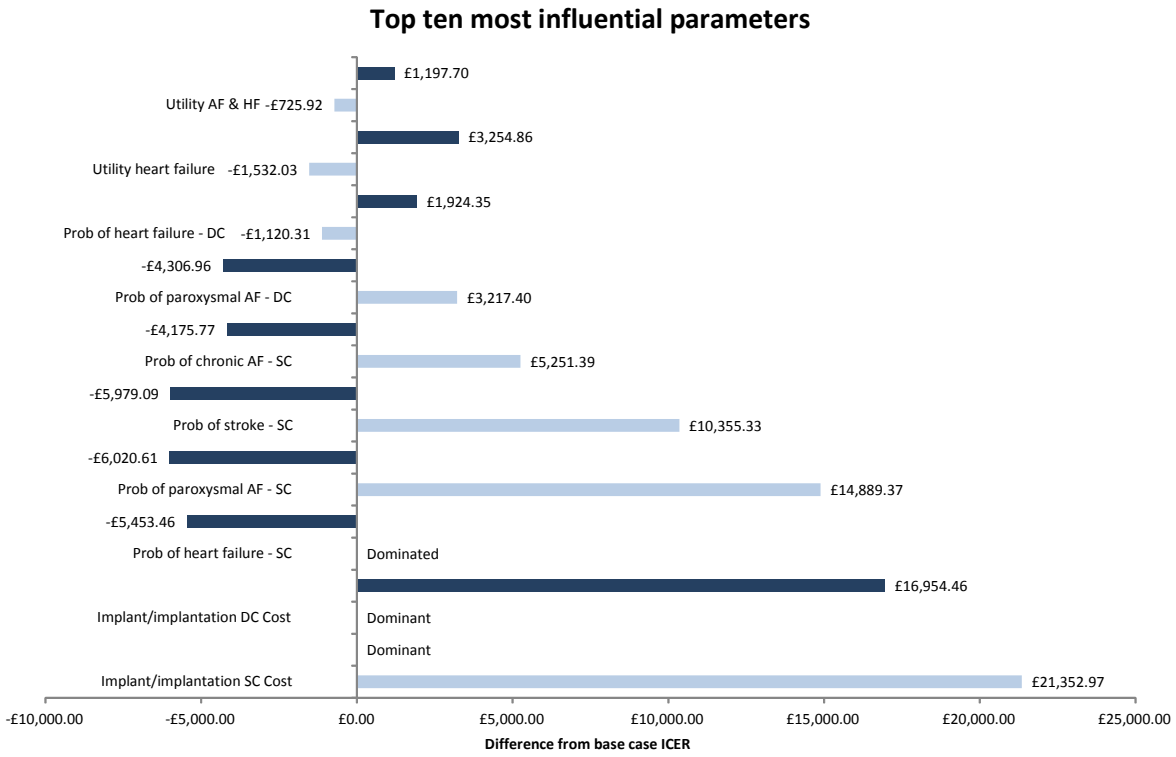
Intervention	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (cost per QALY)
Single-chamber atrial pacemakers	£5,865.68	5.52	–	–	–
Dual-chamber pacemakers	£6,172.05	5.56	£306.37	0.04	£7,691
Abbreviations used in table: QALY, quality adjusted life year.					

One-way sensitivity analysis

As discussed in Section 5.2.12, in addition to probabilistic sensitivity analysis, OWSA has been carried out on the following parameters; age; clinical outcomes; health state utility values; and all-cause mortality. The full results of these analyses are presented in Appendix 5 One way sensitivity analysis. The TAG notes that many of the parameters tested in sensitivity analysis had minimal impact on the deterministic cost-effectiveness results and therefore the parameters that the ICER is most sensitive to are presented in Figure 16 below.

The ICER of dual-chamber pacemakers versus single-chamber atrial pacemakers was most sensitive to probability of HF and probability of paroxysmal AF in patients implanted with single-chamber atrial pacemakers. In the case of HF, dual-chamber pacemakers become dominated when the minimal probability is applied to single-chamber atrial pacemakers (i.e. when risk of HF was less likely to occur in patients with single-chamber atrial pacemakers than dual-chamber pacemakers). The ICER was also sensitive to implant/implantation costs for both dual-chamber and single-chamber atrial pacemakers.

Figure 16. Tornado diagram of parameters to which the cost-effectiveness of dual-chamber pacemakers versus single-chamber atrial pacemakers is most sensitive



Scenario analysis

As discussed in Section 5.2.12, a series of scenario analyses was conducted to test the robustness of the results to alternative sources for parameter estimates or testing broader assumptions (e.g., reprogramming/device replacement in patients developing AF) within the model. The results of the scenario analyses are depicted in Table 62.

Assuming no difference in the risk of developing HF with the two types of implant almost doubles the ICER, increasing it to £20,948 from a base case of £10,288.

The only outcome from the meta-analyses conducted in Section 4.2 that could be implemented in the economic model was stroke. However, utilising the risk of stroke from the TAG's meta-analysis (Section 4.2.2) had only a modest impact on the ICER, increasing it to £10,912.

Using spell level costs for pacemaker implantation increased the costs of dual-chamber pacemaker implantation more than single-chamber atrial pacemaker. This resulted in a modest increase in the

incremental costs of dual-chamber pacemakers, resulting in a slightly higher ICER (£11,837 compared with £10,288). The alternative cost of HF was substantially lower than in the base case and reduced the incremental difference in costs between interventions. This resulted in a low ICER compared with the base case (£1,892 compared with £10,288). The lower alternative cost of stroke from TA88 had a more modest effect on the incremental cost of interventions and a relatively modest change in ICER compared with the base case (£8,866 compared with £10,288). Similarly, the alternative cost per episode of stroke from Saka 2009 had little impact on the incremental cost or the resulting ICER compared with the base case (£10,901 compared with £10,288).

The proportion of patients experiencing AF resulting in either reprogramming or replacement of their pacemaker was estimated as one-third of patients in the base case, based on advice from clinical experts. This was tested in two extreme scenario analyses in which it was assumed either no one required reprogramming/replacement or that 100% of patients required reprogramming/replacement. These two scenarios had a pronounced impact on the resulting ICERs compared with the base case, with an increase in the ICER to £14,806 and a reduction in the ICER to £1,251 in analyses assuming 0% and 100% of people, respectively, required reprogramming/replacement.

Varying the discount rate from 3.5% in the base case to either 0% or 6% had a modest impact on the ICER. While costs and benefits increased overall at a discount rate of 0%, the ICER was reduced to £9,202. Similarly, while increasing the discount rate to 6% decreased the cost and benefits overall, the impact on the ICER was an increase to £11,224.

The final individual scenario analysis undertaken was to increase the proportion of prescribing of the novel oral anticoagulants (NOACs) to a more even level with warfarin. This was achieved by setting the market share for warfarin to 55% and the NOAC market share to 45% (evenly distributed in three blocks of 15% to apixaban, dabigatran, and rivaroxaban). This resulted in an overall increase in costs but a reduction in the incremental cost between the two interventions and a modest reduction in the ICER to £9,174 compared with £10,288 in the base case.

Table 62. Scenario analyses using alternative sources for parameter estimates or testing assumptions used within the base case

Analysis	Intervention	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (cost/QALY)
Base case	**Single**	**£5,566.11**	**5.51**	**–**	**–**	**–**
	Dual	**£6,023.21**	**5.56**	**£457.10**	**0.04**	**£10,288**
Efficacy						
Assuming no impact on heart failure (i.e., HR set to 1)	Single	£5,594.07	5.54	–	–	–
	Dual	£6,023.21	5.56	£429.13	0.02	£20,948
Stroke used from meta-analysis (Section 4.2.2)	Single	£5,557.17	5.51	–	–	–
	Dual	£6,023.21	5.56	£466.04	0.04	£10,912
Cost scenarios						
Spell level costs of pacemaker implantation from NHS Reference costs 2012–2013	Single	£7,770.94	5.51	–	–	–
	Dual	£8,296.88	5.56	525.94	0.04	£11,837
Cycle cost for heart failure from TA88	Single	£8,232.21	5.51	–	–	–
	Dual	£8,316.29	5.56	£84.08	0.04	£1,892
Cycle cost for stroke from TA88	Single	£7,444.03	5.51	–	–	–
	Dual	£7,837.94	5.56	£393.92	0.04	£8,866
Cycle cost for stroke from Saka 2009	Single	£5,913.74	5.51	–	–	–
	Dual	£6,398.11	5.56	£484.37	0.04	£10,901
Reprogramming/device replacement for AF in 0% patients	Single	£5,352.12	5.51	–	–	–
	Dual	£6,009.96	5.56	£657.85	0.04	£14,806

Reprogramming/device replacement for AF in 100% patients	Single	£5,994.09	5.51	–	–	–
	Dual	£6,049.70	5.56	£55.60	0.04	£1,251
Other						
Discount rate 0%	Single	£6,252.39	6.27	–	–	–
	Dual	£6,747.74	6.33	£495.35	0.05	£9,202
Discount rate 6%	Single	£5,173.80	5.07	–	–	–
	Dual	£5,612.20	5.11	£438.40	0.04	£11,224
Market share 55% warfarin 45% NOAC[a]	Single	£6,038.68	5.51	–	–	–
	Dual	£6,446.28	5.56	£407.60	0.04	£9,174

[a] novel oral anticoagulant have equal market share of 15%

Abbreviations used in table: AF, atrial fibrillation; HR, heart rate; NOAC, novel anticoagulant; QALY, quality adjusted life year; TA, technology appraisal.

The results of the individual scenario analyses suggest that the base case ICER is robust to changes in costs of pacemaker implantation, stroke, discount rate and market share of NOACs. In addition, while varying the costs of HF and the proportion of patients requiring reprogramming or replacing their pacemaker due to developing AF to extreme values had a more pronounced impact on the resulting ICER, it was still well below the NICE threshold value of £20,000. In only one scenario, where it was assumed that there is no difference in the development of HF, did the ICER exceed £20,000, and only by £948.

A cumulative "worst case" scenario is depicted in Table 63, where each efficacy and cost scenario analyses found to increase the ICER beyond the base case has been combined. This results in an ICER £49,018 compared to the base case of £10,288 at 10 years. However, if the assumption that reprogramming/device replacement due to AF is reinstated as one-third (as in the base case) the cumulative impact of the other adjustments result in an ICER of £28,905 at 10 years.

Overall, the ICER increases beyond £20,000 but remains below £30,000 with the inclusion of an assumption of reprogramming/device replacement for AF in 0% patients or the inclusion of an

assumption of no impact on HF in the cumulative "worst case" scenario. It only exceeds £30,000 when both are included in the cumulative "worst case" scenario.

Table 63. Summary of cumulative effect of all sensitivity analyses found to increase the ICER from the base case

Analysis	Intervention	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (cost/QALY)
Base case	**Single**	**£5,566.11**	**5.51**	**–**	**–**	**–**
	Dual	**£6,023.21**	**5.56**	**£457.10**	**0.04**	**£10,288**
Cycle cost for stroke from Saka 2009	Single	£5,913.00	5.51	–	–	–
	Dual	£6,397.41	5.56	£484.41	0.04	£10,902
Stroke used from meta-analysis (Section 4.2.2)	Single	£5,892.28	5.51	–	–	–
	Dual	£6,397.41	5.56	£505.13	0.04	£11,827
Spell level costs of pacemaker implantation from NHS Reference costs 2012–2013	Single	£8,097.49	5.51	–	–	–
	Dual	£8,671.08	5.56	£573.59	0.04	£13,430
Reprogramming/device replacement for AF in 0% patients	Single	£7,713.27	5.51	–	–	–
	Dual	£8,657.84	5.56	£944.57	0.04	£22,117
Assuming no impact on heart failure (i.e., HR set to 1)[a]	Single	£7,740.12	5.54	–	–	–
	Dual	£8,657.84	5.56	£917.71	0.02	£49,018

[a] As assumed in Oddershede et al.[59]

Abbreviations used in table: AF, atrial fibrillation; HF, HR, hazard ratio; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; QALY, quality adjusted life year.

The overall adjusted hazard ratio for risk of developing HF used in the base case indicates a non-significant increase in risk with single-chamber atrial pacemakers compared with dual-chamber pacemakers (HR 1.09, 95% CI: 0.88 to 1.35).[45] Based on feedback from our clinical experts, and as was assumed in Oddershede et al.,[59] we conducted a scenario analysis assuming that there was no difference in risk of HF based on implanted device (i.e. HR 1.00).

The results of the scenario analysis and the OWSA highlight how sensitive the results are to risk of HF, with dual-chamber pacemakers being considered cost-effective or dominated by single-chamber atrial pacemakers depending on the data used. These results warranted further investigation into HF for which we assessed the subgroups analysed from DANPACE.[45]

The subgroups identified as statistically significant in an analysis of risk of HF from DANPACE were due to age (p=0.05), all other subgroups assessed were found to be statistically non-significant (p>0.31).[45] As additional scenario analyses we explored the impact of using the HRs for the subgroups based on age (patients >75 years or patients ≤75 years). The results are depicted in Table 64.

Table 64. Additional scenario analyses investigating the impact of heart failure compared to the base case results

Analysis	Intervention	Heart failure HR[a]	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (cost/QALY)
Base case	**Single**	**1.09 (95% CI: 0.88 to 1.35)[b]**	**£5,566.11**	**5.51**	**–**	**–**	**–**
	Dual		**£6,023.21**	**5.56**	**£457.10**	**0.04**	**£10,288**
Assuming no impact on heart failure	Single	1.00 (N/A)	£5,594.07	5.54	–	–	–
	Dual		£6,023.21	5.56	£429.13	0.02	£20,948
Patients >75 years[45]	Single	1.34 (95% CI: 1.00 to 1.80)[c]	£5,491.35	5.45	–	–	–
	Dual		£6,023.21	5.56	£531.86	0.11	£4,918
Patients ≤75 years[45]	Single	0.72 (95% CI: 0.53 to 1.00)[c]	£5,684.86	5.61	–	–	–
	Dual		£6,023.21	5.56	£338.35	-0.06	Dominated

[a] HR for single-chamber atrial pacemaker vs dual-chamber pacemaker

[b] HR adjusted for age, sex, hypertension, diuretic treatment, LVEF, prior myocardial infarction, PQ interval, and NYHA class.

[c] p = 0.05

Abbreviations used in table: HR, hazard ratio; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; QALY, quality adjusted life year.

The additional scenario analyses highlight the impact that risk of heart failure has on the results. When the risk of heart failure is adjusted by age, the ICER is reduced compared to the base case in patients aged >75 years (£4,918 vs £10,288, respectively), whereas dual-chamber pacemakers are dominated by single-chamber atrial pacemakers in patients aged ≤75 years (i.e. they are more costly and less effective).

5.2.15 Summary of the Technology Assessment Group *de novo* economic evaluation

An overall summary of the results from the TAG's economic model is presented in Table 65.

Table 65. Summary of results comparing the cost-effectiveness of dual-chamber pacemakers with single-chamber atrial pacemakers for treating symptomatic bradycardia due to sick sinus syndrome without atrioventricular block

Analysis	Intervention	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (cost/QALY)
Base case	**Single**	**£5,566.11**	**5.51**	**–**	**–**	**–**
	Dual	**£6,023.21**	**5.56**	**£457.10**	**0.04**	**£10,288**
Structural sensitivity analyses						
Time horizon reduced to 5 years	Single	£3,544.22	3.48	–	–	–
	Dual	£3,852.01	3.49	£307.79	0.02	£19,549
Utilising Kaplan–Meier data as the basis for reoperation	Single	£5,865.68	5.52	–	–	–
	Dual	£6,172.05	5.56	£306.37	0.04	£7,691
Probabilistic sensitivity analyses						
Base case	Single	£8,720.68	5.25	–	–	–
	Dual	£8,991.02	5.29	£270.34	0.05	£5,989
Time horizon reduced 5 years	Single	£4,756.14	3.34	–	–	–
	Dual	£4,992.94	3.36	£236.80	0.02	£14,002
Efficacy scenarios						
Stroke used from meta-analysis (Section 4.2.2)	Single	£5,557.17	5.51	–	–	–
	Dual	£6,023.21	5.56	£466.04	0.04	£10,912
Assuming no impact on heart failure (i.e., HR set to 1)[a]	Single	£5,594.07	5.54	–	–	–
	Dual	£6,023.21	5.56	£429.13	0.02	£20,948
Cost scenarios						
Spell level costs of pacemaker implantation from NHS Reference costs 2012–2013	Single	£7,770.94	5.51	–	–	–
	Dual	£8,296.88	5.56	525.94	0.04	£11,837
Cycle cost for heart failure from TA88	Single	£8,232.21	5.51	–	–	–
	Dual	£8,316.29	5.56	£84.08	0.04	£1,892
Cycle cost for stroke from TA88	Single	£7,444.03	5.51	–	–	–
	Dual	£7,837.94	5.56	£393.92	0.04	£8,866

Cycle cost for stroke from Saka 2009	Single	£5,913.74	5.51	–	–	–
	Dual	£6,398.11	5.56	£484.37	0.04	£10,901
Reprogramming/device replacement for AF in 0% patients	Single	£5,352.12	5.51	–	–	–
	Dual	£6,009.96	5.56	£657.85	0.04	£14,806
Reprogramming/device replacement for AF in 100% patients	Single	£5,994.09	5.51	–	–	–
	Dual	£6,049.70	5.56	£55.60	0.04	£1,251
Other scenarios						
Discount rate 0%	Single	£6,252.39	6.27	–	–	–
	Dual	£6,747.74	6.33	£495.35	0.05	£9,202
Discount rate 6%	Single	£5,173.80	5.07	–	–	–
	Dual	£5,612.20	5.11	£438.40	0.04	£11,224
Market share: 55% warfarin and 45% NOAC[b]	Single	£6,038.68	5.51	–	–	–
	Dual	£6,446.28	5.56	£407.60	0.04	£9,174
"Worst case" scenario						
All efficacy and cost scenarios where the ICER increases above the base case	Single	£7,740.12	5.54	–	–	–
	Dual	£8,657.84	5.56	£917.71	0.02	£49,018
Additional scenarios for heart failure						
Patients >75 years (i.e., HR set to 1.34) from Riahi 2012	Single	£5,491.35	5.45	–	–	–
	Dual	£6,023.21	5.56	£531.86	0.11	£4,918
Patients ≤75 years (i.e., HR set to 0.72) from Riahi 2012	Single	£5,684.86	5.61	–	–	–
	Dual	£6,023.21	5.56	£338.35	-0.06	Dominated

[a] As assumed in Oddershede et al.[59]

[b] Novel oral anticoagulants (NOACs)have equal market share of 15% per NOAC.

Abbreviations used in table: AF, atrial fibrillation; HF, HR, hazard ratio; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; QALY, quality adjusted life year.

5.2.16 Discussion of the Technology Assessment Group *de novo* economic evaluation

The economic evaluation conducted by the TAG of dual-chamber pacemakers for treating symptomatic bradycardia due to SSS without AV block is an update of TA88. The previous assessment found dual-chamber pacemakers to be dominated by single-chamber atrial pacemakers (i.e., they are more expensive and less effective). Our own evaluation is based on more up to date

estimates employed within an economic model based on TA88. The findings are quite different in that, while dual-chamber pacemakers are more expensive, they are more clinically effective. Analyses resulted in a deterministic ICER of £10,288 at 10 years.

OWSA was undertaken to identify the key drivers of cost-effectiveness in the economic model. Those likely to increase the deterministic ICER over £20,000 were:

- lowest risk of stroke (ICER £20,643);
- lowest risk of paroxysmal AF (ICER £25,177);
- lowest risk of HF (dual-chamber pacemakers dominated by single-chamber atrial pacemakers);
- highest cost of implant/procedure for dual-chamber pacemaker (ICER £27,242);
- lowest cost of implant/procedure for single-chamber atrial pacemaker (ICER £31,641).

While the result for the lowest risk of HF may appear to dramatically alter the direction of results, it should be borne in mind that the "dominant" ICER for single-chamber atrial pacemakers is being driven by a modest increase in cost (£391) and a modest reduction in benefit (–0.01) compared with dual-chamber pacemakers.

Using the extreme values for cost or implant/implantation increased the ICER substantially with the highest cost associated with dual-chamber pacemakers increasing the ICER to £27,242, and the lowest cost for single-chamber atrial pacemaker resulting in an ICER in excess of £30,000 (£31,641).

One-way sensitivity analysis can be misleading in that it may under represent the impact of parameter uncertainty in the results of the economic model. The results from the probabilistic sensitivity analysis capture the joint uncertainty across parameter estimates. The ICER from this analysis at 10 years is £5,989, which is notably lower than the deterministic result. This is predominantly due to a reduction in the incremental costs rather than a change in the incremental QALYs.

Parameter uncertainty is not the only form of uncertainty found within an economic model. Structural uncertainty also needs to be accounted for. Two structural sensitivity analyses were undertaken in the current evaluation: reducing the time horizon from 10 to 5 years; and utilising the risk of reoperation from Kaplan–Meier data presented in DANPACE in contrast to implementing risk of reoperation as a constant risk.

Reducing the time horizon from 10 years to 5 years was undertaken to assess the impact of extrapolating the results from DANPACE beyond the typical duration of a trial participant. The results are perhaps as might be expected, a halving of the time horizon results in about a halving of the difference in incremental QALYs and about a doubling of the resulting ICER. The deterministic result changes from £10,288 at 10 years to £19,549 at 5 years, while the results from the probabilistic sensitivity analysis go from £5,989 at 10 years to £14,002 at 5 years. Based on feedback from our clinical experts a time horizon of 10 years would appear to be the most appropriate as the development of AV block is expected to increase steadily over time.

In the structural sensitivity analysis, the risk of reoperation was implemented as a time-dependent parameter and all patients requiring reoperation were assumed to be implanted with a dual-chamber device, regardless of the reason for reoperation or which pacemaker was originally implanted. The impact of undertaking this more granular approach to reoperation within the model was modest. The deterministic ICER was reduced to £7,691 at 10 years due to a small reduction in incremental costs. This is likely to be due to the risk being reoperated occurring slightly early than when a constant rate is assumed and indicates that the base case may be considered a conservative assumption.

A variety of scenario analyses were undertaken where an alternative source for a parameter estimate was used. Most had a minor impact on the resulting ICER with the exception of:

- assuming no difference in risk of developing HF (ICER £20,948);
- monthly cost for HF from TA88 (ICER £1,892);
- reprogramming/device replacement for AF in 0% patients (ICER £14,806);
- reprogramming/device replacement for AF in 100% patients (ICER £1,251).

In only one instance did a scenario analysis result in an ICER above £20,000, and then it was by only £948.

The results of the scenario analysis and the OWSA highlight how sensitive the results are to risk of HF, with dual-chamber pacemakers being considered cost-effective or dominated by single-chamber atrial pacemakers depending on the data used. Subgroup analysis from DANPACE identified a significant difference in HF due to age (p=0.05), all other subgroups assessed were non-significant (p>0.31).[45] When the risk of heart failure is adjusted by age, the ICER is reduced compared to the base case in patients aged >75 years (£4,918 vs £10,288, respectively), whereas dual-chamber

pacemakers are dominated by single-chamber atrial pacemakers in patients aged ≤75 years (i.e. they are more costly and less effective).

6 ASSESSMENT OF FACTORS RELEVANT TO THE NHS AND OTHER PARTIES

6.1 End of life criteria

Based on criteria outlined by NICE, the TAG considers that neither dual-chamber pacemakers nor single-chamber atrial pacemakers are eligible for consideration as end-of-life treatments.

7 DISCUSSION

This MTA sought to assess the available evidence for dual-chamber pacemakers for treating symptomatic bradycardia due to SSS without AV block in comparison with single-chamber atrial pacemakers. It is a partial update of NICE TA88 (2005),[19] which had a wider remit investigating dual-chamber pacemakers for the treatment of symptomatic bradycardia due to SSS and/or AV block. With regards to the subset of patients of interest to this research, TA88 recommends single-chamber atrial pacemakers for patients with SSS in whom, after full evaluation, there is no evidence of impaired AV conduction.

The TAG's systematic review of the clinical effectiveness identified six RCTs in the population of interest. Three RCTs[41;42;46] had a parallel group design and three were crossover studies.[37;38;48] The crossover trials were generally small (12–21 patients) with limited follow-up (up to 3 months), which limited their opportunity to inform the outcomes of interest for this research. The parallel group RCTs were relatively large (50–1,415 patients), had longer follow-up (1–5.4 years) than the crossover studies, and measured outcomes that were of direct interest to this research.

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 were predominantly influence by the largest trial DANPACE,[42] which accounted for over 80% of the weight in change in pacing mode, all-cause mortality, and stroke. In no instance did the level of significance of an outcome from DANPACE change due to its combination in a meta-analysis of that outcome (e.g., the OR for change in pacing mode was 0.52, 95% CI: 0.38 to 0.71 from DANPACE and 0.50, 95% CI: 0.37 to 0.67, from the meta-analysis including DANPACE, Albertsen 2008, and Nielsen 2003).

In this review dual-chamber pacing was associated with a lower risk of AF and fewer re-operations than single-chamber atrial pacing. No statistically significant difference was shown between the pacing modes for mortality, heart failure, stroke or quality of life, and there was limited data on adverse effects of pacemaker implantation. However, for patients younger than 75 years of age the risk of heart failure seems to be higher with a dual-chamber pacemaker than a single-chamber atrial pacemaker, and for patients older than 75 years the risk seems to be lower with dual-chamber pacing compared with single-chamber atrial pacing.

DANPACE is a relatively large trial of good quality with long follow up, which gives a reasonable evidence base for dual-chamber pacing compared to single-chamber atrial pacing for people with SSS

without evidence of impaired AV conductance. Although the time horizon in DANPACE was reasonable, the results for patients needing a change in pacing mode and reoperation were probably conservative as the proportion of these due to the development of high grade AV block would be anticipated to increase steadily over time. Additionally, DANPACE did not allow pacemaker algorithms designed to minimize ventricular pacing in patients with intact atrioventricular conduction, which are becoming more common since this trial. Although the DDDR pacemakers in DANPACE were programmed in a way intended to reduce unnecessary ventricular pacing, ventricular pacing was still 65 ± 33 %, which may offset some of the benefit of implanting a dual-chamber pacemaker.

Patients with single-chamber atrial pacing, who do not go on to develop atrioventricular block, will be paced appropriately and avoid any unnecessary ventricular pacing, which may have adverse consequences for cardiac function. Implanting a single-chamber atrial pacemaker may also have additional benefits in terms of shorter implantation procedure and lower risk of complications associated with the implantation of a second lead, and less time at follow up appointments. However, patients who have a dual-chamber pacemaker implanted, who go on to develop atrioventricular block, will be protected by the presence of a ventricular lead and will not need a further operation to upgrade the pacemaker and insert a second lead, which is likely to be associated with higher risk of complications than for first time implant. Additionally, DANPACE has shown that the risk of developing paroxysmal AF is lower with dual-chamber pacing than with single-chamber atrial pacing. In addition, subgroup analysis identified that for patients younger than 75 years of age the risk of heart failure may be higher with a dual-chamber pacemaker than a single-chamber atrial pacemaker, and for patients older than 75 years the risk may be lower with dual-chamber pacing compared with single-chamber atrial pacing.

The systematic review of existing cost-effectiveness analyses only identified one study that evaluated dual-chamber pacemakers for treating symptomatic bradycardia due to SSS without AVB in comparison with single-chamber atrial pacemakers in a UK setting and that was based on the research carried out to inform TA88.[19] In addition, in the update of the cost effectiveness systematic review, a study by Oddershede et al.[59] was identified, which was based on the perspective of the Danish health care system. This study is of particular interest as it includes DANPACE,[42] as well as two other Danish RCTs: the pilot study for DANPACE (Nielsen 2003),[46] and Andersen 1997.[50]

One of the strengths of the Oddershede et al. approach is that it was based on individual patient data that allowed the researchers to account for baseline characteristics such as age, gender, previous

myocardial infarction, and history of AF. The researchers were also able to categorise patients as low risk, high risk, and the remainder patients as moderate risk of a subsequent event. For each of the risk categories, and for an evaluation based on all patients, Oddershede et al. found that the probability of dual-chamber pacemakers being cost effective compared with single-chamber atrial pacemakers was > 50% at a WTP threshold of £20,000. This fell to > 40% at a WTP threshold of £30,000. This is likely to be due to the incremental QALY decrement associated dual chamber pacemakers in their analysis. However, the model developed by Oddershede et al. focused primarily on the occurrence of stroke and death, which may have restricted the comprehensiveness of the analysis to fully assess costs and benefits.

As no pre-existing economic evaluation adequately represents the cost effectiveness of dual-chamber pacemakers for treating symptomatic bradycardia due to SSS without AV block in comparison with single-chamber atrial pacemakers in a UK setting, the TAG developed a *de novo*, economic model to help inform this important question.

As there were concerns around potential clinical heterogeneity as a result of different patient populations (e.g. prior history of atrial fibrillation) and different device programming used (e.g. different % ventricular pacing) in the RCTs identified, the decision was made to base the model on DANPACE. The base case results of the TAG's economic model demonstrate that dual-chamber pacemakers are more expensive but also more effective than single-chamber atrial pacemakers resulting in an ICER of £10,288. Probabilistic sensitivity analysis reduced this figure to £5,989 principally due to a lowering of the incremental cost. This reduction in the difference in cost is likely to be due to the non-linearity of the min-max cost of implant/implantation of a single pacemaker compared to the min-max cost of implant/implantation of a dual pacemaker. The likelihood for dual-chamber pacemakers to be cost effective was found to be over 70% at a threshold of either £20,000 or £30,000.

In order to use a conservative estimate for all subsequent analyses we focused on the deterministic results.

Structural sensitivity analysis looking at a more granular approach to incorporating risk of re-operation using the available Kaplan–Meier data from DANPACE reduced the ICER from £10,288 to £7,691. A second structural sensitivity analysis reducing the time horizon to 5 years almost doubled the base case ICER to £19,549. In essence, halving the time horizon halved the incremental benefit.

One-way sensitivity analysis highlighted the key drivers of cost-effectiveness in the economic model. Those likely to increase the deterministic ICER over £20,000 were:

- lowest risk of stroke (ICER £20,643);
- lowest risk of paroxysmal AF (ICER £25,177);
- lowest risk of HF (dual pacemakers dominated by single atrial pacemakers);
- highest cost of implant/procedure for dual pacemaker (ICER £27,242);
- lowest cost of implant/procedure for single atrial pacemaker (ICER £31,641).

While the result for the lowest risk of HF may appear to dramatically alter the direction of results it should be borne in mind that the "dominant" ICER for single-chamber atrial pacemakers is being driven by a modest increase in cost (£391) and a modest reduction in benefit (-0.01) compared to dual-chamber pacemakers.

A series of scenario analyses were undertaken to test the impact on the results when using alternative sources for parameter estimates or challenge assumptions in the model. The scenario analyses that raised the ICER above the base case were:

- assuming no difference in HF (ICER £20,948);
- using the risk of stroke from the TAG's meta-analysis (ICER £10,912);
- using spell level costs of pacemaker implantation (ICER £11,837);
- using monthly cost of stroke from Saka 2009 (ICER£10,901);
- using reprogramming/device replacement for AF of 0% (ICER £14,806);
- using a discount rate of 6% (ICER £11,224).

Only when we assume the risk of developing HF is the same regardless of implanted device does the ICER increase beyond £20,000; albeit a modest increase to £20,948.

A cumulative "worst case" scenario was also conducted that combined the monthly cost of stroke from Saka 2009, the risk of stroke from the meta-analysis conducted by the TAG, the spell level costs of implantation, reprogramming/device replacement for AF of 0%, and assuming no difference in risk of developing HF between the two types of implant. This resulted in an ICER of £49,018.

The results of the scenario analysis and the one way sensitivity analysis highlight how sensitive the results are to risk of HF, with dual-chamber pacemakers being considered cost-effective or dominated by single-chamber atrial pacemakers depending on the data used. Subgroup analysis from DANPACE identified a significant difference in HF due to age (p=0.05), all other subgroups assessed were non-significant (p>0.31).[45] When the risk of heart failure is assessed by age, the ICER is reduced compared to the base case in patients aged >75 years (£4,918 vs £10,288, respectively), whereas dual-chamber pacemakers are dominated by single-chamber atrial pacemakers in patients aged ≤75 years (i.e. they are more costly and less effective).

7.1 Statement of principal findings

This MTA uses the best available evidence to explore the clinical and cost-effective implications for using dual-chamber pacemakers rather than single-chamber atrial pacemakers for treating symptomatic bradycardia due to SSS without AV block. DANPACE has demonstrated a significant reduction in re-operation due to need for surgical change of mode of pacing, where it was found to be significantly higher in patients implanted with a single-chamber atrial pacemaker compared with patients implanted with a dual-chamber pacemaker (9.3% vs 0.6%, $p < 0.001$).[42] The difference is primarily due to the development of AV block requiring upgrade to a dual-chamber device. DANPACE also demonstrated a reduced risk of paroxysmal AF with dual-chamber pacing compared to single-chamber atrial pacing (OR 0.75, 95% CI: 0.59 to 0.96). No statistically significant difference was shown between the pacing modes for mortality, heart failure, stroke or quality of life. However, the risk of developing heart failure may vary with age and device.

The *de novo* economic model developed by the TAG shows that dual-chamber pacemakers are more expensive and more effective than single-chamber atrial devices resulting in a base case ICER of £10,288. The ICER remains below £20,000 in probabilistic sensitivity analysis, structural sensitivity analysis, and most scenario analyses and one-way sensitivity analyses.

A potentially important finding of this MTA is the impact that HF may have on the decision to use dual-chamber pacemakers or single-chamber atrial pacemakers for treating symptomatic bradycardia due to SSS without AV block. The results from an analysis based on age (>75 years or ≤75 years) and risk of HF, indicates that using dual-chamber pacemakers in older patients is cost-effective, with an ICER of £4,918, while using dual-chamber pacemakers is dominated (i.e. more expensive and less effective) in younger patients compared to single-chamber atrial pacemakers. However, these results are based on a subgroup analysis and should be treated with caution.

7.2 Strengths and limitations of the assessment

Strengths

- The evidence used to inform the decision problem that is the focus of this MTA has been identified following the general principles published by the Centre for Reviews and Dissemination (CRD).
- Economic analyses have been carried out in accordance with NICE guide to methods of technology appraisal and ISPOR guidance for decision analytic models.
- The economic model used to provide a framework for analysis is based primarily on the economic model constructed in TA88. In addition, parameter estimates have been informed by the best available evidence.
- Expert clinical input has been sought and received throughout the project, in particular with respect to assumptions made in clinical and economic analyses and the face validity of final results and conclusions.

Weaknesses

- The limited number of RCTs available to inform this decision question and the lack of reporting in a consistent manner in those trials identified.
- Rapid development of the technologies under investigation so that trials using current single-chamber atrial pacemakers or dual-chamber pacemakers are likely to be superseded by newer implants (and/or pacing algorithms) prior to their completion.
- A cohort approach using the adjusted trial level data from DANPACE was used to populate the efficacy parameters within the economic model rather than a microsimulation informed by individual patient data.
- The costs for the individual pacemakers under consideration were unavailable for use within the economic model and so the average costs reported within the appropriate HRG codes were used.

7.3 Uncertainties

The results from DANPACE represent the single largest RCT that has been conducted to compare single-chamber atrial pacemakers and dual-chamber pacemakers in patients with symptomatic

bradycardia due to SSS and no evidence of AV block. However, it does not conclusively answer the clinically relevant questions concerning a difference in risk of HF, stroke, and all-cause mortality. It seems unlikely that larger studies will be conducted to investigate these outcomes – particularly not with the same pacemakers used in DANPACE – as pacemaker design and the development of new pacing modes have rapidly changed over time and look likely to continue to change in the future.

Typically in a cost-effectiveness analysis the acquisition cost of the interventions are known and uncertainty in costs lies elsewhere. However, as the manufacturers declined the opportunity to make a submission and were unable to supply costs for devices in the time allowed, the costs for the individual pacemakers under consideration in this MTA were unavailable. We had to use the average costs reported within the appropriate HRG codes, which incorporate the cost of device plus the cost of implantation. There was considerable uncertainty in the economic evaluation due to implementing these costs. It was not possible to disentangle the uncertainty relating to cost of devices and cost of implantation.

7.4 Other relevant factors

Based on criteria outlined by NICE, the TAG considers that neither dual-chamber pacemakers nor single-chamber atrial pacemakers are eligible for consideration as end-of-life treatments.

8 CONCLUSIONS

8.1 Implications for service provision

Feedback from our clinical experts indicates that many centres are generally implanting dual-chamber pacemakers rather than single-chamber atrial pacemakers in patients with symptomatic bradycardia due to SSS. Individual patient characteristics may dictate the use of single-chamber atrial pacemakers, e.g. concerns over potential ventricular remodelling over a prolonged period of time, but these would be in specific circumstances only. As such, it appears that there would be minimal implications for service provision if dual-chamber pacemakers are to be advocated for use in favour of single-chamber atrial pacemakers.

8.2 Suggested research priorities

Further randomised controlled trials investigating the impact of dual-chamber pacemakers compared to 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 conclusively answer these important clinical questions may be prohibitively expensive.

Assessment of the impact of treatments on patient quality of life may be of interest to the wider clinical community, particularly in patients 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.

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10 APPENDICES

Appendix 1 Literature search strategies

Clinical effectiveness studies

OVID MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present (initially searched 6 January 2014 and updated 12 May 2014)

#	Term
1	exp Pacemaker, Artificial/
2	exp Cardiac Pacing, Artificial/
3	(pacing or pacemaker$ or pace maker$ or paced or pacer$).ti, ,ab.
4	or/1-3
5	((dual or double) adj4 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab.
6	(physiological$ adj2 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab.
7	((av or atrioventricular) adj2 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab.
8	((av or atrioventricular) adj2 (synchron$ or sequential) adj (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab.
9	(dual adj2 chamber).mp.
10	(dual adj2 pac$).mp.
11	(double adj2 chamber).mp.
12	(physiologic$ adj2 pac$).mp.
13	(AV adj2 synchron$).mp.
14	(atrioventricular adj2 synchron$).mp.
15	(AV adj2 sequential).mp.
16	(atrioventricular adj2 sequential).mp.
17	DDD.mp.
18	DDDR.mp.
19	DDI.mp.
20	DDIR.mp.
21	VDD.mp.
22	VDDR.mp.
23	VDI.mp.
24	VDIR.mp.

25	or/5-24
26	(single adj2 chamber).mp.
27	(single adj2 pac$).mp.
28	(atrial adj2 pac$).mp.
29	AAI.mp.
30	AAIR.mp.
31	or/26-30
32	Randomized Controlled Trials as Topic/
33	randomized controlled trial/
34	Random Allocation/
35	Double Blind Method/
36	Single Blind Method/
37	clinical trial/
38	clinical trial, phase i.pt.
39	clinical trial, phase ii.pt.
40	clinical trial, phase iii.pt.
41	clinical trial, phase iv.pt.
42	controlled clinical trial.pt.
43	randomized controlled trial.pt.
44	multicenter study.pt.
45	clinical trial.pt.
46	exp Clinical Trials as topic/
47	(clinical adj trial$).tw.
48	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
49	PLACEBOS/
50	placebo$.tw.
51	randomly allocated.tw.
52	(allocated adj2 random$).tw.
53	or/32-52
54	case report.tw.
55	letter/
56	historical article/
57	or/54-56
58	53 not 57

59	4 and 25 and 31 and 58

OVID: EMBASE (searched from inception to 6 January 2014 and updated 12 May 2014)

#	**Term**
1	exp artificial heart pacemaker/
2	heart pacing/
3	(pacing or pacemaker$ or pace maker$ or paced or pacer$).ti,ab.
4	or/1-3
5	((dual or double) adj4 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab.
6	(physiological$ adj2 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab.
7	((av or atrioventricular) adj2 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab.
8	((av or atrioventricular) adj2 (synchron$ or sequential) adj (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab.
9	(dual adj2 chamber).mp.
10	(dual adj2 pac$).mp.
11	(double adj2 chamber).mp.
12	(physiologic$ adj2 pac$).mp.
13	(AV adj2 synchron$).mp.
14	(atrioventricular adj2 synchron$).mp.
15	(AV adj2 sequential).mp.
16	(atrioventricular adj2 sequential).mp.
17	DDD.mp.
18	DDDR.mp.
19	DDI.mp.
20	DDIR.mp.
21	VDD.mp.
22	VDDR.mp.
23	VDI.mp.
24	VDIR.mp.
25	or/5-24
26	(single adj2 chamber).mp.
27	(single adj2 pac$).mp.
28	(atrial adj2 pac$).mp.

29	AAI.mp.
30	AAIR.mp.
31	or/26-30
32	Clinical trial/
33	Randomized controlled trial/
34	Randomization/
35	Single blind procedure/
36	Double blind procedure/
37	Crossover procedure/
38	Placebo/
39	Randomi?ed controlled trial$.tw.
40	Rct.tw.
41	Random allocation.tw.
42	Randomly allocated.tw.
43	Allocated randomly.tw.
44	(allocated adj2 random).tw.
45	Single blind$.tw.
46	Double blind$.tw.
47	((treble or triple) adj blind$).tw.
48	Placebo$.tw.
49	Prospective study/
50	or/32-49
51	Case study/
52	Case report.tw.
53	Abstract report/ or letter/
54	or/51-53
55	50 not 54
56	4 and 25 and 31 and 55

Cochrane Library (initially searched 7 January 2014 and updated 15 May 2014)

#	**Term**
1	MeSH descriptor: [Pacemaker, Artificial] explode all trees
2	MeSH descriptor: [Cardiac Pacing, Artificial] explode all trees

3	(pacing or pacemaker* or pace maker* or paced or pacer*):ti,ab
4	or #1-#3
5	((dual or double) next/4 (pacing or pacemaker* or pace maker* or paced or pacer*)):ti,ab
6	(physiological* next/2 (pacing or pacemaker* or pace maker* or paced or pacer*)):ti,ab
7	((av or atrioventricular) next/2 (pacing or pacemaker* or pace maker* or paced or pacer*)):ti,ab
8	((av or atrioventricular) next/2 (synchron* or sequential) next (pacing or pacemaker* or pace maker* or paced or pacer*)):ti,ab
9	dual next/2 "chamber"
10	dual next/2 pac*
11	double next/2 "chamber"
12	physiologic* next/2 pac*
13	AV next/2 synchron*
14	atrioventricular next/2 synchron*
15	AV next/2 "sequential"
16	atrioventricular next/2 "sequential"
17	DDD
18	DDDR
19	DDI
20	DDIR
21	VDD
22	VDDR
23	VDI
24	VDIR
25	or #5-#24
26	single next/2 "chamber"
27	single next/2 pac*
28	atrial next/2 pac*
29	AAI
30	AAIR
31	or #26-#30
32	#4 and #25 and #31

Economic evaluations

MEDLINE (Ovid)

Full database title: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present

#	Terms
1	exp Pacemaker, Artificial/
2	exp Cardiac Pacing, Artificial/
3	(pacing or pacemaker$ or pace maker$ or paced or pacer$).ti,ab
4	or/1-3
5	((dual or double) adj4 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab.
6	(physiological$ adj2 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab.
7	((av or atrioventricular) adj2 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab.
8	((av or atrioventricular) adj2 (synchron$ or sequential) adj (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab.
9	(dual adj2 chamber).mp.
10	(dual adj2 pac$).mp.
11	double adj2 chamber.mp.
12	physiologic$ adj2 pac$.mp.
13	(AV adj2 synchron$).mp.
14	(atrioventricular adj2 synchron$).mp.
15	(AV adj2 sequential).mp
16	(atrioventricular adj2 sequential).mp.
17	DDD.mp.
18	DDDR.mp.
19	DDI.mp.
20	DDIR.mp.
21	VDD.mp.
22	VDDR.mp.
23	VDI.mp.
24	VDIR.mp.
25	or/5-24
26	(single adj2 chamber).mp.
27	(single adj2 pac$).mp.
28	(atrial adj2 pac$).mp.
29	AAI.mp.

30	AAIR.mp.
31	(ventricular adj2 pac$).mp.
32	VVI.mp
33	VVIR.mp
34	or/26-33
35	Health Economics.mp
36	Economic evaluation.mp
37	exp Costs and Cost Analysis/
38	cost benefit analysis/
39	exp models economic/
40	exp fees/
41	exp budgets/
42	(economic adj2 burden).tw.
43	(expenditure* not energy).tw.
44	Cost Effectiveness Analysis.mp
45	(unit cost or unit-cost or unit-costs or unit costs or drug cost or drug costs or hospital costs or health-care costs or health care cost or medical cost or medical costs).tw.
46	Cost Minimization Analysis.mp
47	(cost adj2 (util$ or effective$ or efficac$ or benefit$ or consequence$ or analys$ or minimi$ or allocation$ or control$ or illness$ or affordable$ or fee$ or charge$)).tw.
48	(decision adj1 (tree* or analys* or model*)).tw.
49	(econom* or price* or pricing or financ*or fee* or pharmacoeconomic* or pharmaeconomic* or pharmaco-economic*).tw.
50	((value or values or valuation) adj2 (money or monetary or life or lives or costs or cost)).tw.
51	Markov*.tw
52	or/35-51
53	4 and 25 and 34 and 52

EMBASE (Ovid)

Full database title: Embase 1974 to 2013 December 03

#	**Terms**
1	exp Pacemaker, Artificial/
2	exp Cardiac Pacing, Artificial/

3	(pacing or pacemaker$ or pace maker$ or paced or pacer$).ti,ab
4	or/1-3
5	((dual or double) adj4 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab.
6	(physiological$ adj2 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab.
7	((av or atrioventricular) adj2 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab.
8	((av or atrioventricular) adj2 (synchron$ or sequential) adj (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab.
9	(dual adj2 chamber).mp.
10	(dual adj2 pac$).mp.
11	double adj2 chamber.mp.
12	physiologic$ adj2 pac$.mp.
13	(AV adj2 synchron$).mp.
14	(atrioventricular adj2 synchron$).mp.
15	(AV adj2 sequential).mp
16	(atrioventricular adj2 sequential).mp.
17	DDD.mp.
18	DDDR.mp.
19	DDI.mp.
20	DDIR.mp.
21	VDD.mp.
22	VDDR.mp.
23	VDI.mp.
24	VDIR.mp.
25	or/5-24
26	(single adj2 chamber).mp.
27	(single adj2 pac$).mp.
28	(atrial adj2 pac$).mp.
29	AAI.mp.
30	AAIR.mp.
31	(ventricular adj2 pac$).mp.
32	VVI.mp
33	VVIR.mp
34	or/26-33
35	Health Economics.mp
36	Economic evaluation.mp

37	exp Costs/ and Cost Analysis/
38	cost benefit analysis/
39	exp models economic/
40	fees/
41	exp budgets/
42	(economic adj2 burden).tw.
43	(expenditure* not energy).tw.
44	Cost Effectiveness Analysis.mp
45	(unit cost or unit-cost or unit-costs or unit costs or drug cost or drug costs or hospital costs or health-care costs or health care cost or medical cost or medical costs).tw.
46	Cost Minimization Analysis.mp
47	(cost adj2 (util$ or effective$ or efficac$ or benefit$ or consequence$ or analys$ or minimi$ or allocation$ or control$ or illness$ or affordable$ or fee$ or charge$)).tw.
48	(decision adj1 (tree* or analys* or model*)).tw.
49	(econom* or price* or pricing or financ*or fee* or pharmacoeconomic* or pharmaeconomic* or pharmaco-economic*).tw.
50	((value or values or valuation) adj2 (money or monetary or life or lives or costs or cost)).tw.
51	Markov*.tw
52	or/35-51
53	4 and 25 and 34 and 52

HTA database (HTA, Cochrane)

Search terms (and fields searched)	Pacemakers (all fields) Atrioventricular block (all fields) Sick sinus syndrome (all fields)

NHS Economic Evaluations Database (NHS EED, Cochrane)

Search terms (and fields searched)	Pacemakers (all fields) Atrioventricular block (all fields) Sick sinus syndrome (all fields)

Health related quality of life

MEDLINE (Ovid)

Full database title: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present

#	Terms
1	exp Pacemaker, Artificial/
2	exp Cardiac Pacing, Artificial/
3	(pacing or pacemaker$ or pace maker$ or paced or pacer$).ti,ab
4	or/1-3
5	((dual or double) adj4 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab.
6	(physiological$ adj2 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab.
7	((av or atrioventricular) adj2 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab.
8	((av or atrioventricular) adj2 (synchron$ or sequential) adj (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab.
9	(dual adj2 chamber).mp.
10	(dual adj2 pac$).mp.
11	double adj2 chamber.mp.
12	physiologic$ adj2 pac$.mp.
13	(AV adj2 synchron$).mp.
14	(atrioventricular adj2 synchron$).mp.
15	(AV adj2 sequential).mp
16	(atrioventricular adj2 sequential).mp.
17	DDD.mp.
18	DDDR.mp.
19	DDI.mp.
20	DDIR.mp.
21	VDD.mp.
22	VDDR.mp.
23	VDI.mp.
24	VDIR.mp.
25	or/5-24
26	(single adj2 chamber).mp.

27	(single adj2 pac$).mp.
28	(atrial adj2 pac$).mp.
29	AAI.mp.
30	AAIR.mp.
31	(ventricular adj2 pac$).mp.
32	VVI.mp
33	VVIR.mp
34	or/26-33
35	Quality of Life/
36	((quality adj3 life) or life quality or QOL).ti,ab.
37	(HRQL or HRQOL or HRQol).ti,ab.
38	(value adj2 life).ti,ab. or exp Value of Life/
39	(life adj2 qualit$3).tw.
40	(quality-adjusted life year$1 or QALY or QALYs or quality adjusted life year$1).ti,ab. or exp Quality-Adjusted Life Years/
41	daly.ti,ab.
42	(disabilit$3 adj2 life).ti,ab.
43	exp Health Status Indicators/
44	(sf36 or sf-36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).tw.
45	(sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
46	(sf6d or sf 6d or sf-6d or short form 6d or shortform 6d or sf six dimension$1 or short form six dimension$1).tw
47	(sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).tw.
48	(sf16 or sf 16 or sf-16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
49	(sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).tw.
50	(euroqol or euro qol or eq5d or eq 5d or eq-5d).tw.
51	(hye or hyes or health$ year$ equivalent$).tw.
52	hui$1.tw.
53	(willing$ adj2 pay).tw.
54	(willing$ adj2 accept).tw.
55	standard gamble$.tw.

56	(health adj3 (utilit$3 or value$2 or preference$2)).tw.
57	(visual analog$3 scale or VAS).tw.
58	patient preference$2.tw.
59	(person$ trade-off or person$ trade off or PTO).ti,ab.
60	(Contingent value or contingent valuation).ti,ab.
61	discrete choice.ti,ab.
62	health status.ti,ab. or exp Health Status/
63	((quality adj3 wellbeing index) or QWB).ti,ab.
64	(health utilities index or HUI).ti,ab.
65	(time trade off or time tradeoff or TTO or time trade-off).ti,ab.
66	(utility or utilities).ti,ab.
67	disutil$.ti,ab.
68	disability.tw.
69	(wellbeing or well-being or well being or qwb).ti,ab.
70	quality of well being.tw.
71	quality of wellbeing.tw.
72	or/35-71
73	4 and 25 and 34 and 72

EMBASE (Ovid)

Full database title: Embase 1974 to 2013 December 04

#	Terms
1	exp Pacemaker, Artificial/
2	exp Cardiac Pacing, Artificial/
3	(pacing or pacemaker$ or pace maker$ or paced or pacer$).ti,ab
4	or/1-3
5	((dual or double) adj4 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab.
6	(physiological$ adj2 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab.
7	((av or atrioventricular) adj2 (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab.
8	((av or atrioventricular) adj2 (synchron$ or sequential) adj (pacing or pacemaker$ or pace maker$ or paced or pacer$)).ti,ab.
9	(dual adj2 chamber).mp.

10	(dual adj2 pac$).mp.
11	double adj2 chamber.mp.
12	physiologic$ adj2 pac$.mp.
13	(AV adj2 synchron$).mp.
14	(atrioventricular adj2 synchron$).mp.
15	(AV adj2 sequential).mp
16	(atrioventricular adj2 sequential).mp.
17	DDD.mp.
18	DDDR.mp.
19	DDI.mp.
20	DDIR.mp.
21	VDD.mp.
22	VDDR.mp.
23	VDI.mp.
24	VDIR.mp.
25	or/5-24
26	(single adj2 chamber).mp.
27	(single adj2 pac$).mp.
28	(atrial adj2 pac$).mp.
29	AAI.mp.
30	AAIR.mp.
31	(ventricular adj2 pac$).mp.
32	VVI.mp
33	VVIR.mp
34	or/26-33
35	exp Quality of Life/
36	((quality adj3 life) or life quality or QOL).ti,ab.
37	(HRQL or HRQOL or HRQol).ti,ab.
38	(value adj2 life).ti,ab. or exp Value of Life/
39	(life adj2 qualit$3).tw.
40	(quality-adjusted life year$1 or QALY or QALYs or quality adjusted life year$1).ti,ab. or exp Quality-Adjusted Life Years/
41	daly.ti,ab.
42	(disabilit$3 adj2 life).ti,ab.
43	exp Health Status Indicators/

44	(sf36 or sf-36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).tw.
45	(sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
46	(sf6d or sf 6d or sf-6d or short form 6d or shortform 6d or sf six dimension$1 or short form six dimension$1).tw.
47	(sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).tw.
48	(sf16 or sf 16 or sf-16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
49	(sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).tw.
50	(euroqol or euro qol or eq5d or eq 5d or eq-5d).tw.
51	(hye or hyes or health$ year$ equivalent$).tw.
52	hui$1.tw.
53	(willing$ adj2 pay).tw.
54	(willing$ adj2 accept).tw.
55	standard gamble$.tw.
56	(health adj3 (utilit$3 or value$2 or preference$2)).tw.
57	(visual analog$3 scale or VAS).tw.
58	patient preference$2.tw.
59	(person$ trade-off or person$ trade off or PTO).ti,ab.
60	(Contingent value or contingent valuation).ti,ab.
61	discrete choice.ti,ab.
62	health status.ti,ab. or exp Health Status/
63	((quality adj3 wellbeing index) or QWB).ti,ab.
64	(health utilities index or HUI).ti,ab.
65	(time trade off or time tradeoff or TTO or time trade-off).ti,ab.
66	(utility or utilities).ti,ab.
67	disutil$.ti,ab.
68	disability.tw.
69	(wellbeing or well-being or well being or qwb).ti,ab.
70	quality of well being.tw.
71	quality of wellbeing.tw.
72	or/35-71
73	4 and 25 and 34 and 72

HTA database (HTA, Cochrane)

Search terms (and fields searched)	Pacemakers (all fields) Atrioventricular block (all fields) Sick sinus syndrome (all fields **)** **and** quality of life (all fields) or qol (all fields) or qaly (all fields)

NHS Economic Evaluations Database (NHS EED, Cochrane)

Search terms (and fields searched)	Pacemakers (all fields) Atrioventricular block (all fields) Sick sinus syndrome (all fields) **and** quality of life (all fields) or qol (all fields) or qaly (all fields)

Appendix 2 Data abstraction

Clinical effectiveness studies

Parallel group RCTs

Albertsen 2008[41]

Study information	
Study ID (Author name, year, or acronym)	Albertsen 2008
Reference details for all refs relating to the trial	Albertsen AE, Nielsen JC, Poulsen SH, Mortensen PT, Pedersen AK, Hansen PS, et al. DDD(R)-pacing, but not AAI(R)-pacing induces left ventricular desynchronization in patients with sick sinus syndrome: tissue-Doppler and 3D echocardiographic evaluation in a randomized controlled comparison 2. *Europace* 2008 Feb;10(2):127-33.
Language of publication	English

Type of report	Full paper	
Trial location and number of sites	One centre, Department of Cardiology, Aarhus University Hospital, Skejby, Denmark	
Trial sponsor	The study was supported by grants from The Danish Heart Foundation.	
Conflicts of interest	None declared	
Recruitment period	August 2003 to March 2005	
Patient enrolment	All patients referred to the Department of Cardiology, Aarhus University Hospital, Skejby, Denmark, for their first pacemaker implantation were screened for inclusion in the study.	
Trial design	Parallel RCT	
Trial duration (including any run-in and follow-up period)	All data were collected at baseline within 12 hours before pacemaker implantation and again at 3 and 12 months of follow-up	
Inclusion criteria	Patients with SSS (syncope, dizzy spells or heart failure) in combination with the electrocardiographic criteria (sinus arrest >2 s, tachybrady syndrome with sinus pauses > 2 s or sinus bradycardia [<40 beats/min in awake hour].	
Exclusion criteria	Atrioventricular/bundle branch block; chronic atrial fibrillation; atrial fibrillation at randomisation; carotid sinus syndrome; pacemaker implantation during surgery; impaired walking; no ECG documentation available; refusal; heart transplanted patients; vaso-vagal syncope; dementia or life expectancy < 1 year	
Outcomes	**Primary outcome**: changes in LV dyssynchrony from baseline to 12 months of follow-up recorded by tissue-Doppler echocardiography and LVEF measured with 3D echocardiography **Secondary outcomes:** NT-proBNP and 6-min walk test	
Subgroups	Not reported	
Power calculation	Power calculation was done on the basis of LVEF. Calculation was performed before including patients in the study. The risk of type 1 error was set to 5% and the statistical power to 80%. On the basis of earlier studies from our laboratory the standard deviation of the LVEF measured by means of 3D echocardiography was assumed to be 6%. With a minimal relevant difference of 5% (absolute percent) between LVEF in the AAI(R)- and DDD(R)-group, a total of 44 patients were needed in the study. With an expected dropout rate of 10%, the total number of patients included was decided to be 50.	
Intervention/comparator	Dual-chamber pacing DDD(R)	Atrial pacing AAI(R)
Pacemaker (type, brand, etc.)	Dual-chamber pacemakers from several different companies were used (Medtronic®, St. Jude Medical®, Guidant®, ELA®).	Single-chamber pacemakers from several different companies were used (Medtronic®, Sct. Jude Medical®, Guidant®, ELA®).
Implantation	Active fixation bipolar atrial leads were inserted transvenously in the right atrial	All patients received active fixation bipolar atrial leads inserted transvenously in the

	appendage. An additional active fixation lead was inserted transvenously in the RV apex.	right atrial appendage.	
Programming	DDD(R) All pacemakers were programmed with a basal rate of 60 bpm and with rate modulation active to maximum 120–140 bpm. The paced AV-delay was programmed to a maximum of 220–225 ms and rate adaptive. The sensed AV-delay was programmed 20 ms shorter than the paced AV-delay. Mode-switch was active.	AAI(R) All pacemakers were programmed with a basal rate of 60 bpm and with rate modulation active to maximum 120–140 bpm.	
Randomised, n	26	24	
Withdrawals, n (change in pacing mode, loss to follow-up)	None	Switch to DDDR 2 (due to Wenkebach block at atrial pacing 100 bpm during the implantation procedure) Lost to follow up 1	
atrial pacing, %	62%	53%	
ventricular pacing, %	66%	The two patients who received right ventricular leads were paced in the ventricle 3 and 99% of the time, respectively.	
Follow up	Total follow up12 months		
Baseline patient characteristics	Dual-chamber pacing, n (%)	Atrial pacing, n (%)	p value
Age, years (mean, SD)	73±13	72±10	>0.05
Male gender, n (%)	8 (31)	10 (42)	>0.05
Previous history of AF, n (%)	Not reported		
Previous stroke, n (%)	1	5	<0.05
Cardiovascular medication, n	Beta-blockers 11 Calcium channel blockers 5 ACE inhibitors/ARBs 10 Diuretics 11 Aspirin 14	Beta-blockers 6 Calcium channel blockers 5 ACE inhibitors/ARBs 11 Diuretics 14 Aspirin 20	<0.05 for other drugs p>0.05
Pacing indication, n	Sinus arrest/sinus-atrial block 16 Brady-tachy syndrome 12 Sinus bradycardia 8	Sinus arrest/sinus-atrial block 14 Brady-tachy syndrome 11 Sinus bradycardia 4	Not reported

NYHA class, n I II III IV	 18 8 0 0			 19 3 2 0				Not reported
Outcome	**Definition**							
Heart failure	NYHA classification at 12 month follow-up.							
Exercise capacity	Six-minutes walk test at 3 and 12 months follow-up.							
Adverse effects	Complications following implantation: lead displacements, infections or haematomas							
Dichotomous outcomes	Dual-chamber pacing		Atrial pacing					p value
	n	**N**	**n**	**N**				
Heart failure NYHA I II III IV	 14 10 1 1	 26	 18 5 0 0	 23				 NR
Adverse Events								
Lead displacements	0	26	0	24				NA
Infections	0	26	0	24				NA
Haematomas	0	26	0	24				NA
Continuous outcome	Timeframe	Dual-chamber pacing			Atrial pacing			p value
		mean	SD	N	mean	SD	N	
Exercise capacity	baseline	415	76	26	444	105	24	>0.05
Six-minute walking test (m)	12 months	446	96	26	500	89	23	<0.05
Abbreviations used in table: SSS sick sinus syndrome; CI, confidence interval; n, number of patients with the outcome; N, number of patients assessed; RCT, randomised controlled trial; SD, standard deviation; bpm beats per minute; LVEF left ventricular ejection fraction; ECG electrocardiography; NYHA New York Heart Association Functional Classification; NR not reported; NA not applicable; m meter; NT-proBNP N-terminal prohormone of brain natriuretic peptide.								

DANPACE[41;42]

Study information	
Study ID (Author name, year, or acronym)	DANPACE (The Danish Multicenter Randomized Trial on Single Lead Atrial Pacing vs. Dual-chamber Pacing in Sick Sinus Syndrome)

Reference details for all refs relating to the trial	Andersen HR, Svendsen JH. The Danish multicenter randomized study on atrial inhibited versus dual-chamber pacing in sick sinus syndrome (The DANPACE study): Purpose and design of the study. *Heart Drug* 2001;1(2):67-70. 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 196. *European Heart Journal* 2011 Mar;32(6):686-96. Riahi S, Nielsen JC, Hjortshoj S, Thomsen PE, Hojberg S, Moller M, et al. Heart failure in patients with sick sinus syndrome treated with single lead atrial or dual-chamber pacing: no association with pacing mode or right ventricular pacing site 240. *Europace* 2012 Oct;14(10):1475-82.(42-45)
Language of publication	English
Type of report	Full papers
Trial location and number of sites	Patients were enrolled from all Danish pacemaker centres and from selected centres in UK and Canada. Number of sites not reported.
Trial sponsor	Unrestricted grants from Medtronic, St Jude Medical, Boston Scientific, Ela Medical, Pfizer, and The Danish Heart Foundation (10-04-R78-A2954-22779).
Conflicts of interest	J.C.N. and J.H.S. have received consultant honoraries and speakers fees from Medtronic, St Jude Medical, and Biotronik. L.S.M. is an employee of UNI-C, and has been paid consultants fees for his participation in designing the study, taking care of data management and statistical analysis in the study, being a member of the study data monitoring board, and reviewing the manuscript. W.D.T. has received a grant from Medtronic for follow-up of patients enrolled in a clinical trial of cardiac resynchronization therapy. J.S.H. reports receiving a research grant from Boston for conduct of the SIMPLE trial—a 2500 patient study of implantable defibrillators; consulting fees and consultant honoraries from St Jude Medical; and speakers' fees from Boston Scientific and St Jude Medical. The other authors report no conflicts.
Recruitment period	10 March 1999 to 30 June 2008
Patient enrolment	Patients were enrolled from all Danish pacemaker centres and from selected centres in UK and Canada. All patients referred for first pacemaker implantation were evaluated for inclusion.
Trial design	Parallel group RCT
Trial duration	Follow-up took place after 3 months and again every year after implantation up to 10 years. Mean follow-up was 5.4±2.6 years.
Inclusion criteria	Symptomatic bradycardia; documented sino-atrial block or sinus-arrest with pauses >2 s or sinus bradycardia <40 bpm for more than 1 min while awake; PR interval ≤0.22 s if aged 18–70 years or PR interval ≤0.26 s if aged ≥70 years; and QRS width <0.12 s; or bradycardia-tachycardia with QRS >2secs (spontaneously or related to antiarrhytmic treatment; and age >18 years at study enrolment; and able to attend outpatient study visits.
Exclusion criteria	Atrioventricular block; bundle branch block; long-standing persistent atrial fibrillation (>12

	months); atrial fibrillation with ventricular rate <40 bpm for ≥1 min or pauses >3 s; a positive test for carotid sinus hypersensitivity; planned cardiac surgery; or a life-expectancy shorter than 1 year; need for an ICD; cancer; severe psychiatric disease; severe dementia; planned major surgery in the near future. Documented paroxysmal atrial fibrillation was not an exclusion criterion.	
Outcomes	**Primary outcome**: death from any cause. **Secondary outcomes:** paroxysmal atrial fibrillation; chronic atrial fibrillation; first cardioversion for atrial fibrillation; stroke; peripheral embolism; heart failure (hospitalization with heart failure as reported diagnosis and patients classified with new heart failure); % VP at each follow-up; mean % VP throughout the total follow-up period; % MS; cardiovascular mortality; need for pacemaker re-operation, and quality of life.	
Subgroups	Age > or ≤ 75 years; gender; hypertention; LVEF < or ≥ 50%; history of AF; previous MI; PQ interval > or ≤ 180ms; diabetes; NYHA I or II-IV; left atrial diameter > or ≤ 39; BMI ≥ or < 25; diuretics	
Power calculation	It was assumed that the relative difference in mortality between AAIR pacing and DDDR pacing would be half the difference observed between AAIR pacing and single-lead ventricular pacing. Therefore, the study was planned to include 1900 patients followed for a mean of 5.5 years to identify a 6% absolute difference (32 vs. 26%) in death from any cause between treatment groups, with a power of 80% and an overall α = 0.05. Due to the increasing use of dual-chamber pacemakers with new features prolonging or eliminating the atrio-ventricular interval in order to minimize ventricular pacing in patients with sick sinus syndrome, which were not permitted in the trial, the recruitment rate decreased in several Danish centres from 2005. Fewer than the planned 1900 patients were included in the study. From a planned interim analysis, it could be foreseen that no significant difference could be reached with respect to the primary outcome even with the planned 1900 patients.	
Intervention/ comparator	**Dual-chamber pacing**	**Atrial pacing**
Pacemaker (type, brand, etc.)	Contemporary DDDR pacemaker models (Boston Scientific, Medtronic, and St Jude Medical)	Not reported
Implantation	A bipolar lead was implanted in the right atrium and an additional lead was implanted in the right ventricle	A bipolar lead was implanted in the right atrium. An atrial pacing test was performed at 100 bpm in all patients and 1:1 atrio-ventricular conduction was required for implantation of an AAIR pacemaker. In patients randomized to AAIR pacing demonstrating atrio-ventricular block when paced at 100 bpm, a ventricular lead and a DDDR pacemaker were implanted.

Programming	DDDR The rate adaptive function was activated in all pacemakers and programmed with a lower rate of 60 bpm and an upper rate of 130 bpm. The paced atrioventricular interval was programmed to 140–220 ms according to a pre-specified algorithm: the paced atrio-ventricular interval was initially programmed to a value 10% longer than either the interval measured from the atrial pacing spike to start of the conducted QRS complex at 60 bpm or the PR interval if the sinus rate was faster than 60 bpm. If ventricular pacing occurred with this programming, the paced atrio-ventricular interval was gradually increased in steps of 20 ms until ventricular pacing ceased or until a maximum of 220 ms was reached. If ventricular pacing still occurred at a programmed interval of 220 ms, the paced atrio-ventricular interval was shortened to a length of 140–160 ms, and the atrio-ventricular hysteresis function was activated to allow automatic search for intrinsic atrio-ventricular conduction with an atrio-ventricular interval of 220 ms. The atrio-ventricular interval after sensed atrial beats was set 20–30 ms shorter than the paced interval, and automatic shortening of the atrio-ventricular interval was allowed during rate increases. The maximum tracking rate was individualized and the mode switch function was activated. The mean programmed maximum paced atrio-ventricular delay in the dual-chamber group was 225±39 ms New features prolonging or eliminating the atrio-ventricular interval in order to minimize ventricular pacing in patients with sick sinus syndrome were not permitted in the trial.	AAIR The rate adaptive function was activated in all pacemakers and programmed with a lower rate of 60 bpm and an upper rate of 130 bpm. The investigators were asked to only change the pacing mode from AAIR to DDDR pacing in cases of high-grade atrio-ventricular block or documented symptomatic atrio-ventricular block of the Wenckebach type. The incidental finding of a low Wenckebach block point at a follow-up visit was not an indication for change of pacing mode.
Randomised, n	708	707
Withdrawals, n (%) (change in pacing	First pacemaker implantation: 6 AAIR	First pacemaker implantation: 46 DDDR

mode, loss to follow-up)	2 single lead ventricular pacemaker 639 patients were treated as randomized throughout the entire study period 0 lost to follow up	1 single lead ventricular pacemaker 584 patients were treated as randomized throughout the entire study period 0 lost to follow up	
Atrial pacing, %	59±31%	58±29%	
Ventricular pacing, %	65±33%	Pacemaker memory data were recorded in 103 of 122 patients who had a ventricular lead implanted at the first operation or at some point during follow-up. These 103 patients had a mean of 53±35% ventricular pacing.	
Follow up	Average follow up 5.4±2.6 years		
Baseline patient characteristics	Dual-chamber pacing, n (%)	Atrial pacing, n (%)	p value
Age, years (mean, SD)	72.4±11.4	73.5±11.2	0.054
Male gender, n (%)	267 (37.7)	235 (33.2)	0.08
Previous history of AF, n (%)	318 (44.9)	303 (42.9)	0.44
Previous stroke, n (%)	53 (7.5)	61 (8.6)	0.43
Medication, n (%)	Anticoagulation 89 (12.6) Aspirin 361 (51.1) Sotalol 44 (6.2) Beta-blocker other than sotalol 132 (18.7) Calcium-channel blocker 142 (20.1) Digoxin 62 (8.8) Amiodarone 24 (3.4) Class I antiarrhythmics 20 (2.8) Angiotensin-converting-enzyme inhibitors 170 (24.0) Diuretics 263 (37.2)	Anticoagulation 108 (15.3) Aspirin 369 (52.2) Sotalol 43 (6.1) Beta-blocker other than sotalol 159 (22.5) Calcium-channel blocker 137 (19.4) Digoxin 73 (10.3) Amiodarone 25 (3.5) Class I antiarrhythmics 14 (2.0) Angiotensin-converting-enzyme inhibitors 160 (22.6) Diuretics 304 (43.0)	0.14 0.67 0.91 0.08 0.75 0.32 0.88 0.30 0.53 0.03
Pacing indication, n	Not reported		
NYHA class, n	I 522 (73.9) II 158 (22.4) III 24 (3.4)	I 503 (71.4) II 172 (24.4) III 29 (4.1)	0.33

	IV 2 (0.3)		IV 0			
Outcome	**Definition**					
Mortality	New deaths were identified by checking the study database against the Danish Civil Registration System and supplementary information regarding deceased patients was collected from hospitals and general practitioners.					
AF	Paroxysmal AF, defined as the first diagnosis of AF detected in the 12-lead electrocardiogram (ECG) and verified by the pacemaker telemetry at a planned follow-up visit and chronic atrial fibrillation was defined as atrial fibrillation at two consecutive follow-up visits and at all subsequent follow-up visit.					
Stroke	Stroke was defined as: the sudden development of focal neurological symptoms lasting more than 24 h.					
Heart failure	New York Heart Association (NYHA) functional class, use of diuretics, and hospitalization for heart failure were used as indicators of heart failure. Patients were classified with new heart failure if: (i) they presented in NYHA functional class IV or (ii) if two or more of the following indicators were present: presence of oedema, presence of dyspnea, and NYHA functional class III.					
Requirement of further surgery	Need for pacemaker reoperation was decided by the physician in charge of follow-up.					
Adverse events	Not reported					
Health related quality of life	Measured using SF-36					
Dichotomous outcomes	Dual-chamber pacing		Atrial pacing		Estimate of effect	95% CI, p value
	n	N	n	N	AAIR vs DDDR	
Mortality	193	708	209	707	**HR 1.06** **(adjusted HR 0.94)**	**0.88– 1.29, 0.53** **(adjusted 0.52)**
Heart failure (leading to hospitalisation)	28	708	27	707	**HR 1.06**	**0.62–1.79, 0.84**
Heart failure (new)	169	708	170	707	**HR 1.00**	**0.79–1.22, 0.87**
Heart failure NYHA I II III IV	 341 260 61 4	666	 364 231 67 4	666	**Not reported**	**0.43**
Heart failure – diuretic use	328	695	324	692	**Not reported**	**0.89**
AF (Paroxysmal)	163	708	201	707	**HR 1.27** **(adjusted HR 1.24)**	**1.03– 1.56, 0.024** **(adjusted 0.042)**

AF (Chronic)	76	708	79	707	**HR 1.02 (adjusted HR 1.01)**	**0.74–1.39, 0.93 (adjusted 0.93)**
Stroke	34	708	39	707	HR 1.13 (adjusted HR 1.11)	**0.72–1.80, 0.59 (adjusted 0.65)**
Reoperation	84	708	156	707	HR 1.99 (adjusted HR 2.00)	**1.53–2.59, <0.001 (adjusted <0.001)**
Battery depletion	42	708	59	707		**0.09**
Need for surgical change of mode of pacing	4	708	66	707		**< 0.001**
Lead complications	30	708	37	707		**0.42**
Surgical or mechanical complications	7	708	10	707		**0.52**
Infection	3	708	3	707		**0.98**
Skin erosion	3	708	1	707		**0.31**
Device failure	2	708	2	707		**0.99**
Abbreviations used in table: ICD implantable cardioverter defibrillator; VP ventricular pacing; MS mode-switch; LVEF left ventricular ejection fraction; AF atrial fibrillation; MI myocardial infarction; NYHA New York Heart Association; bmp beats per minute; ECG electriocardiogram; CI, confidence interval; n, number of patients with the outcome; N, number of patients assessed; QoL, quality of life; RCT, randomised controlled trial; SD, standard deviation.						

Nielsen 2003[46]

Study information	
Study ID (Author name, year, or acronym)	Nielsen 2003
Reference details for all refs relating to the trial	Kristensen L, Nielsen JC, Mortensen PT, Pedersen OL, Pedersen AK, Andersen HR, et al. Incidence of atrial fibrillation and thromboembolism in a randomised trial of atrial versus dual chamber pacing in 177 patients with sick sinus syndrome. *Heart* 2004 Jun;90(6):661-6. Nielsen JC, Kristensen L, Andersen HR, Mortensen PT, Pedersen OL, Pedersen AK, et al. A randomized comparison of atrial and dual-chamber pacing in 177 consecutive patients with sick sinus syndrome: echocardiographic and clinical outcome. *Journal of the American College of Cardiology* 2003 Aug 20;42(4):614-23.
Language of	English

publication		
Type of report	Full papers	
Section 2: Study information		
Trial location and number of sites	Denmark, 2 sites, Skejby University Hospital, Aarhus and Viborg County Hospital.	
Trial sponsor	Not reported	
Conflicts of interest	Not reported	
Recruitment period	Recruitment between December 1994 and March 1999.	
Patient enrolment	The trial included consecutive patients referred to Skejby University Hospital, Aarhus, Denmark, for their first pacemaker implantation. In a one-year period, patients were furthermore enrolled at the neighboring Viborg County Hospital.	
Trial design	Parallel group RCT	
Trial duration	Follow-up visits were after 3 months, 12 months, and then once a year.	
Inclusion criteria	Patients with SSS, normal AV conduction, no bundle branch block, symptomatic bradycardia <40 bpm or symptomatic QRS pauses of more than 2 s	
Exclusion criteria	Patients with AV block grade 1, 2, or 3; Chronic AF; Bundle branch block; AF >50% of time; AF with QRS rate <40 beats/min; Cerebral disease including dementia; Cardiac surgery planned; Cancer; Pacing for hypertrophic cardiomyopathy; Age <18 years; Prior heart transplant; Major surgery, non-cardiac; Bradycardia and ventricular tachycardia; Wenckebach block <100 beats/min, known before implantation; Carotid sinus syndrome; AF with RR intervals >3 s.	
Outcomes	**Primary outcome:** changes in LA size and LV size and function during follow-up measured by M-mode echocardiography **Secondary outcomes:** Cardiographic end points: changes in LA volume and LV volume and left ventricular ejection fraction (LVEF) measured by two dimensional echocardiography. Clinical end points: AF, thromboembolism, all-cause and cardiovascular mortality, and congestive heart failure.	
Subgroups	Not reported	
Power calculation	Power calculations were based on M-mode echocardiographic data from an AAI versus VVI study. With a statistical power of 80% and a 0.05 level of significance, a total of 450 patients were to be included in the study to detect a 10% difference between the AAIR group and the DDDR group in LA diameter. No differences between the DDDR-s and the DDDR-l groups were expected. However, inclusion was stopped after randomization of 177 patients, because at that time a national multi-center trial of AAIR versus DDDR pacing in patients with SSS was initiated and started in Denmark (the Randomized comparison of AAIR and DDDR pacing in 1,900 patients with SSS [DANPACE] trial). Patients included in the present study were not rolled over into the DANPACE study.	
Intervention/	**Dual-chamber pacing**	**Atrial pacing**

comparator	DDDR-s	DDDR-l	AAIR
Pacemaker (type, brand, etc.)	Standard rate-adaptive dual-chamber pacemakers (Cardiac Pacemakers Inc. [St. Paul, Minnesota], Pacesetter [St. Paul, Minnesota], Medtronic [Minneapolis, Minnesota])		Standard rate-adaptive single-chamber pacemakers (Cardiac Pacemakers Inc. [St. Paul, Minnesota], Pacesetter [St. Paul, Minnesota], Medtronic [Minneapolis, Minnesota]) .
Implantation	All atrial leads were implanted in the upper parts of the right atrial wall. Among patients randomized to DDDR pacing, 37 patients had unipolar leads, and 86 patients had bipolar leads in the right atrium. All patients randomized to DDDR pacing had unipolar leads with passive fixation implanted in the RV apex.		All atrial leads were implanted in the upper parts of the right atrial wall. Among patients randomized to AAIR pacing, 19 patients had unipolar leads, and 35 patients had bipolar leads.
	Atrial fibrillation at the time of pacemaker implantation was not a reason for implanting another pacemaker rather than according to the randomized mode. During implantation, an atrial pacing test at 100 beats/ min was performed; 1:1 AV conduction was required for an atrial pacemaker to be implanted. If Wenckebach block occurred at a rate of 100 beats/min, the patient received a DDDR pacemaker.		
Programming	The rate response function was active in all but two patients. Lower and upper rates were programmed individually		
	Lower and upper rates were programmed individually. Mode-switch function was active in all patients implanted with DDD pacemakers.		
	In patients randomized to DDDR-s pacing, the AV delay was 150 ms and rate adaptive but even shorter if necessary to obtain ventricular pacing with full capture.	In patients randomized to DDDR-l pacing, the AV delay was fixed at 300 ms. In four patients a shorter AV delay had to be programmed to avoid induction of endless loop tachycardia during initial pacemaker testing.	
Randomised, n	60	63	54
Withdrawals, n (%) (change in pacing mode, loss to follow-up)	VVI 2 Lost to follow-up 0	AAIR 1 VVI 2 Lost to follow-up 0	DDDR 6 Lost to follow-up 0
atrial pacing, %	57%	67%	69%

ventricular pacing, %	90%	17%		
Follow up	2.8 ± 1.5	2.8± 1.4	3.1 ± 1.3	
	Average follow-up was 2.9 ± 1.1 years (range: 6 days to 5.3 years)			
Baseline patient characteristics	Dual-chamber pacing, n (%)		Atrial pacing, n (%)	p value
	DDDR-s	**DDDR-l**	**AAIR**	
Age, years (mean, SD)	74 ±9	74±9	74 ±9	NR
Male gender, n (%)	23 (43)	26 (43)	24 (38)	NR
Previous history of AF, n (%)	Not reported			
Previous stroke, n (%)	Not reported			
Medication, n	Beta-blocker 5 Ca-blocker 7 Digoxin 9 Sotalol 8 Aspirin 40 Warfarin 5	Beta-blocker 7 Ca-blocker 11 Digoxin 11 Sotalol 10 Aspirin 36 Warfarin 11	Beta-blocker 4 Ca-blocker 14 Digoxin 11 Sotalol 7 Aspirin 35 Warfarin 5	NR
Pacing indication, n	Sinus bradycardia 5 Sino-atrial block 17 BTS 38	Sinus bradycardia 11 Sino-atrial block 16 BTS 36	Sinus bradycardia 8 Sino-atrial block 19 BTS 27	NR
NYHA class, n I II III IV	 38 22 0 0	 46 14 3 0	 32 18 2 1	NR
Outcome	**Definition**			
Mortality	Cause of death was obtained by interviewing the doctors who had care of the patient and by review of hospital and necropsy reports.			
Cardiovascular mortality	Cause of death was obtained by interviewing the doctors who had care of the patient and by review of hospital and necropsy reports. Cardiovascular death included sudden death, death due to congestive HF, arterial thromboembolism, or a pulmonaryembolus.			
AF	Atrial fibrillation was diagnosed by standard 12-lead ECG at planned follow-up visits			
Stroke	Stroke was diagnosed when neurological symptoms of presumably cerebral ischemic origin persisted for more than 24 h or if patients died within 24 h from an acute cerebrovascular event.			
Heart failure	Heart failure was classified according to NYHA criteria and quantitated by the daily dose of			

	diuretics.						
Dichotomous outcomes	Dual-chamber pacing				Atrial pacing		p value
	DDDR-s		**DDDR-l**		**AAIR**		
	n	**N**	**n**	**N**	**n**	**N**	
Mortality	14	60	14	63	9	54	0.51
Cardiovascular mortality	11.7%	60	14.3%	63	7.4%	54	0.43
Heart failure – increase in consumption of diuretics	32%	60	21%	63	28%	54	0.34
Heart failure – increase in at least one NYH class	30%	60	46%	63	31%	54	0.17
AF	14	60	11	63	4	54	0.03
Stroke	7	60	4	63	3	54	0.32
Abbreviations used in table: SSS sick sinus syndrome; AV atrioventricular; bpm beats per minute; AF atrial fibrillation; LVEF left ventricular ejection fraction; NYHA New York Heart Association; n, number of patients with the outcome; N, number of patients assessed; RCT, randomised controlled trial.							

Crossover RCTs

Gallick1994[37]

Study information	
Study ID (Author name, year, or acronym)	Gallick 1994
Reference details for all refs relating to the trial	Gallik DM, Guidry GW, Mahmarian JJ, Verani MS, Spencer WH, III, Gallik DM, et al. Comparison of ventricular function in atrial rate adaptive versus dual chamber rate adaptive pacing during exercise. *Pacing & Clinical Electrophysiology* 1994 Feb;17(2):179-85.
Language of publication	English
Type of report	Full paper
Trial location and number of sites	Not reported
Trial sponsor	Supported in part through a grant from TLL Temple Foundation, Lufkin, Texas. Computational assistance was provided by the CLINFO Project, funded by the Division of

	Research Resources of the National Institutes of Health, Bethesda, Maryland, under grant RR-00350
Conflicts of interest	Not reported
Recruitment period	Not reported
Patient enrolment	Not reported
Trial design	Two period crossover RCT (AAIR, DDDR)
Trial duration	Exercise tests for each patient were separated by a rest period of 0.5 to 1 hour to allow heart rate and blood pressure to return to baseline.
Inclusion criteria	Patients with sinus node disease, implanted dual-chamber, rate adaptive, multiprogrammable (DDDR) pacemaker, no history of second –degree AV block, no intraventricular conduction delay, and demonstrated1:1 AV conduction at an atrial pacing rate of 120 bpm.
Exclusion criteria	Evidence of AV node disease, pregnancy, patients unable to exercise or those in whom exercise testing was contraindicated.
Outcomes	Exercise, hemodynamic parameter
Subgroups	Not reported
Power calculation	Not reported
Intervention/ comparator	
Pacemaker (type, brand, etc.)	All patients had Synergyst II or Elite pacemakers(Medtronic, Inc., Minneapolis, MN, USA)
Implantation	Patients recruited to the study had already had the pacemaker implanted
Programming	DDDR with AV delay set at 100 ms to maintain 100% ventricular capture and all other parameters left at the patient's currently programmed settings, and AAIR. Rate response parameters were programmed to low threshold, rapid rate response (setting: 8) to try to achieve a maximal exercise test.
Randomised, n	12
Withdrawals, n (%) (change in pacing mode, loss to follow-up)	Data was collected for all randomised patients
atrial pacing, %	Not reported
ventricular pacing, %	Not reported
Follow up	Both pacing modes were studied on the same day with 0.5-1.0 hour rest in-between. No follow up stated.
Baseline patient characteristics	

Age, years (mean, SD)	61±4(SE)					
Male gender, n (%)	8 (67)					
Previous history of AF, n (%)	Not reported					
Previous stroke, n (%)	Not reported					
Medication, n	Ca channel blockers 4 Cardiac glycoside 3 Beta blocker 4					
Pacing indication, n	Not reported					
NYHA class, n	Not reported					
Outcome	**Definition**					
Exercise capacity	Upright bicycle exercise was performed with an initial workload of 200 kpm, with in increments in workload of 200 kpm every 3 minutes until peak heart rate ≥ 85% predicted based on age.					
Continuous outcomes		Dual-chamber pacing		Atrial pacing		p value
	N	mean	SD	mean	SD	
Exercise capacity						
Exercise time* (sec)	12	416	140	411	122	0.74
*Data for exercise time was calculated from individual patient data provided in the full publication. Abbreviations used in table: AV atrioventricular; bpm beats per minutes; CI, confidence interval; n, number of patients with the outcome; N, number of patients assessed; RCT, randomised controlled trial; SD, standard deviation; SE, standard error; NR not reported.						

Lau 1994[38]

Study information	
Study ID (Author name, year, or acronym)	Lau 1994
Reference details for all refs relating to the trial	Lau CP, Tai YT, Leung WH, Wong CK, Lee P, Chung FL, et al. Rate adaptive pacing in sick sinus syndrome: effects of pacing modes and intrinsic conduction on physiological responses, arrhythmias, symptomatology and quality of life. *European Heart Journal* 1994 Nov;15(11):1445-55.
Language of publication	English
Type of report	Full paper
Trial location and	Not reported

number of sites		
Trial sponsor	UPCG research grant HKU37/91 (Account code 338/041/0004)	
Conflicts of interest	Not reported	
Recruitment period	Not reported	
Patient enrolment	Not reported	
Trial design	Triple crossover RCT (AAIR, DDDR, VVIR)	
Trial duration	Acute invasive testing phase, which was performed at admission of the patients into the study, and which was completed within a single clinical attendance. This was followed by a 12 week ambulatory phase in which the pacemaker was randomised to one of the three pacing modes for three 4-week periods.	
Inclusion criteria	Sick sinus syndrome and intact AV conduction (1:1 conduction up to 100 bpm and a pacing spike to R interval ≤ 220ms)	
Exclusion criteria	Not reported	
Outcomes	Holter monitoring, ambulatory blood pressure monitoring, symptoms and quality of life assessments	
Subgroups	Not reported	
Power calculation	Not reported	
Intervention/ comparator		
Pacemaker (type, brand, etc.)	Dual-chamber rate adaptive pacemaker with either activity of minute ventilation sensors for rate adaptation. Minute ventilation pacemaker (META-DDDR, Model 1250, Telectronics Pacing Systems, Colorado, USA) Activity sensing pacemaker (Relay, Model 294-03, Intermedics INC., Angleton, Texas, USA	
Implantation	Not reported	
Programming	A lower and upper rate of 60 and 150 bpm respectively were programmed, and the nominal rate adaptive AV interval was used in all patients: 96±7 to 140±5 ms	
Randomised, n	15	
Withdrawals, n (%) (change in pacing mode, loss to follow-up)	3 withdrawals: 2 pacemaker failure 1 patient non-compliance	
	DDDR mode	AAIR mode
Atrial pacing, %	Not reported	Not reported
Ventricular pacing, %	64±11	N/A
Follow up	Total follow-up was 3 months for each pacing mode.	
Baseline patient		

characteristics	
Age, years (mean, SD)	62±2
Male gender, n (%)	5 (42)
Previous history of AF, n (%)	Some of the patients
Previous stroke, n (%)	Not reported
Medication, n	Cardiac glycosides 3 Potassium channel blockers 1 Calcium channel blockers 2 Beta blocker 1 Angiotensin converting enzyme inhibitor 1 Acetylsalicylic acid 1 Nitrates 2
Pacing indication, n	Not reported
NYHA class, n	Not reported
Outcome	**Definition**
Health related quality of life	**Visual analogue scale (VAS) for general well-being, 12-item General Health Questionnaire and the somatic symptoms inventory adapted for local use from the Bradford Somatic Inventory.**

Continuous outcomes		Dual-chamber pacing		Atrial pacing		Mean difference	p value
	N	mean	SD	mean	SD		
general well-being* (VAS)	12	7.1	1.2	6.8	1.3	0.25	0.32
12-item General Health Questionnaire	12	14.3	SE 2.2	15.2	SE 2.1	NR	NS
The somatic symptoms inventory adapted from the Bradford Somatic Inventory.	12	71.5	SE 3.3	70.2	SE 3.5	NR	NS
Symptoms**							
Dyspnoea	12	3.4	0.45	3.95	0.25	-0.55	NS
Palpitations	12	4.25	0.25	3.95	0.3	0.3	NS
Dizziness	12	4.25	0.25	3.95	0.3	0.3	NS
Chest pain	12	4.55	0.25	4.6	0.25	-0.05	NS

Sleep disturbance	12	4.2	0.25	4.6	0.2	-0.4	NS
Neck pulsations	12	4.95	0.1	4.95	0.1	0	NS

*Data for general well-being calculated from individual patient data provided in the full publication.

** Data for symptoms were estimated from figure 3 in the full publication.

Abbreviations used in table: AV atrioventricular; bpm beats per minute; N/A not applicable; CI, confidence interval; n, number of patients with the outcome; N, number of patients assessed; HRQoL health related quality of life; RCT randomised controlled trial; SD, standard deviation; SE, standard error.

Schwaab 2001[48]

Study information	
Study ID (Author name, year, or acronym)	Schwaab 2001
Reference details for all refs relating to the trial	Schwaab B, Kindermann M, Schatzer-Klotz D, Berg M, Franow H, Frohlig G, et al. AAIR versus DDDR pacing in the bradycardia tachycardia syndrome: a prospective, randomized, double-blind, crossover trial 262. *Pacing & Clinical Electrophysiology* 2001 Nov;24(11):1585-95.
Language of publication	English
Type of report	Full paper
Trial location and number of sites	Germany, number of sites not reported.
Trial sponsor	All costs were paid for by the university clinic in Homburg/Saar
Conflicts of interest	Not reported
Recruitment period	Not reported
Patient enrolment	Not reported
Trial design	Two period crossover RCT (AAIR, DDDR)
Trial duration	Four weeks after implantation, patients were randomised to either AAIR or DDDR mode. 3 months after randomisation data was collected and the pacing mode switched to the other mode. After another 3 months data was collected again.
Inclusion criteria	Patients had to have experienced at least two documented paroxysms of atrial tachyarrythmia, be on antiarrhythmic medication for the prevention of atrial flutter or fibrillation, and be eligible for a dual-chamber pacing system for spontaneous or medically induced symptomatic sinus bradycardia. Patients had to comply with each of the following definitions of chronotropic incompetence: peak exercise heart rate<100 bpm, peak exercise heart rate < (220-age)*0.75 and heart rate at half the maximum work load < 60+2 bpm per

	mL O_2/kg/min.	
Exclusion criteria	Complete bundle branch block, a bifascicular block, PQ interval > 240 ms during sinus rhythm at rest, second or third degree AV block identified on preimplant 24 hour Holter ECG, significant valvular heart disease diagnosed by ECHO or Doppler echocardiography.	
Outcomes	Quality of life, left ventricular outflow, aortic flow (peak flow velocity, time to peak flow velocity, the area under the systolic time velocity curve, cardiac output), mitral flow (peak flow velocity of the early wave, time to peak flow velocity, decelaration of early diastolic flow, filling time, early diastolic closure rate of the anterior mitral valve leaflet), bicycle cardiopulmonary exercise testing (to assess exercise duration, development of AV block, oxygen consumption, carbon dioxide production, minute ventilation, breathing rate, respiratory rate exchange ratio, ventilatory equivalents for O_2 and CO_2, number of episodes and total duration of atrial tachyarrhythmia, incidence of AV block type I, II or III and maximum duration of the longest pause, percentage of paced atrial and ventricular beats.	
Subgroups	Not reported	
Power calculation	Not reported	
Intervention/ comparator		
Pacemaker (type, brand, etc.)	Any type of DDDR pacemaker	
Implantation	Not reported	
Programming	DDDR or AAIR. Maximum pacing rate was set as (220-age) x 0.9 and at least 10 bpm below the Wenkebach point unless a lower rate was clinically indicated. AV-delay was optimised based on the maximum time velocity integral of the aortic flow. Rate adaptation was tailored individually during self-determined casual and brisk walks. Mode switch was not initiated in all patients.	
Randomised, n	21	
Withdrawals, n (%) (change in pacing mode, loss to follow-up)	2 withdrawals: 1 chronic atrial fibrillation in AAIR mode 1 death in DDDR mode	
	DDDR mode	AAIR mode
Atrial pacing, %	95±5%	96±5%
Ventricular pacing, %	99±2%	N/A
Follow up	Total follow-up was 3 months for each pacing mode.	
Baseline patient characteristics	**Note: Baseline characteristics for 19 patients who completed follow-up**	
Age, years (mean, SD)	70±7	

Male gender, n (%)	11 (58)						
Previous history of AF, n (%)	Not reported						
Previous stroke, n (%)	Not reported						
Medication, n	Sotalol 13 Flecainide 2 Amiodarone 5						
Pacing indication, n	Not reported						
NYHA class, n	Not reported						
Outcome	**Definition**						
Exercise capacity	Bicycle ergometry was performed under the same conditions and at the same time of day for each patient. An incremental exercise test to exhaustion was performed using workload increments of 15 Watt/min in every patient. Exercise duration and maximal workload in Watts were measured.						
Cognitive function	**One dimension of first quality of life questionnaire using visual analog scale (VAS) to assess cognitive functioning**						
Health related quality of life	**Symptoms were assessed using four self administered questionnaires: 1) visual analog scales (VAS) for general well-being, physical, emotional, and cognitive functioning; 2) VAS Karolinska questionnaire including 16 questions on cardiovascular symptoms relevant to pacemaker patients; 3) Specific Activity Scale (SAS) functional status questionnaire for physical capacity, grading patients from Class I (unlimited exercise capacity) to Class IV (very low exercise tolerance); 4) 5-point category scale to estimate the severity and prevalence of specific symptoms caused by pacemaker induced hemodynamic dysfunction as occurs in the pacemaker syndrome. 1 = severe and nearly persistent to 5 = free of symptoms.**						
Continuous outcomes	Dual-chamber pacing			Atrial pacing			p value
	mean	SD	N	mean	SD	N	
Exercise capacity							
Maximum exercise duration (sec)	402	102	19	423	127	19	<0.05
Maximum workload (Watt)	96	27	19	103	31	19	<0.05
Self-perceived health status (%)							
General well-being	**67**	**20**	**19**	**67**	**23**	**19**	NS
Physical functioning	59	25	19	56	25	19	NS
Emotional functioning	63	27	19	63	27	19	NS

Cognitive functioning	**56**	**23**	**19**	**51**	**27**	**19**	NS
Karolinska questionnaire (%)							
Chest pain	73	20	19	76	19	19	NS
Palpitations	78	17	19	79	20	19	NS
Dizziness	71	16	19	82	11	19	<0.05
Dyspnea	67	24	19	71	20	19	NS
SAS (1-4)	1.6	0.74	19	1.6	0.67	19	NS

Abbreviations used in table: bpm beats per minute; ECG electrocardiogram; AV atrioventricular; N/A not applicable; VAS visual analogue scale; NS not significant; CI, confidence interval; n number of patients with the outcome; N number of patients assessed; RCT, randomised controlled trial; SD, standard deviation.

Economic evaluations

Author , year	Caro J, 2006, UK
Perspective,discounting and cost year	UK NHS perspective, discounting: costs 6% and benefits 1.5%, cost year 2003
Model type	Discrete event simulation, cost utility, 5-year time horizon
Patient population	Bradycardia due to SND or AVB. Patient characteristics sourced from CTOPP. Age distribution based on 2002 UK pacemaker implantation population. Systolic BP distribution
Intervention/comparator	Dual-chamber (DDD [52%]or DDDR [48%]) vs. single-chamber ventricular pacemakers (VVI [35%] or VVIR [65%])
Costs (source)	Procedure costs, (NHS reference costs 2002): *Initial procedure*: outpatient (£1962), elective inpatient (£3177), non-elective inpatient (£3217). *Re-operation*: day case (£1503), inpatient elective (£2395), inpatient non-elective (£2785). Pacemaker costs, (Consortium of Pacemaker Manufacturers, personal communication): DDD (£1260),DDDR (£1864),VVI (£673), VVIR (£937). Anticoagulation, (SPC and NHS ref costs 2002):cost of warfarin 5 mg per day (£0.06) and six physicians' visits per year associated with monitoring Stroke, (NHS ref costs 2002) :£2157 per patient.
Outcomes (source)	Post-operative complications: baseline rate (MOST);[66] HR for single-chamber device (CTOPP).[64] AF, (CTOPP).[64;65] Clinically relevant pacemaker symptoms, (CTOPP).[115]

	Stroke, in AF patients only (Framingham Heart Study). [67] Death, assumed equivalent (CTOPP). [116] QALYs, utility data (MOST).[70]
Results (including uncertainty	Post-operative complications, single-chamber (6.4%) dual-chamber (7.7%). AF, single-chamber (22%) dual-chamber (18%) Death, 29.1% of the patients in each cohort died within 5 years of the implant Mean discounted cost over 5 years, £4300 per patient in either cohort Mean additional cost per patient, £43 Mean cost-utility, £477 per discounted QALY Univariate sensitivity analysis, results are sensitive to the proportion of patients with a VVI(R) who would have a replacement device because of pacemaker syndrome Multivariate sensitivity analyses: dual-chamber pacemakers dominant in 29% of replications, ICER < £1000/QALY in 31% of replications . ICER did not exceed £10 000/QALY in any analysis.

Author, year	Castelnuovo E, 2005, UK
Perspective,discounting and cost year	UK NHS perspective, discounting: costs 6% and benefits 1.5%, cost year 2003
Model type	A series of Excel-based Markov models, cost-utility, 5 year time horizon (10 years explored in sensitivity analysis
Patient population	3 homogeneous hypothetical cohorts of individuals with SSS or AVB.
Intervention/comparator	The models compared three treatment options: dual-chamber versus single-chamber ventricular pacemakers in the AVB population dual-chamber versus single-chamber ventricular pacemakers in the SSS population dual-chamber versus single-chamber atrial pacemakers in the SSS population.
Costs (source)	Hardware, (unpublished at the time UKPACE): VVI (£690); VVIR (£1,099); DDD (£1,365);DDDR (£2,107);Atrial lead (£175); Ventricular lead (£172). Implantation procedure costs, (Resource cost initiative database): single-chamber pacemaker (£4,025); dual-chamber pacemaker (£4,925) Perioperative complications, (NHS Resource costs 2002): single-chamber ventricular pacemaker (£816);single-chamber atrial pacemaker (£894);dual-chamber pacemaker (£894) Pacemaker syndrome, (NHS Reference costs 2002), excludes upgrade costs:Mild (£40);Severe (£176) Development of AVB, (NHS Reference costs 2002), in SSS only patients, excludes upgrade costs, £176. Atrial fibrillation, (NHS reference costs 2002) £41 per month, including antithrombotic treatment, GP visits, INR monitoring and outpatient anticoagulation clinic visits. Heart failure, based on assumptions of hospital admission and drug use, £152 per month. Stroke, (Kavanagh et al,[80] NHS Reference costs 2002) £816 per cycle.
Outcomes (source)	Proportion of patients receiving each device type, is as reported in clinical trials. Incidence of perioperative complications, (review of, PASE and CTOPP),[64;69] incidence rate doubled for upgrades.

	Pacemaker syndrome, time dependent incidence, proportion leading to upgrade (MOST and CTOPP).[64;70] Development of AVB, in SSS only patients, 1.9% per annum (Nielsen et al).[46] Progression to AF: SSS patients with single-chamber ventricular pacemaker, 39% cumulative over 36 months, 12% in the first 6 months, 27% in the following 30 months (MOST);[70] AVB patients with single-chamber ventricular pacemaker, (UKPACE); SSS patients with single-chamber atrial pacemaker, RR versus dual chamber pacemaker = 0.42 (Nielsen et al).[46] Heart failure: AF patients, 3.3% (Wang et al);(72) non-AF, single-chamber ventricular pacing, 2.6% (meta-analysis); non-AF, dual-chamber pacing, 2.5% (meta-analysis); non-AF, single-chamber atrial pacing, RR = 1.07 versus dual-chamber pacing (Nielsen et al).[46] Stroke: AF patients, 3.2% (Chugh et al);(71) non-AF, single-chamber ventricular pacing, 1.25% (meta-analysis); non-AF, dual-chamber pacing, 1.25% (meta-analysis); non-AF, single-chamber atrial pacing, RR = 0.62 versus dual-chamber pacing (Nielsen et al).[46] Reimplantation at the end of generator life: dual-chamber pacemaker, 0.7% in year 2, increasing to 25.5% in year 10 (The National Pacemaker Database); single-chamber pacemaker, 0.6% in year 2, increasing to 18% in year 10 The National Pacemaker Database). Mortality: Perioperative mortality, 2.5 per 1,000 (PASE);Perioperative mortality following upgrade operation, double initial operation perioperative mortality (assumption);All-cause mortality (ONS 2002); Stroke mortality, 33%, (Appelros et al);[74]

	Heart failure mortality, 20.8% (MacIntyre et al).[75] Utilty:Pacemaker implant/AVB prior to upgrade, 0.76 (PASE);Perioperative/subsequent complications, 0.75, assumption based on PASE);Well with pacemaker, 0.925 (PASE);Mild pacemaker syndrome, 0.80 (PASE);Severe pacemaker syndrome, 0.62 (PASE);Perioperative complications during upgrade, 0.915 (PASE);AF, 0.875 (Harvard database);Heart failure, 0.64, (PASE); Stroke, 0.39 (Tengs et al)[82]
Results (including uncertainty	Deterministic: dual-chamber versus single-chamber ventricular pacemakers in the AVB population (5-years: £8,458 per QALY [10 years: £5,483 per QALY]) dual-chamber versus single-chamber ventricular pacemakers in the SSS population (5-years: £9,552 per QALY [10 years: £5,732 per QALY]) dual-chamber versus single-chamber atrial pacemakers in the SSS population (5-years: Atrial pacing dominates [10 years: atrial pacing dominates]) One-way sensitivity analysis, identified cost of implant , utility associated with mild pacemaker syndrome and incidence of AF as key model drivers. Probabilistic sensitivity analysis, revealed high levels of uncertainty.

Author , year	Clarke, 1998, UK
Perspective,discounting and cost year	UK NHS, no discounting, cost year 1995/96
Model type	Retrospective cost comparison/cost saving
Patient population	People with SSS and no AVB

Intervention/comparator	Single chamber atrial pacemaker versus dual chamber pacemaker
Costs (source)	Device (including implant) costs only, within institution cost (single-chamber atrial pacemaker: £2,885; dual-chamber pacemaker: £3,844
Outcomes (source)	Development of AVB (retrospective analysis of within institution records from 1992-1996)
Results (including uncertainty	Based on observed percentage of upgrades procedures, cost savings were estimated at £103,000 per year.

Author , year	Deniz, 2008, Italy (based on model outlined in publication by Caro et al)
Perspective,discounting and cost year	Italian government perspective, 3% discounting for costs and benefits, cost year 2004
Model type	Cost-utility, DES, 5-year time horizon
Patient population	Individuals with SSS or AVB. Patient characteristics sourced from CTOPP.[65] Age distribution based on 2002 UK pacemaker implantation population. Systolic BP distribution from the Framingham Heart Study for patients with AF.[67]
Intervention/comparator	Dual-chamber (DDD [52%]or DDD(R) vs. single-chamber ventricular pacemakers VVI(R).
Costs (source)	Procedure costs, (Istat):*Initial procedure*:outpatient (€5,867), elective inpatient (€6,934). *Re-operation*: day case (€2,820);inpatient elective (€4,302). Pacemaker costs, (Medtronic Europe, Italy, personal communication): DDD (€2,953); DDDR (€3,723); VVI (€1,336); VVIR (€2,110).

	Stroke, (Istat) hospital stay (€3,567). Anticoagulation (Istat), includes warfarin 5 mg/day and a physician visit (€106 per year).
Outcomes (source)	complications: baseline rate (MOST);[66] HR for single-chamber device (CTOPP).[64] AF, (CTOPP).[64;65] 6.6% of VVI(R) patients developed AF(documented episode lasting > 15 mins); 18% risk reduction observed for “physiological” pacing 3.84% of VVI(R) patients developed chronic F (lasting at least one week); 27% risk reduction of chronic AF with”physiological” pacing. Stroke, in AF patients only (Framingham Heart Study). [67] Clinically relevant pacemaker symptoms, (CTOPP.[115] and MOST[70]) Death, assumed equivalent (CTOPP). [116] QALYs, utility data (MOST).[70]
Results (including uncertainty	Based on the mean of 100 replications of the simulation of 1000 patients ICER: €260 per QALY (£215 per QALY)[a] Multivariate analysis based on 1000 replications of 1000 simulated patients accounting for parameter uncertainty indicated that dual-chamber devices were less costly and more effective in 45% of replications. Univariate sensitivity analysis indicated that the cost-effectiveness results were sensitive to assumptions around device replication following the onset of pacemaker syndrome.

Author , year	Mahoney, 1994, US
Perspective,discounting and cost year	US Payer perspective, no discounting, cost year not stated
Model type	Comparison of benefits and costs, time horizon is stated as “long-term”
Patient population	Patients receiving dual or single-chamber pacemakers
Intervention/comparator	Dual-chamber (DDD) or single-chamber atrial (AAI) versus single-chamber ventricular (VVI) pacemakers
Costs (source)	Treatment (of outcomes associated with pacing, e.g. AF) costs (National average urban Diagnostic Related Group payment, Minneapolis), Device costs (Source not stated)
Outcomes (source)	AVB, AF, CHF, pacemaker syndrome, stroke, thromboembolism, mortality (meta –analysis of 35 published studies comparing dual- to single-chamber pacing modes
Results (including uncertainty	Benefits, When compared with VVI pacing, DDD pacing significantly reduces the incidence of AF< pacemaker syndrome, thromboembolism, stroke and mortality. When compared with VVI pacing, AAI pacing significantly reduces the incidence of AF, thromboembolism, stroke, CHF and mortality. However, the probability of AVB development of is greater in AAI versus VVI pacing. Costs, the cost of treating patients for AF, CHF, stroke and pacemaker syndrome is higher in VVI pacing versus DDD and versus AAI pacing. VVI vs DDD: AF, +279%;CHF, +62%;Stroke, +241%;Pacemaker syndrome, +147%. VVI vs AAI: AF, +343%;CHF, +228%;Stroke, +327%; Pacemaker syndrome, +179%. Including device cost, the overall cost of VVI versus DDD is 24%-27% higher and the overall cost of VVI versus AAI is 34%-35% higher. Note: The diagrammatic representation of treatment costs seems to contradict the percentage cost increases reported. That is, in the figure, the treatment costs associated with AAI appear higher than those associated with DDD, and yet VVI is reported as costing proportionally more in comparison to AAI than to DDD pacing.

Author , year	O'Brien, 2005, Canada
Perspective,discounting and cost year	Provincial government health care payer (mostly Ontario) perspective, discounting 3% per annum, 2004 C$
Model type	Economic evaluation alongside clinical trial, cost-effectiveness analysis, 5.2 year time horizon
Patient population	Patients without chronic atrial fibrillation who were scheduled for a first implantation of a pacemaker to treat symptomatic bradycardia
Intervention/comparator	Physiological pacing (dual or single-chamber atrial pacemakers) versus single-chamber ventricular pacemakers
Costs (source)	Resource use and costs were collected from a subset of patients enrolled in CTOPP. Resource use included: Initial pacemaker implantation, adjustment and replacement of pacemaker, length of (initial and subsequent) hospital stay, follow-up physician visits and consultations and antiarrhythmic drugs. Costs (adjusted for censoring using methods of Lin et al): [(84)] Hospital costs (Ontario Case Costing Project), device costs (Canadian market prices weighted by market share),physician's services (Ontario Schedule of Benefits) and antiarrhythmic drugs (Ontario Drug Benefits schedule).
Outcomes (source)	Life-expectancy: Kaplan-Meier data from (CTOPP – all patients). AF, event data (CTOPP – all patients).
Results (including uncertainty	Cost-effectiveness[a]: C$297,600 [£164,611] per life year gained (all patients); C$16,343 [£9,040] per life year gained (people with IHR ≤ 60 bpm) Physiologic pacing is dominated by single-chamber ventricular pacing in people with IHR < 60; C$74,000 [£40,931] per AF event avoided (all patients); C$102,275 [£56,571] per AF event avoided (people with IHR ≤ 60 bpm)

	C$40,400 [£22,346] per AF event avoided (people with IHR < 60). Sensitivity analysis: *CEACs*, probability of cost-effectiveness at WTP threshold of C$300,000 per life-year gained is <50% when all patients are considered, and 98% at WTP of C$50,000 in patients with IHR ≤ 60.
Author , year	Oddershede L, 2014, Denmark
Perspective,discounting and cost year	Danish health care system, discounting: costs and benefits 3.5 %, costs were converted from 2012 Danish Kroner to 2013 GBP.
Model type	Markov model was used, cost utility, life-time horizon.
Patient population	Patients with sick sinus syndrome and preserved atrioventricular conduction. Patients were divided into 3 groups with different levels of risk in terms of their predicted survival probability according to a Cox proportional hazard model. 'Risk Group 1' was the group with the highest probability of deaths and 'Risk Group 3' was that with lowest probability of deaths.
Intervention/comparator	Dual chamber (DDDR) pacing vs. Single –lead atrial (AAIR) pacing.
Costs (source)	Procedure costs Mean cost of initial pacemaker implantation: AAIR: £6,304(SE 85), DDDR: £5,661 (SE 97) (Resource consumption during surgery, occurrence of complications and duration of initial hospitalisation were calculated from DANPACE trial information). Follow up and Complication costs (Danish diagnosis related group(DRG) and Danish ambulatory group (DAG) costs 2012) Follow up visits costs £101 (SD 10) at 3 months, 2 years, 4 years and every following year. Stroke £13,348 (SD 1,335) Death £ 1,314 (SD 131)

Outcomes (source)	Stroke First stroke Second stroke Death QALYs (Clinical data was pooled from the DANPACE trial and 2 previous Danish trials comparing both pacing modes in the population of interest.)		
Results (including uncertainty)	Adjusted -Incremental costs (£) : Risk Group 1: -3366 Risk Group 2: -2570 Risk Group 3: -5045 -Incremental effectiveness (QALYs): Risk Group 1: -0.022 Risk Group 2: -0.029 Risk Group 3: -0.041	Adjusted pooled -Incremental costs (£) : Risk Group 1: -4170 Risk Group 2: -3856 Risk Group 3: -7521 -Incremental effectiveness (QALYs): Risk Group 1: -0.103 Risk Group 2: -0.170 Risk Group 3: -0.218 -Net monetary benefit (£):	Unadjusted multistate -Incremental costs (£): -2310 -Incremental effectiveness (QALYs): 0.277 -Net monetary benefit (£): 7,847 (10,615) Probabilistic sensitivity analysis: At a willingness to pay threshold of £20,000 DDDR pacing was cost-effective across all the scenarios. However, at a

	-Net monetary benefit (£): Risk Group 1: 2,918 (2,694) Risk Group 2: 1,996 (1,709) Risk Group 3: 2,608 (3,442)	Risk Group 1: 2,103 (1,069) Risk Group 2: 460 (-1238) Risk Group 3: 3,160 (980)	willingness to pay threshold of £30,000 DDDR pacing was not cost-effective in Risk Group 2.

Author , year	Osman, 2010, UK
Perspective,discounting and cost year	Single center perspective, no discounting, cost year 2005/06
Model type	No model, Safety and cost assessment of inpatient versus same pay elective pacemaker implant, one-year time horizon for costs, 5.5 year time horizon for safety
Patient population	780 Patients scheduled for new pacemaker implant, included: AVB (33.2%); SND (32.1%; AF with bradycardia (24.5%); AVB and SND (4.1%; Other (6.1%).
Intervention/comparator	Same day procedure versus procedure followed by an overnight stay for new pacemaker implant.
Costs (source)	Cost of an overnight stay, £203.60, (Finance department of single-center).
Outcomes (source)	Peri- and post-implant complications, hospital admissions after pacemaker implantation, mortality (single center pacing database)
Results (including uncertainty	*Unplanned overnight stay*, 41 (5.3%) required an overnight stay as a result of:

	hematoma (12 patients); pneumothorax (3 patients); observation at physician's request (13 patients); social reasons (7 patients); the development of angina (3 patients); Af (1 patient); Warfarin with INR > 2.0 (2 patients); *Immediate complications*, < 24 hours after implant, occurred in 6 patients: Displaced atrial leads (2 patients); Elevated ventricular threshold(1 patient); Sensing problems on the atrial lead (2 patients); Hematoma (1 patient). *Early complications*, > 24 hours to 6 weeks after implantation, occurred in 17 patients: Lead displacements (5 patients); High pacing thresholds (6 patients); Wound infection (3 patients); Sensing problems (2 patients); Subclavian vein thrombosis (1 patient). *Cost savings*, with respect to overnight stays avoided, Of 109 patients undergoing elective same day new pacemaker implantation between November 2005 and November 2006, 2 patients required an overnight stay as a result of lead displacement, resulting in cost-savings of £21,785.

Author , year	Ray, 1992, UK
Perspective,discounting and cost year	Single center perspective, no discounting, cost year 1991
Model type	No model, Clinical practice and cost audit, 18-month time horizon
Patient population	Patients undergoing a first pacemaker implantation
Intervention/comparator	Any pacing device
Costs (source)	Average cost of pacemaker unit (single center cost records): VVI (£631); VVIR (£1,773); AAI (£927); AAIR (£1,642); DDD (£1,811); DDDR (£1,992); DD! (£1,845). Average cost of pacing type including the cost of any replacement lead or generator that had to be inserted within a month of the initial procedure (single center cost records)
Outcomes (source)	N/A
Results (including uncertainty	Change in practice: The proportion of SND patients receiving atrial (AAI/AAIR or DDD/DDDR) pacing as oppose to ventricular pacing (VVI/VVIR) increased from 24% to 59%. The proportion of AVB patients receiving a dual-chamber pacemaker increased from 12% to 19%.

	The proportion of patients with AVB & AF receiving VVIR pacing increased from 10% to 22%. Cost impact of full guideline adherence Full guideline adherence was estimated as increasing the budget for pacing hardware by 94% (from 333,535 to 647,163) over the 18 month study period.

Author , year	Rinfret, 2005, US
Perspective,discounting and cost year	Societal, 3% discounting, 2001
Model type	In-trial cost effectiveness analysis, extrapolated with a Markov model, CUA, In-trial time horizon 4 years and Markov extrapolation time horizon is lifetime
Patient population	Patients paced for sick sinus syndrome
Intervention/comparator	DDDR vs VVIR
Costs (source)	Pacemaker implantation costs, inc: hardware (IMS hospital supply index); hospitalization (single centre); professional fees (Medicare physician fee schedule). Follow-up outpatient costs, inc emergency department visits, unscheduled outpatient visits and 50% of scheduled visits during the MOST trial (MOST trial data). Medication costs (2001 Redbook costs) Rehospitalization as a result of cardiovascular events (MOST trial data).

	Cross over - VVIR to DDDR -costs (single centre) Generator change (single centre) – resource use based on expert opinion of 8 and 11 years before replacement of DDDR and VVIR devices, respectively.
Outcomes (source)	AF (MOST trial data) Hospitalization for heart failure (MOST trial data) Stroke (MOST trial data) Death (MOST trial data) Utility data (data from TTO instrument administered in MOST) Age-specific background mortality (US life tables)
Results (including uncertainty	In-trial cost-effectiveness results: $52,814 per QALY over 4 years. Lifetime Markov model CEA result: $6,800 per QALY Sensitivity analysis, bootstrap analyses estimated that DDDR pacing would be cost-effective at a threshold of $50,000 in 91.9% of samples.

Author , year	Sutton, 1996, UK
Perspective,discounting and cost year	Not stated, but includes costs relevant to UK NHS perspective, no discounting, cost year 1991
Model type	“Computer model”, Cost-benefit, 10 year time horizon
Patient population	Patients with SSS and/or AVB:
Intervention/comparator	Dual-chamber (DDD) pacing versus single-chamber ventricular (VVI) pacing
Costs (source)	Generic units of currency (based on UK prices) are used, with the cost of a VVI device equivalent to 100 cost units Device costs, (a survey of 6 manufacturer’s active on the UK market) Implantation costs, 45 mins assumed for single-chamber, 60 mins for dual-chamber plus 2 overnight stays for both (single center costs). Follow-up costs (single center) AF (single center costs) Stroke, assumed 7 days of inpatient care (single centre costs) Disability from stroke (local area costs of long-term care). Heart failure, includes the cost of therapy with ACE inhibitor and frusemide at average doses (standard Uk prices) plus one week of inpatient care per year (single center costs). Upgrade, includes dual-chamber device costs, plus 60 mins of operating time and one night inpatient stay, plus “waste of resourcesinvolved in disposing of the redundant generator.
Outcomes (source)	Complications including: AF, stroke, disability as a result of stroke, heart failure, pacemaker syndrome and mortality. Also AVB in SSS patients paced with an AAI device Note: DDD and AAI pacing are considered equivalent (with the exception of AVB leading to upgrade. AF, SSS pts paced with VVI, 10% yr 1, 7% yr 2+ (average incidence of 24 reports, including 4111 pts);

	SSS pts paced DDD, 2% in yr 1, 1.5% in yr 2+ (average incidence of 24 reports, including 4111 pts); AVB pts paced VVI, 5% in yr 1, 3% in yr 2+ (average incidence of 4 reports comprising 675 pts); AVB pts paced DDD, 1% in yr 1, 0.5% in yr 2+ (average incidence of 4 reports comprising 675 pts). Stroke, assumed to be 30% of AF rate. Heart failure, 6.5% in VVI paced pts, 2.1% in DDD paced pts (average incidence of 4 reports, including 414 pts). Mortality, SSS pts paced VVI, 6% (source unclear); SSS pts paced DDD, 3% (source unclear); AVB pts paced VVI, 7% (source unclear); AVB pts paced DDD, 5% (source unclear).
Results (including uncertainty	Benefits, Survival, greater in patients initially implanted with a DDD, also 24/57 surviving SSS/VVI pts had upgraded to DDD. Similarly, 21/51 surviving AVB/VVI pts had upgraded to a DDD. Heart failure, incidence reduced by half with DDD pacing. Disability from stroke, 5-fold reduction in DDD pts as a result of reduction in AF. Costs (not including generator replacement costs), approximately equal 3 years after implantation. 10 year cumulative cost of VVI in SSS pts is 12 times that of DDD. The 10 year cumulative cost of VVI pacing in AVB is 8 times that of DDD. Sensitivity analysis, AF incidence, stroke incidence, disability costs and incidence of heart failure explored. Cost of DDD in SSS pts increases for all SA, but at a faster rate than VVI in SSS pts with increasing disability costs and stroke

	incidence. Conversely, DDD costs in SSS pts increases at a lower rate than VVI costs in SSS pts with increasing AF and heart failure incidence. In AVB pts, costs of DDD pacing increases faster than costs of VVI pacing with increasing AF and heart failure incidence. Conversely, costs of DDD pacing increases slower than the cost of VVI pacing with increasing disability costs and stroke incidence.

Author , year	Wiegand U, 2001, Germany
Perspective,discounting and cost year	Not stated
Model type	No model was used. Cost-benefit analysis, Mean follow-up was 42(SD 15) months, ranging from 3 to 76 months.
Patient population	Patients with atrioventricular block and normal sinus function admitted to the University Hospital of Luebeck between 1992 and 1997.
Intervention/comparator	Single –lead VDD vs DDD devices
Costs (source)	Primary costs of pacemaker implantation included: two nights of hospital stay, antibiotic prophylaxis with three doses of cefacolin (Elzogram), one routine pacemaker interrogation, one 24-h Holter-ECG and one chest X-ray. Secondary costs of pacemaker implantation included: hospital fees due to prolonged stay or re-admission of patients, cost of laboratory examinations and antibiotic therapy as well as of additional chest X-rays, Holter recordings and pacemaker interrogations. Expenses due to operative revision, device explantation and re-implantation and costs associated with treatment of atrial arrhythmias. Devices, leads, single-use operation material and sterilization (average costs incurred by single centre) Implanting physicians, nurses and medical technicians (German standard implantation charges)

Outcomes (source)	Kaplan–Meier curves for maintenance of atrioventricular synchrony and event-free survival of patients (single-centre prospective study)
Results (including uncertainty	Costs: Average costs of VDD and DDD pacemaker devices did not differ; Cost of entire pacemaker system was lower for VDD pacing – as a result of requiring one rather than two leads; Implantation costs were lower for VDD pacing – as a result of shorter implantation time and fewer demands for lead introducers for subclavian vein puncture; Cumulative costs of DDD pacing were significantly higher compared with VDD pacing during follow-up Benefits: Mean postoperative hospitalization was significantly prolonged in the DDD group No significant difference in AF, cardiac disease or pacemaker-related complications No significant difference between maintenance of atrioventricular synchroncy and event-free survival.

Health related quality of life

Author, year, country	Population and methods	Health states	Instrument (valuation)	Utility results
Fleishmann, 2009, USA	The study analysed serial data from the MOST trial which randomised 2,010 patients with sick sinus syndrome to singe chamber ventricular (VVIR) or	1. Patients without atrial fibrillation (AF) 2. Patients	Time trade-off SF-36 Special Activities Scale (measure of cardiac	Baseline utilities were not reported. Only change in utility values compared to values at baseline and 3 months were reported.

	dual chamber (DDDR) pacing. The average age of the study cohort was 73 years, 52% of patients were male. The majority of patients were white and 22% had a history of diabetes. Prior myocardial infarction was reported in 26% and prior stroke in 11%. Prior heart failure was present on 18% of VVIR patients and 22% of DDDR patients. The quality of life scores were measured at 3 months and 12 months visits then yearly afterwards. After initial unadjusted analysis, change in QoL measures was stratified by age, gender, history of AF, history of HF, treatment arm, and baseline QOL score for each measure. The last known QoL values were carried forward for patients who crossed over to dual chamber pacing as a result of severe pacemaker syndrome.	who developed paroxysmal atrial fibrillation (PAF) but not chronic atrial fibrillation. 3. Patients with chronic atrial fibrillation (CAF).	function)	Change in QoL scores at 12 months compared to baseline Change in QoL scores at 12 months compared to 3 months

Scale	No AF	PAF	CAF
SF-36			
Physical function	+0.06	-2.92	-3.29
Role physical	+22.22	+16.88	+14.32
Mental Health	+2.55	+1.57	+2.09
Role emotional	+6.85	+4.10	+12.39
Vitality	+7.68	+7.04	+4.46
Pain	+3.46	+1.46	-3.20
Health perception	-1.29	-2.96	-1.29
Social function	+6.80	+4.98	+6.61
Physical summary	+2.50	+0.90	-0.30
Mental summary	+2.50	+2.32	+2.87
Time trade-off	+0.07	+0.06	+0.11
SAS	+0.03	+0.15	+0.21

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<table>
<tr><th>Scale</th><th>No AF</th><th>PAF</th><th>CAF</th></tr>
<tr><td>SF-36</td><td></td><td></td><td></td></tr>
<tr><td>Physical function</td><td>-2.21</td><td>-4.36</td><td>-3.45</td></tr>
<tr><td>Role physical</td><td>+2.44</td><td>-1.80</td><td>+0.83</td></tr>
<tr><td>Mental Health</td><td>+0.25</td><td>+0.50</td><td>-3.31</td></tr>
<tr><td>Role emotional</td><td>+0.99</td><td>-0.34</td><td>+1.66</td></tr>
<tr><td>Vitality</td><td>-1.21</td><td>-1.43</td><td>-0.95</td></tr>
<tr><td>Pain</td><td>-0.92</td><td>-3.13</td><td>-7.09</td></tr>
<tr><td>Health perception</td><td>+3.28</td><td>+2.27</td><td>+0.79</td></tr>
<tr><td>Social function</td><td>-1.24</td><td>+0.15</td><td>-1.06</td></tr>
<tr><td>Physical summary</td><td>-0.60</td><td>-2.49</td><td>-0.50</td></tr>
<tr><td>Mental summary</td><td>0.11</td><td>+0.80</td><td>-0.74</td></tr>
<tr><td>Time trade-off</td><td>-0.00</td><td>-0.02</td><td>+0.03</td></tr>
<tr><td>SAS</td><td>+0.05</td><td>+0.12</td><td>+0.44</td></tr>
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<tr>
<td>Fleishmann, 2006, USA</td>
<td>Serial Quality of life data was collected and analysed as part of the Mode Selection Trial. The paper refers to Lamas et al, 2002 for details of enrolment and data collection.
A total of 2,010 patients with sick sinus syndrome took part in the MOST trial</td>
<td>Utility was measured at baseline and at different time points after implantation of single or dual</td>
<td>Time trade-off
SF-36
Special Activities Scale (measure of cardiac function)</td>
<td>
<table>
<tr><th colspan="3">Mean scores adjusted for age and gender</th></tr>
<tr><th></th><th>TTO</th><th>SAS</th></tr>
<tr><td>Baseline (n=1,935)</td><td></td><td></td></tr>
<tr><td>DDDR</td><td>0.72</td><td>1.97</td></tr>
<tr><td>VVIR</td><td>0.73</td><td>2.00</td></tr>
</table>
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between 1995 and1999.

Quality of life was measured at 3 months and 12 months visits then yearly afterwards.

In patients who crossed over due to severe pacemaker syndrome, a primary analysis was performed in which the last known QoL prior to cross-over was carried forward.

The baseline characteristics of the cohort are presented in the table below

	VVIR (n=996)	DDDR (n=1,014)
Age (yr)	73.1±11.0	72.9±11.1
Male	519 (52%)	536 (53%)
Nonwhite	144 (14%)	162 (16%)
Diabetes	204 (20%)	246 (24%)
Hypertensi	608	640 (63%)

chamber pacemakers.

3 months(n=1,736)		
DDDR	0.83	1.92
VVIR	0.82	1.94
12 months(n=1,639)		
DDDR	0.83	1.99
VVIR	0.82	1.97
24 months (n=1,208)		
DDDR	0.83	1.99
VVIR	0.81	2.01
36 months (n=748)		
DDDR	0.86	2.01
VVIR	0.83	1.98
48 months (n=392)		
DDDR	0.83	2.01
VVIR	0.87	2.03

on	(61%)	
Hyperchole sterolemia	340 (34%)	376 (37%)
Current smoker	85 (9%)	84 (8%)
Prior angina	280 (28%)	288 (28%)
Prior myocardial infarction	234 (24%)	279 (28%)
Prior heart failure	183 (18%)	221 (22%)
Prior stroke	108 (11%)	116 (11%)
Charlston comorbidity index	1.46 ±1.65	1.54±1.67

Mean scores adjusted for age and gender			
	Baseline	1 yr	2 yrs
Physical function	58.9	61.0	58.6
DDDR	58.9	59.0	58.3
VVIR			
Role physical	34.6	65.5	65.3
DDDR	35.7	56.2	59.9
VVIR			
Mental Health	72.1	76.7	78.7
DDDR	72.0	74.7	77.1
VVIR			
Role emotional	74.0	85.9	89.1
DDDR	74.1	81.9	80.1
VVIR			
Vitality	42.6	51.5	52.1
DDDR	41.9	49.2	49.8
VVIR			
Pain	42.6	71.1	73.0
DDDR	41.9	69.9	76.7
VVIR			
Health perception	67.0	58.4	58.6
DDDR	67.6	57.0	56.2
VVIR	60.3	71.4	73.8
Social function	60.0	70.5	71.6
DDDR			
VVIR			

<table>
<tr>
<td>Shukla,
2005,
USA</td>
<td>The study reported a post hoc analysis of elderly patients who were enrolled in the MOST trial and received pacemakers that utilised accelerometer, piezoelectric crystal or blended sensors which were the most frequently used across a broad range of manufacturers. The quality of life data of 1,245 (613 DDDR and 632 VVIR) patients was analysed .
Demographic, clinical and quality of life data were collected at baseline, at 3 months and then annually in the trial.</td>
<td>Quality of life values were compared according to type of sensor received.</td>
<td>Time trade-off
SF-36
Specific Activity scale
0-100 scale</td>
<td>
<table>
<tr><th>Instrument</th><th>Utility</th><th>P value</th></tr>
<tr><td>Time trade-off</td><td></td><td></td></tr>
<tr><td>Accelorometer</td><td>0.83 (0.015)</td><td>0.45</td></tr>
<tr><td>Blended</td><td>0.80 (0.021)</td><td></td></tr>
<tr><td>Piezoelectric crystal</td><td>0.82 (0.012)</td><td></td></tr>
<tr><td>Specific activities scale</td><td></td><td></td></tr>
<tr><td>Accelorometer</td><td>2.38 (0.043)</td><td>0.16</td></tr>
<tr><td>Blended</td><td>2.34 (0.56)</td><td></td></tr>
<tr><td>Piezoelectric crystal</td><td>2.30 (0.37)</td><td></td></tr>
<tr><td>0 – 100 scale</td><td></td><td></td></tr>
<tr><td>Accelorometer</td><td>70.9 (0.91)</td><td>0.33</td></tr>
<tr><td>Blended</td><td>69.0 (1.3)</td><td></td></tr>
<tr><td>Piezoelectric crystal</td><td>70.9 (0.75)</td><td></td></tr>
</table>
<table>
<tr><th>Instrument</th><th>Utility</th><th>P value</th></tr>
<tr><td>SF-36
Physical function</td><td></td><td></td></tr>
<tr><td>Accelorometer</td><td>59.2 (1.2)</td><td>0.009</td></tr>
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				Blended	53.7 (1.7)		
				Piezoelectric crystal	58.1 (1.0)		
				Role, physical function			
				Accelorometer	65.3 (1.9)	0.08	
				Blended	59.8 (2.8)		
				Piezoelectric crystal	61.5 (1.5)		
				Pain			
				Accelorometer	72.1 (1.2)	0.79	
				Blended	70.8 (1.7)		
				Piezoelectric crystal	71.8 (1.0)		
				Health perception			
				Accelorometer	58.9 (0.9)	0.11	
				Blended	56.0 (1.3)		
				Piezoelectric crystal	58.0 (0.8)		
				Energy			
				Accelorometer	51.9 (1.1)	0.98	
				Blended	51.9 (1.5)		
				Piezoelectric crystal	51.8 (0.9)		
				Social function			
				Accelorometer	72.2 (1.1)	0.42	
				Blended	70.1 (1.6)		

				Piezoelectric crystal	72.2 (0.9)	
				Role, mental health		
				Accelorometer	83.9 (1.4)	0.79
				Blended	84.1 (2.2)	
				Piezoelectric crystal	83.0 (1.2)	
				Mental health		
				Accelorometer	77.3 (0.8)	0.51
				Blended	76.3 (1.1)	
				Piezoelectric crystal	76.5 (0.6)	
				Physical summary		
				Accelorometer	41.0 (0.50)	0.039
				Blended	39.1 (0.70)	
				Piezoelectric crystal	40.4 (0.41)	
				Emotional summary		
				Accelorometer	52.1 (0.42)	0.77
				Blended	52.1 (0.61)	
				Piezoelectric crystal	51.8 (0.35)	
Link, 2004, USA	The paper reports on the quality of life of the subset of patients that took part in the MOST trial who developed severe pacemaker syndrome according to the study protocol. A total of 182	Utility was measured at baseline and before and after	Time trade-off SF-36 Specific Activity scale 0-100 scale Method of utility valuation			

	Mean (SD) Baseline N=153	Mean (SD) at crossover	Mean (SD) after crossover

	patients assigned to VVIR pacing developed pacemaker syndrome. Quality of life was evaluated before and after crossover.	crossover.	was not stated.			N=80	N=136
				TTO 0-1 TTO	0.75 (0.34)	0.73 (0.35)	0.82 (0.31)
				SF-36 Physical-composite	35.8 (10.7)	33.3 (10.1)	38.0 (11.6)
				Mental-composite	51.5 (9.5)	49.8 (10.9)	52.7 (11.6)
				Physical-function	56.4 (27.6)	39.8 (28.1)	55.0 (29.7)
				Role-physical	28.4 (38.7)	28.4 (39.3)	50.6 (43.0)
				Pain	66.8 (29.1)	70.9 (24.7)	69.5 (26.3)
				Health perception	57.2 (21.1)	52.4 (20.7)	56.5 (21.5)
				Energy	39.6 (23.2)	32.1 (21.4)	49.9 (24.5)
				Social-function	67.7 (24.7)	62.2 (26.5)	71.1 (24.1)
				Role-emotional	80.4 (34.7)	75.4 (39.2)	83.6 (32.9)
				Mental health	77.4 (17.2)	73.5 (19.6)	77.5 (17.8)
				SAS 1-4 SAS	2.09 (0.93)	2.50 (0.91)	2.07 (0.94)

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<table>
<tr><td>0 – 100 scale</td><td>65.8 (19.8)</td><td>60.6 (20.0)</td><td>70.8 (19.5)</td></tr>
</table>

Change in quality of life and p-values associated with the change are also reported in the paper.
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<tr>
<td>Lamas, 2002, USA</td>
<td>Quality of life data was collected by trained research co-ordinators as part of the MOST trial. A total of 2010 patients were enrolled from September 1995 to October 1999, at 91 clinical sites. Patients had to be at least 21 years old, undergoing initial implantation of a dual chamber, rate modulated pacing system for sinus-node dysfunction and were in sinus rhythm when allocated to treatment. To be eligible for Quality of life analysis patients had to score 17 or higher on the Mini-Mental State Examination before implantation. Patients with serious concurrent illness as determined by the investigator at each site were excluded.

The baseline characteristics of the</td>
<td>Utility was measured at baseline and at different time points after implantation of single or dual chamber pacemakers.</td>
<td>Time trade-off
SF-36
SAS</td>
<td>
<table>
<tr><td>Quality of life scale</td><td>Ventricular</td><td>Dual</td></tr>
<tr><td>Time trade-off</td><td></td><td></td></tr>
<tr><td>Baseline</td><td>73</td><td>72</td></tr>
<tr><td>3 months</td><td>+7</td><td>+8</td></tr>
<tr><td>12 months</td><td>+5</td><td>+8</td></tr>
<tr><td>24 months</td><td>+4</td><td>+7</td></tr>
<tr><td>36 months</td><td>+4</td><td>+8</td></tr>
<tr><td>48 months</td><td>+6</td><td>+6</td></tr>
<tr><td>Change from baseline after 48 months</td><td colspan="2">+2 , p=0.06</td></tr>
<tr><td>Specific Activities Scale</td><td></td><td></td></tr>
<tr><td>Baseline</td><td>2.01</td><td>1.97</td></tr>
<tr><td>3 months</td><td>-0.04</td><td>-0.06</td></tr>
<tr><td>12 months</td><td>0.00</td><td>+0.02</td></tr>
<tr><td>24 months</td><td>+0.03</td><td>+0.05</td></tr>
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cohort are presented in the table below

	VVIR (n=996)	DDDR (n=1,014)
Median age (yr)	74	74
Female	477 (48%)	478 (47%)
Nonwhite	144 (14%)	162 (16%)
Diabetes	204 (20%)	246 (24%)
Hypertension	608 (61%)	640 (63%)
Hypercholesterolemia	340 (34%)	376 (37%)
Current smoker	85 (9%)	84 (8%)
Prior angina	280 (28%)	288 (28%)
Prior myocardial infarction	234 (24%)	279 (28%)
Prior heart	183 (18%)	221 (22%)

36 months	+0.04	+0.11
48 months	+0.16	+0.13
Change from baseline after 48 months	+0.002 , p=0.94	

SF-36 scale	Baseline	48 months	Change from baseline at 48 months
Physical function			
Ventricular	58.8	-3.2	+1.9, p=0.04
Dual	58.9	-0.1	
Physical role			
Ventricular	34.6	+18.0	+8.6,p <0.01
Dual	35.7	+26.7	
Social function			
Ventricular	72.1	+6.4	+2.5,p<0.01
Dual	72.0	+9.8	
Energy			
DDDR	74.0	+3.6	+4.1,p<0.01
VVIR	74.1	+5.2	

	failure					Mental health			
	Prior stroke	108 (11%)	116 (11%)			DDDR	42.6	+4.7	+1.2,p=0.05
						VVIR	41.9	+4.6	
	Charlston comorbidity index	1.46 ±1.65	1.54±1.67			Emotional role			
						DDDR	42.6	+4.8	+3.6,p<0.01
						VVIR	41.9	+12.3	
						Pain			
						DDDR	67.0	+6.9	+0.5,p=0.57
						VVIR	67.6	+5.1	
						Health perception			
						DDDR	60.3	-3.5	+1.1,p=0.09
						VVIR	60.0	-2.5	
						Mental summary			
						DDDR	48.4	+2.4	+1.1,p<0.01
						VVIR	48.4	+3.5	
						Physical summary			
						DDDR	38.5	+1.0	+1.2,p<0.01
						VVIR	38.4	+2.2	

				Values of SF-36 components at 3 months, 12 months, 24 months and 36 are also reported in the paper.

Appendix 3 Quality assessment

Clinical effectiveness studies

Parallel group RCTs

Albertsen 2008[41]

Outcome	Risk of Bias	Risk assessment[a]	Comments
	Random sequence generation	?	Not described
	Allocation concealment	?	Not described
	Selective reporting	✓	Results for all pre-specified outcomes of interest were reported
Heart failure	Blinding (who [participants, personnel], and method)	?	Not described
	Blinding of outcome assessment	x	Knowledge of the pacing mode during collection of data at follow-up visits might have lead to bias regarding NYHA classification
	Incomplete outcome data	✓	Only one patient was lost to follow up in the AAIR group (4.2%) and none in the DDDR group.(Also note 2 patients in AAIR group received DDDR)
Exercise capacity	Blinding (who [participants, personnel], and method)	?	Not described
	Blinding of outcome assessment	x	Knowledge of the pacing mode during collection of data at follow-up visits might have lead to bias regarding 6-min walk test
	Incomplete outcome data	✓	Only one patient was lost to follow up in the AAIR group (4.2%) and none in the DDDR group.(Also note 2 patients in AAIR group received DDDR)
Adverse effects of pacemaker implantation	Blinding (who [participants, personnel], and method)	?	Not described
	Blinding of outcome assessment	?	Not described

	Incomplete outcome data	✓	Only one patient was lost to follow up in the AAIR group (4.2%) and none in the DDDR group.(Also note 2 patients in AAIR group received DDDR)

[a] Key for risk assessment: ✓ = low risk of bias; ? = unclear risk of bias; and x = high risk of bias.

Abbreviations used in table: NYHA New York Heart Association

DANPACE[41;42]

Outcome	Risk of Bias	Risk assessmenta	Comments
	Random sequence generation	?	Not described
	Allocation concealment	✓	"Randomization by sealed envelope was performed before pacemaker implantation."
	Selective reporting	x	A published protocol stated quality of life as one of the outcomes to be captured in the trial. However no results for this outcome were published in the primary or subsequent publications.
Mortality	Blinding (who [participants, personnel], and method)	✓	The trial was open label. However the lack of blinding was deemed to have limited effect on the incidence of mortality.
	Blinding of outcome assessment	✓	The trial was open label. However the lack of blinding was deemed to have limited effect on the incidence of mortality.
	Incomplete outcome data	?	No patients were lost to follow up. However, the number of patients who switched pacing mode during follow up was relatively uneven between the study arms (DDDR 9.7% and AAIR 17.4%)
Stroke	Blinding (who [participants, personnel], and method)	✓	The trial was open label. However the lack of blinding was deemed to have limited effect on the incidence of stroke.

	Blinding of outcome assessment	✓	A Clinical Event Committee, which was unaware of the assigned pacing mode adjudicated stroke and thrombo-embolic events.
	Incomplete outcome data	?	No patients were lost to follow up. However, the number of patients who switched pacing mode during follow up was relatively uneven between the study arms (DDDR 9.7% and AAIR 17.4%)
Atrial fibrillation	Blinding (who [participants, personnel], and method)	?	The trial was open label
	Blinding of outcome assessment	?	The trial was open label
	Incomplete outcome data	?	No patients were lost to follow up. However, the number of patients who switched pacing mode during follow up was relatively uneven between the study arms (DDDR 9.7% and AAIR 17.4%)
Heart failure	Blinding (who [participants, personnel], and method)	?	The trial was open label
	Blinding of outcome assessment	?	The trial was open label
	Incomplete outcome data	?	No patients were lost to follow up. However, the number of patients who switched pacing mode during follow up was relatively uneven between the study arms (DDDR 9.7% and AAIR 17.4%)
Requirement of further surgery	Blinding (who [participants, personnel], and method)	?	The trial was open label
	Blinding of outcome assessment	?	The trial was open label
	Incomplete outcome data	✓	No patients were lost to follow up.
[a] Key for risk assessment: ✓ = low risk of bias; ? = unclear risk of bias; and x = high risk of bias.			

Nielsen2003[46]

Outcome	Risk of Bias	Risk assessmenta	Comments
	Random sequence generation	?	Not described

	Allocation concealment	?	Not described
	Selective reporting	✓	Results for all pre-specified outcomes of interest were reported
Mortality	Blinding (who [participants, personnel], and method)	✓	Not described
	Blinding of outcome assessment	✓	Not described
	Incomplete outcome data	✓	The number of patients who switched pacing mode during follow up was relatively low in all treatment arms, but also uneven (DDD-s 3.33%, DDDR-l 4.76%, and AAIR 11.11%)
Stroke	Blinding (who [participants, personnel], and method)	✓	Not described
	Blinding of outcome assessment	✓	Not described
	Incomplete outcome data	✓	The number of patients who switched pacing mode during follow up was relatively low in all treatment arms, but also uneven (DDD-s 3.33%, DDDR-l 4.76%, and AAIR 11.11%)
Atrial fibrillation	Blinding (who [participants, personnel], and method)	?	Not described
	Blinding of outcome assessment	?	Not described
	Incomplete outcome data	✓	The number of patients who switched pacing mode during follow up was relatively low in all treatment arms, but also uneven (DDD-s 3.33%, DDDR-l 4.76%, and AAIR 11.11%)
Heart failure	Blinding (who [participants, personnel], and method)	?	Not described
	Blinding of outcome assessment	?	Not described
	Incomplete outcome data	✓	The number of patients who switched pacing mode during follow up was relatively low in all treatment arms, but also uneven (DDD-s 3.33%, DDDR-l 4.76%, and AAIR 11.11%)
[a] Key for risk assessment: ✓ = low risk of bias; ? = unclear risk of bias; and x = high risk of bias.			

Crossover RCTs

Gallick 1994[37]

Outcome	Risk of Bias	Risk assessmenta	Comments
	Random sequence generation	?	Not described
	Allocation concealment	?	Not described
	Selective reporting	✓	Individual patient data were reported for exercise duration
Exercise capacity	Blinding (who [participants, personnel], and method)	?	Not described
	Blinding of outcome assessment	?	Not described
	Incomplete outcome data	✓	Data was collected for all randomised patients
[a] Key for risk assessment: ✓ = low risk of bias; ? = unclear risk of bias; and x = high risk of bias.			

Lau 1994[38]

Outcome	Risk of Bias	Risk assessmenta	Comments
	Random sequence generation	?	Not described
	Allocation concealment	?	Not described
	Selective reporting	?	Individual patient data were reported for general wellbeing. However, for other quality of life measurements data for the individual treatment periods were reported, but results of paired t tests for each outcome were not.
Health related quality of life	Blinding (who [participants, personnel], and method)	✓	Double blind. Method of blinding not described
	Blinding of outcome assessment	✓	Assessed by research nurse and a clinical psychologist who were blind to the pacemaker mode of the patient
	Incomplete outcome data	✓	3 patients were excluded from the trial

[a] Key for risk assessment: ✓ = low risk of bias; ? = unclear risk of bias; and x = high risk of bias.

Schwaab 2001[48]

Outcome	Risk of Bias	Risk assessment[a]	Comments
	Random sequence generation	?	The randomisation sequence was generated by the principal investigator (B. Schwaab) in advance.
	Allocation concealment	✓	The randomisation sequence was hidden in envelopes that were closed. Thus it was concealed to the personnel at the time of recruitment. After written consent had been obtained by the patients, the envelope was opened and the first pacing mode was programmed.
	Selective reporting	x	Data for the individual treatment periods were reported. However, results of paired t tests for each outcome were not reported.
Exercise capacity	Blinding (who [participants, personnel], and method)	✓	Patients and all investigating physicians were blinded for the pacing mode.
	Blinding of outcome assessment	✓	Patients and all investigating physicians were blinded for the pacing mode.
	Incomplete outcome data	✓	2 patients were excluded from the trial
Cognitive function	Blinding (who [participants, personnel], and method)	✓	Patients and all investigating physicians were blinded for the pacing mode.
	Blinding of outcome assessment	✓	Patients and all investigating physicians were blinded for the pacing mode.
	Incomplete outcome data	✓	2 patients were excluded from the trial
Health related quality of life	Blinding (who [participants, personnel], and method)	✓	Patients and all investigating physicians were blinded for the pacing mode.
	Blinding of outcome assessment	✓	Patients and all investigating physicians were blinded for the pacing mode.
	Incomplete outcome data	✓	2 patients were excluded from the trial

[a] Key for risk assessment: ✓ = low risk of bias; ? = unclear risk of bias; and ✗ = high risk of bias.

Cost-effectiveness evidence

NICE reference case

Caro 2006

Element of health technology assessment	Reference case	Does the de novo economic evaluation match the reference case?
Defining the decision problem	The scope developed by NICE	No, patient population is SND or AVB, comparator is ventricular pacing, whereas NICE scope specifies atrial pacing
Comparator(s)	As listed in the scope developed by NICE	No, comparator is ventricular pacing
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	No, 5-year time horizon, devices may be expected to last beyond 5 years
Synthesis of evidence on health effects	Based on systematic review	No; utilities were obtained from head-to-head trial data (MOST)
Measuring and valuing health effects	Health effects should be expressed in QALYs.The EQ-5D is the preferred measure of health-related quality of life in adults.	Partial, quality of life weights are reported to be "based on the data collected using the time trade-off approach during MOST", however, no further details are given as to the calculation of these weights and none are reported in the cited main trial report by Lamas et al[70]

Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes, patient response data was collected in MOST
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Unclear
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Partial, 6% for costs and 1.5% for benefits is used in the base case, 3.5% for both costs and benefits is used in sensitivity analysis
NICE, National Institute for Health and Care Excellence; NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

Castelnuovo 2005

Element of health technology assessment	**Reference case**	**Does the de novo economic evaluation match the reference case?**
Defining the decision problem	The scope developed by NICE	Yes, however, the scope of this review exceeds the scope of the current review

Comparator(s)	As listed in the scope developed by NICE	Yes, plus single-chamber ventricular pacing
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	Yes
Measuring and valuing health effects	Health effects should be expressed in QALYs.The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes, TTO
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	No, patient valuation
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use	Costs should relate to NHS and PSS resources and should be	Yes

and costs	valued using the prices relevant to the NHS and PSS	
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes, but in sensitivity analysis only
NICE, National Institute for Health and Care Excellence; NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

Clarke 1998

Element of health technology assessment	Reference case	Does the de novo economic evaluation match the reference case?
Defining the decision problem	The scope developed by NICE	No, simple cost comparison
Comparator(s)	As listed in the scope developed by NICE	Yes
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	No
Perspective on costs	NHS and PSS	No, only device and implant costs accounted for
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	No, simple cost comparison
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	No, 4 years of follow-up considered
Synthesis of evidence on health effects	Based on systematic review	No; none other than development of AVB considered, within institution data used
Measuring and valuing health effects	Health effects should be expressed in QALYs.The EQ-5D is the preferred measure of health-related quality of life in adults.	No, none

Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	No, none
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	No, none
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	N/A
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Only device and implant costs considered
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	No, none
NICE, National Institute for Health and Care Excellence; NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

Deniz 2008

Element of health technology assessment	**Reference case**	**Does the de novo economic evaluation match the reference case?**
Defining the decision problem	The scope developed by NICE	No, patient population is SND or AVB, comparator is ventricular pacing, whereas NICE scope specifies atrial pacing
Comparator(s)	As listed in the scope developed by NICE	No, comparator is ventricular pacing

Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	No, Italian government perspective
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	No, 5-year time horizon, devices may be expected to last beyond 5 years
Synthesis of evidence on health effects	Based on systematic review	No; utilities were obtained from head-to-head trial data (MOST)
Measuring and valuing health effects	Health effects should be expressed in QALYs.The EQ-5D is the preferred measure of health-related quality of life in adults.	Partial, quality of life weights are reported to be “based on the data collected using the time trade-off approach during MOST”, however, no further details are given as to the calculation of these weights and none are reported in the cited main trial report by Lamas et al[70]
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes, patient response data was collected in MOST
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Unclear
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use	Costs should relate to NHS and PSS resources and should be	No

and costs	valued using the prices relevant to the NHS and PSS	
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Partial, 3% for costs and benefits is used in the base case, 3.5% for both costs and benefits is used in sensitivity analysis
NICE, National Institute for Health and Care Excellence; NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

Mahoney 1994

Element of health technology assessment	**Reference case**	**Does the de novo economic evaluation match the reference case?**
Defining the decision problem	The scope developed by NICE	Unclear, patient population is not stated
Comparator(s)	As listed in the scope developed by NICE	Indirectly, comparison is VVI versus DDD and AAI
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	No, US payer perspective
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	No, non-simple comparison of benefits and costs.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Unclear, not stated
Synthesis of evidence on health effects	Based on systematic review	No, HRQoL was not considered
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related	No, HRQoL was not considered

	quality of life in adults.	
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	No, HRQoL was not considered
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	No, HRQoL was not considered
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No, HRQoL was not considered
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	No, US payer perspective
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	No, discounting was not used
NICE, National Institute for Health and Care Excellence; NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

O'Brien 2005

Element of health technology assessment	**Reference case**	**Does the de novo economic evaluation match the reference case?**
Defining the decision problem	The scope developed by NICE	Partial, patient population (people with no AF and bradycardia) is broader than NICE scope

Comparator(s)	As listed in the scope developed by NICE	No, comparator is ventricular pacing
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	No, provincial Canadian government health care payer (mostly Ontario)
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	No, cost-effectiveness analysis
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	No, 5.2-year time horizon, devices may be expected to last beyond 5 years
Synthesis of evidence on health effects	Based on systematic review	No; HRQoL is not considered
Measuring and valuing health effects	Health effects should be expressed in QALYs.The EQ-5D is the preferred measure of health-related quality of life in adults.	No; HRQoL is not considered
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	No; HRQoL is not considered
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	No; HRQoL is not considered
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No; HRQoL is not considered
Evidence on resource use	Costs should relate to NHS and PSS resources and should be	No, provincial Canadian government health care payer (mostly Ontario)

and costs	valued using the prices relevant to the NHS and PSS	
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	No, 3% for costs and benefits.
NICE, National Institute for Health and Care Excellence; NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

Osman 2010

Element of health technology assessment	**Reference case**	**Does the de novo economic evaluation match the reference case?**
Defining the decision problem	The scope developed by NICE	No, mixed patient population, procedure rather than intervention considered
Comparator(s)	As listed in the scope developed by NICE	No comparator considered
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	No, complications only
Perspective on costs	NHS and PSS	No, single centre costs
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	No, safety and costs associated with same day procedure
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	No, 5.5-year time horizon, devices may be expected to last beyond 5 years
Synthesis of evidence on health effects	Based on systematic review	No; complications only
Measuring and valuing health effects	Health effects should be expressed in QALYs.The EQ-5D is the preferred measure of health-related quality of life in adults.	No, HRQoL not considered

Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	No, HRQoL not considered
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	No, HRQoL not considered
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No, HRQoL not considered
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	No, single centre costs
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	No discounting
NICE, National Institute for Health and Care Excellence; NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

Ray 1992

Element of health technology assessment	**Reference case**	**Does the de novo economic evaluation match the reference case?**
Defining the decision problem	The scope developed by NICE	No, audit study with a mixed patient population
Comparator(s)	As listed in the scope developed by NICE	No, audit study

Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	No
Perspective on costs	NHS and PSS	No, single centre costs
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	No, audit study
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	No, HRQoL not considered
Synthesis of evidence on health effects	Based on systematic review	No, HRQoL not considered
Measuring and valuing health effects	Health effects should be expressed in QALYs.The EQ-5D is the preferred measure of health-related quality of life in adults.	No, HRQoL not considered
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	No, HRQoL not considered
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	No, HRQoL not considered
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No, HRQoL not considered
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	No, single centre costs

Discounting	The same annual rate for both costs and health effects (currently 3.5%)	No discounting
NICE, National Institute for Health and Care Excellence; NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

Rinfret 2005

Element of health technology assessment	Reference case	Does the de novo economic evaluation match the reference case?
Defining the decision problem	The scope developed by NICE	No, patient population is patients paced for SSS; however, comparator is ventricular pacing
Comparator(s)	As listed in the scope developed by NICE	No, comparator is ventricular pacing
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	No, US societal perspective
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes, 4-year in-trial CEA plus lifetime Markov model extrapolation.
Synthesis of evidence on health effects	Based on systematic review	No; utilities were obtained from head-to-head trial data (MOST)
Measuring and valuing health effects	Health effects should be expressed in QALYs.The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes, TTO instrument used
Source of data	Reported directly by patients and/or	Yes, patient response data was collected in MOST

for measurement of health-related quality of life	carers	
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	No, valuation carried out by patients
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	No, US societal perspective
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	No, 3% for costs and benefits
NICE, National Institute for Health and Care Excellence; NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

Sutton 1996

Element of health technology assessment	**Reference case**	**Does the de novo economic evaluation match the reference case?**
Defining the decision problem	The scope developed by NICE	No, mixed patient population and, with the exception of developing AVB, AAI pacing is assumed equivalent to DDD.
Comparator(s)	As listed in the scope developed by NICE	No, comparator is VVI
Perspective on	All direct health effects, whether for	Yes

outcomes	patients or, when relevant, carers	
Perspective on costs	NHS and PSS	Unclear, perspective not stated, but appears to include all relevant NHS&PSS costs
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	No, cost-benefit
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes, 10-year time horizon
Synthesis of evidence on health effects	Based on systematic review	No; HRQoL not considered
Measuring and valuing health effects	Health effects should be expressed in QALYs.The EQ-5D is the preferred measure of health-related quality of life in adults.	No; HRQoL not considered
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	No; HRQoL not considered
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	No; HRQoL not considered
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No; HRQoL not considered
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Partial, prices relevant to NHS used to inform cost estimates
Discounting	The same annual rate for both costs	No discounting

	and health effects (currently 3.5%)	
NICE, National Institute for Health and Care Excellence; NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

Wiegand 2001

Element of health technology assessment	Reference case	Does the de novo economic evaluation match the reference case?
Defining the decision problem	The scope developed by NICE	No, patient population is AVB, comparator is single-lead VDD pacing
Comparator(s)	As listed in the scope developed by NICE	No, comparator is single-lead VDD pacing
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	No
Perspective on costs	NHS and PSS	No, costs from a single centre
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	No
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	No, follow-up was an average of 42 months
Synthesis of evidence on health effects	Based on systematic review	No; HRQoL not included
Measuring and valuing health effects	Health effects should be expressed in QALYs.The EQ-5D is the preferred measure of health-related quality of life in adults.	No; HRQoL not included
Source of data for	Reported directly by patients and/or carers	No; HRQoL not included

measurement of health-related quality of life		
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	No; HRQoL not included
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No; HRQoL not included
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	No, costs were from a single-centre
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	No discounting reported
NICE, National Institute for Health and Care Excellence; NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

Philips checklist

Caro 2006

Attribute	Assessment	Comment
Structure		
S1: Statement of decision problem/objective	Yes	Stated
S2: Statement of scope/perspective	Yes	Stated
S3: Rationale for structure	Partial	Stated; however, the exclusion of heart failure compromises consistency with the disease area considered
S4: Structural	Yes	Stated

assumptions		
S5: Strategies/comparators	Yes	Stated
S6: Model type	Yes	Stated, discreet event simulation
S7: Time horizon	No	The 5 year time horizon may be insufficient to reflect all important differences between options, such as generator lifespan
S8: Disease states/pathways	Partial	Heart failure is excluded
S9: Cycle length	–	N/A
Data		
D1: Data identification	Yes	Clearly stated and appropriate
D2: Pre-model data analysis	Yes	Stated
D2a: Baseline data	Yes	Stated
D2b: Treatment effects	Yes	Stated
D2c: Costs	Yes	Stated
D2d: Quality of life weights (utilities)	Yes	Stated
D3: Data incorporation	Partial	Derivation of utility weights is not clearly reported
D4: Assessment of uncertainty	Partial	Univariate and multivariate
D4a: Methodological	No	Not reported
D4b: Structural	No	Not reported
D4c: Heterogeneity	No	Not reported
D4d: Parameter	Yes	Assessed through deterministic and probabilistic analysis
Consistency		
C1: Internal consistency	No	Not reported
C2: External consistency	Yes	Stated
Abbreviations used in table: OS, overall survival; PFS, progression free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; TAG, Technology Assessment Group.		

Castelnuovo 2005

Attribute	Assessment	Comment
Structure		
S1: Statement of decision problem/objective	Yes	The objective of the model is specified and consistent with the stated decision problem
S2: Statement of scope/perspective	Yes	The perspective of the model has been stated and the inputs used and outcomes considered are consistent with this perspective
S3: Rationale for structure	Yes	The model structure represents a coherent theory of the health condition under consideration.
S4: Structural assumptions	Yes	Model assumptions have been clearly stated and justified
S5: Strategies/comparators	Yes	All feasible and practical options have been evaluated
S6: Model type	Yes	Markov model, appropriate for the decision problem
S7: Time horizon	Yes	Both 5 and 10 year time horizons have been considered to facilitate understanding of the shorter term cost-effectiveness of the interventions and cost-effectiveness over the "clinically realistic lifetime of the technologies".
S8: Disease states/pathways	Partial	The health states considered are generally appropriate, however no rationale is provided for the exclusion of subsequent complications following upgrade to a dual-chamber pacemaker
S9: Cycle length	Partial	Cycle length is stated but not justified
Data		
D1: Data identification	Partial	Generally the data sources used were systematically identified, quality assessment and choices between sources justified. However, the identification of some data sources, for example Chugh et al for the progression to stroke after AF, have not been explained
D2: Pre-model data analysis	Yes	Pre-model data analysis has been clearly stated
D2a: Baseline data	Partial	Baseline data has been stated and justified. Half cycle correction is not used and no explanation provided.
D2b: Treatment effects	Yes	Treatment effects have been appropriately synthesised. Extrapolation has been described and justified and the potential impact explored in sensitivity analysis.

D2c: Costs	Yes	Cost sources have been clearly described and included costs justified
D2d: Quality of life weights (utilities)	Yes	Quality of life weights have been clearly described. Patient valuation utilities have been used in the absence of valuations from the general population
D3: Data incorporation	Yes	All data incorporated into the model have been described and referenced in sufficient detail
D4: Assessment of uncertainty	Partial	Structural, heterogeneity and parameter uncertainty have been assessed
D4a: Methodological	No	Not stated
D4b: Structural	Yes	Structural uncertainty has been assessed through the use of different time horizons and assumption, for example pertaining to the time dependency of AF risk
D4c: Heterogeneity	Yes	The patient population that is the scope of this review have been assessed as homogeneous subgroups
D4d: Parameter	Yes	Univariate and multivariate sensitivity analysis has been carried out
Consistency		
C1: Internal consistency	No	Not stated
C2: External consistency	Yes	Results have been sufficiently explained and contextualised by the existing literature, areas of remaining uncertainty, for example conflicting trial results, have been highlighted.
Abbreviations used in table: OS, overall survival; PFS, progression free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; TAG, Technology Assessment Group.		

Deniz 2008

Attribute	Assessment	Comment
Structure		
S1: Statement of decision problem/objective	Yes	Stated
S2: Statement of scope/perspective	Yes	Stated
S3: Rationale for structure	Partial	Stated; however, the exclusion of heart failure compromises consistency with the disease area considered

S4: Structural assumptions	Yes	Stated
S5: Strategies/comparators	Yes	Stated
S6: Model type	Yes	Stated, discreet event simulation
S7: Time horizon	No	The 5 year time horizon may be insufficient to reflect all important differences between options, such as generator lifespan
S8: Disease states/pathways	Partial	Heart failure is excluded
S9: Cycle length	–	N/A
Data		
D1: Data identification	Yes	Clearly stated and appropriate
D2: Pre-model data analysis	Yes	Stated
D2a: Baseline data	Yes	Stated
D2b: Treatment effects	Yes	Stated
D2c: Costs	Yes	Stated
D2d: Quality of life weights (utilities)	Yes	Stated
D3: Data incorporation	Partial	Derivation of utility weights is not clearly reported
D4: Assessment of uncertainty	Partial	Univariate and multivariate
D4a: Methodological	No	Not reported
D4b: Structural	No	Not reported
D4c: Heterogeneity	No	Not reported
D4d: Parameter	Yes	Assessed through Univariate and multivariate sensitivity analysis
Consistency		
C1: Internal consistency	No	Not reported
C2: External consistency	Yes	Stated
Abbreviations used in table: OS, overall survival; PFS, progression free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; TAG, Technology Assessment Group.		

Rinfret 2005

Attribute	Assessment	Comment
Structure		
S1: Statement of decision problem/objective	Yes	Stated
S2: Statement of scope/perspective	Yes	Stated
S3: Rationale for structure	Yes	Stated
S4: Structural assumptions	Yes	Stated
S5: Strategies/comparators	Yes	Stated
S6: Model type	Yes	Stated, calibrated Markov model used to extrapolate in-trial CEA
S7: Time horizon	Yes	Lifetime
S8: Disease states/pathways	Yes	Stated
S9: Cycle length	Yes	Annual
Data		
D1: Data identification	Yes	Clearly stated and appropriate
D2: Pre-model data analysis	Yes	Stated
D2a: Baseline data	Yes	Stated
D2b: Treatment effects	Yes	Stated
D2c: Costs	Yes	Stated
D2d: Quality of life weights (utilities)	Yes	Stated
D3: Data incorporation	Yes	Clearly stated and appropriate
D4: Assessment of uncertainty	Partial	Univariate, multivariate and structural
D4a: Methodological	No	Not reported
D4b: Structural	Yes	Modelled rather than actual data used to inform first 4 years of analysis
D4c: Heterogeneity	No	Not reported

D4d: Parameter	Yes	Assessed through univariate and bootstrap analysis
Consistency		
C1: Internal consistency	Yes	Stated
C2: External consistency	Yes	Stated
Abbreviations used in table: OS, overall survival; PFS, progression free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; TAG, Technology Assessment Group.		

Sutton 1996

Attribute	Assessment	Comment
Structure		
S1: Statement of decision problem/objective	Yes	Stated
S2: Statement of scope/perspective	Partial	Perspective is unclear
S3: Rationale for structure	Partial	Limited information is provided on the model structure
S4: Structural assumptions	Partial	Unclear whether all assumptions have been stated
S5: Strategies/comparators	Yes	Stated
S6: Model type	Yes	Stated
S7: Time horizon	Yes	10-year time horizon, long enough to capture device lifetime
S8: Disease states/pathways	Partial	All relevant sequelae seem to have been incorporated, but unclear which pathways are used
S9: Cycle length	No	Not stated
Data		
D1: Data identification	Partial	Identification of cost sources is clearly stated, however, there is a lack of clarity regarding the source of estimates for the incidence of all considered complications
D2: Pre-model data analysis	Partial	That average incidence is frequently used is stated, however, not all estimates are clearly explained
D2a: Baseline data	No	Not stated

D2b: Treatment effects	Partial	The derivation of incidence data is not clearly described for all outcomes
D2c: Costs	Yes	Stated
D2d: Quality of life weights (utilities)	No	Not used
D3: Data incorporation	Partial	Incorporation of data not consistently described
D4: Assessment of uncertainty	Partial	Univariate analysis
D4a: Methodological	No	Not reported
D4b: Structural	No	Not reported
D4c: Heterogeneity	No	Not assessed
D4d: Parameter	Yes	Assessed through selected univariate sensitivity analysis
Consistency		
C1: Internal consistency	No	Not reported
C2: External consistency	Yes	Stated
Abbreviations used in table: OS, overall survival; PFS, progression free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; TAG, Technology Assessment Group		

Appendix 4 Table of excluded studies

Clinical effectiveness review

Full reference details	**Reason for exclusion**
Castelnuovo L, Stein K, Pitt M, Garside R, Payne E. The effectiveness and cost effectiveness of dual chamber pacing compared to single pacing for bradycardia - NICE Technology Assessment Report (Structured abstract). Health Technology Assessment Database 2005;(4):1.	Systematic review
Charalampopoulos AP. The effect of AAIR versus DDDR pacing mode in left ventricular ejection fraction, synchronization and NT-proBNP levels- A prospective study in sick sinus syndrome and normal ventricular function. *European Heart Journal* 2010 Sep;Conference:September.	Pre-clinical study (left ventricular function, left atrial size, NT-proBNP levels), no outcomes of interest
Clarke KW, Connelly DT, Charles RG. Single chamber atrial pacing: an underused and cost-effective pacing modality in sinus node disease. *Heart* 1998;80(4):387-9.	Non randomised study
Davy JM, Hoffmann E, Frey A, Jocham K, Rossi S, Dupuis JM, et al. Near	DDD(R) vs dual-chamber pacing

elimination of ventricular pacing in SafeR mode compared to DDD modes: a randomized study of 422 patients 1. *Pacing Clin Electrophysiol* 2012 Apr;35(4):392-402.	with VP minimising features
Delfaut P, Saksena S, Prakash A, Krol RB, Delfaut P, Saksena S, et al. Long-term outcome of patients with drug-refractory atrial flutter and fibrillation after single- and dual-site right atrial pacing for arrhythmia prevention. *Journal of the American College of Cardiology* 1998 Dec;32(7):1900-8.	Patients with drug-refractory symptomatic AF or flutter
Dretzke J, Lip G, Raftery J, Toff W, Fry-Smith A, Taylor R. Dual versus single chamber pacemaker therapy for atrioventricular block and sick sinus syndrome. Health Technology Assessment Database 2002;(4):110.	Systematic review
Fitts SM, Hill MR, Mehra R, Friedman P, Hammill S, Kay GN, et al. Design and implementation of the Dual Site Atrial Pacing to Prevent Atrial Fibrillation (DAPPAF) clinical trial. DAPPAF Phase 1 Investigators. *Journal of Interventional Cardiac Electrophysiology* 1998 Jun;2(2):139-44.	Dual-chamber atrial pacing vs single-chamber atrial pacing
French WJ, Haskell RJ, Wesley GW, Florio J. Physiological benefits of a pacemaker with dual chamber pacing at low heart rates and single chamber rate responsive pacing during exercise. *Pacing and clinical electrophysiology* : PACE 1988;11(11 Pt 2):1840-5.	Patients with complete heart block
Fukuoka S, Nakagawa S, Fukunaga T, Yamada H, Fukuoka S, Nakagawa S, et al. Effect of long-term atrial-demand ventricular pacing on cardiac sympathetic activity. *Nuclear Medicine Communications* 2000 Mar;21(3):291-7.	Non randomised study
Hildick-Smith DJW. Single-chamber versus dual-chamber pacemakers. *The New England journal of medicine* 1998;339(9):630-2.	Editorial correspondence
Jutzy RV, Florio J, Isaeff DM, Feenstra L, Briggs B, Levine PA. Limitations of testing methods for evaluation of dual chamber versus single chamber adaptive rate pacing. *American Journal of Cardiology* 1991;68(17):1715-7.	Dual vs ventricular pacing
Kuhne M, Schaer B, Kaufmann C, Moulay N, Cron T, Cueni T, et al. A randomized trial comparing two different approaches of pacemaker selection. *Europace* 2007 Dec;9(12):1185-90.	Standard (DDD for sinus rhythm) or tailored approach (AAI, VDD, or DDD depending on AV conduction and cronotrophic incompetence)
Maity AK, Ghosh SP, Dasbiswas A, Chatterjee SS, Chaudhury D, Das MK. Haemodynamic advantage with single chamber rate responsive pacemakers over dual chamber pacemakers during exercise in chronotropic incompetence. *Indian Heart Journal* 1992;44(4):231-4.	Patients with complete heart block
Miki Y, Ishikawa T, Inoue N, Yamakawa Y, Kobayashi T, Matsushita K, et al. Efficacy of consistent atrial pacing algorithm for suppression of atrial	DDDR versus atrial preference pacing (APP) algorithm

arrhythmias in patients with sick sinus syndrome and atrial fibrillation. *International Heart Journal* 2008 May;49(3):273-80.	
Mizutani N, Kobayashi T, Kato I. Optimal pacing mode for sick sinus syndrome. *Japanese Journal of Artificial Organs* 1997;26(2):369-74.	Non randomised study
Nielsen JC, Bottcher M, Nielsen TT, Pedersen AK, Andersen HR, Nielsen JC, et al. Regional myocardial blood flow in patients with sick sinus syndrome randomized to long-term single chamber atrial or dual chamber pacing--effect of pacing mode and rate. *Journal of the American College of Cardiology* 2000 May;35(6):1453-61.	Pre-clinical study (myocardial blood flow), no outcomes of interest
Nielsen JC, Thomsen PE, Hojberg S, Moller M, Riahi S, Dalsgaard D, et al. Atrial fibrillation in patients with sick sinus syndrome: the association with PQ-interval and percentage of ventricular pacing 195. *Europace* 2012 May;14(5):682-9	Subgroup cohort
O'Brien BJ, Blackhouse G, Goeree R, Healey JS, Roberts RS, Gent M, et al. Cost-effectiveness of physiologic pacing: results of the Canadian Health Economic Assessment of Physiologic Pacing. *Heart Rhythm* 2005;2(3):270-5.	Dual vs ventricular pacing
Prakash AG. Impact of atrial and ventricular pacing on prevention of atrial fibrillation: Insights from the preface study. *Heart Rhythm* 2009;Conference:S310.	DDD vs dual-chamber pacing with VP minimising features (anti-AA algorithms + SafeR, SafeR)
Psychari SN, Apostolou TS, Iliodromitis EK, Charalampopoulos A, Kremastinos DT. DDDR pacing results in left ventricular asynchrony with preservation of ejection fraction and NT-proBNP: a prospective study in sick sinus syndrome and normal ventricular function. *International Journal of Cardiology* 2010;144(2):310-2.	Pre-clinical study (left ventricular function, left atrial size, NT-proBNP levels), no outcomes of interest
Sami M. Are we ready for dual-site right atrial pacing? *Journal of the American College of Cardiology* 2002;40(6):1151-2.	Editorial correspondence
Theodorakis G, Fitzpatrick A, Vardas P, Sutton R. Resting echo-Doppler estimation of cardiac output during AAI and DDD pacing, with varying AV delay, at different pacing rates. *European journal of cardiac pacing & electrophysiology* 1992;2(1):22-5.	Unable to obtain
Vardas PE, Simantirakis EN, Parthenakis FI, Chrysostomakis SI, Skalidis, EI. AAIR versus DDDR pacing in patients with impaired sinus node chronotropy: an echocardiographic and cardiopulmonary study*. Pacing and clinical electrophysiology* : PACE 1997;20(7):1762-8.	Non randomised study
Xue-Jun R, Zhihong H, Ye W, Huifeng D, Jinrong Z, Fang C, et al. A clinical comparison between a new dual-chamber pacing mode-AAIsafeR and DDD mode. *American Journal of the Medical Sciences*	DDDR vs dual-chamber pacing with VP minimising features (AAISafeR)

2010;339(2):145-7.	
Zhang YY, Wu DY, Fu NK, Lu FM, Xu J, Zhang Yy, et al. Neuroendocrine and haemodynamic changes in single-lead atrial pacing and dual-chamber pacing modes. *Journal of International Medical Research* 2013 Aug;41(4):1057-66.	Pre-clinical study (neuroendocrine and haemodynamic changes), no outcomes of interest

Economic evaluations

Bibliographic reference	Reasons for exclusion
Bauer A, Bauer J, Bauer M, et al. [Efficiency potential in the pacemaker/implantable cardioverter defibrillator outpatient clinic]. [German]. Herzschrittmachertherapie und Elektrophysiologie. 2006;17:26-34.	Non-UK costing study
Biffi M, Ziacchi M, Bertini M, et al. Longevity of implantable cardioverter-defibrillators: implications for clinical practice and health care systems. Europace. 2008;10:1288-1295.	Not pacing
Goldberger Z, Elbel B, McPherson CA, et al. Cost advantage of dual-chamber versus single-chamber cardioverter-defibrillator implantation. Journal of the American College of Cardiology. 2005;46:850-857.	Not pacing
Roda JRB. Modeling of the clinical benefit and economic impact of pacemakers implantation with managed ventricular pacing. Pharmacoeconomics – Spanish Research Articles. 2009;6:115-125	Irretrievable
Dretzke J, Lip G, Raftery J, et al. Dual versus single chamber pacemaker therapy for atrioventricular block and sick sinus syndrome. Report. 2002. URL: http://www.rep.bham.ac.uk/2002/pacemaker.pdf	Review
L'Agence Nationale d'Accreditation d'Evaluation en Sante (ANAES). Clinical and economic evaluation of cardiac pacemakers. Report. 1999. URL: http://www.has-sante.fr/	Irretrievable
National Institute for Clinical Excellence. Dual-chamber pacemakers for symptomatic bradycardia due to sick sinus syndrome and/or atrioventricular block. Report. 2005. URL: http://www.nice.org.uk/page.aspx?o=243281	Duplicate of Castlenuovo
ECRI. Dual-chamber versus single-chamber pacemakers for sinus node dysfunction and atrioventricular block. Plymouth Meeting, PA: ECRI. 2005;116 URL: http://www.ecri.org.uk/	Irretrievable
Mundy L, Hiller JE. MRI compatible dual chamber pacemaker. Report. 2010.	Not EE/Cost
Marshall DA, Levy AR, Vidaillet H, et al. Cost-effectiveness of rhythm versus rate control in atrial fibrillation. Annals of Internal Medicine. 2004;141(9):653-661.	Not pacing
Mitton CR, Rose S, Sheldon RS. A cost-utility analysis of pacemakers for the	Not AVB or SSS

treatment of neurally mediated syncope. Title to be Checked. 1998;1-24. URL: http://www.ipe.ab.ca/	
Namboodiri KK, Sharma YP, Bali HK, et al. Re-use of explanted DDD pacemakers as VDD-clinical utility and cost effectiveness. Indian Pacing and Electrophysiology Journal. 2004;4(1):3-9.	Re-use of explanted pacemakers
Holt ND, Parry G, Tynan MM, et al. Permanent pacemaker implantation after cardiac transplantation: extra cost of a conservative policy. Heart. 1996;76(5):439-441.	Not SSS or AVB
Kuhne M, Schaer B, Kaufmann C, et al. A randomized trial comparing two different approaches of pacemaker selection. Europace. 2007;9:1185-1190.	Non-UK costing study
Yamamura KH, Kloosterman EM, Alba J, et al. Analysis of charges and complications of permanent pacemaker implantation in the cardiac catheterization laboratory versus the operating room. Pacing and Clinical Electrophysiology. 1999;22(12):1820-1824.	Non-UK costing study
Abbreviations used in table: AVB, atrioventricular block; EE, economic evaluation; SSS, sick sinus syndrome.	

Health related quality of life

Bibliographic reference	Reasons for exclusion
Alt E, Alt E. Quality of life and clinical outcomes in elderly patients treated with ventricular pacing as compared with dual-chamber pacing. Pacing & Clinical Electrophysiology. 1999;22:141-142.	Not QoL
Fitts SM, Hill MR, Mehra R, et al. Design and implementation of the Dual Site Atrial Pacing to Prevent Atrial Fibrillation (DAPPAF) clinical trial. DAPPAF Phase 1 Investigators. Journal of Interventional Cardiac Electrophysiology. 1998;2:139-144.	Not QoL
Funck RC, Adamec R, Lurje L, et al. Atrial overdriving is beneficial in patients with atrial arrhythmias: first results of the PROVE Study.[Erratum appears in Pacing Clin Electrophysiol 2001 Feb;24(2):viii]. Pacing & Clinical Electrophysiology. 2000;23:1891-1893.	Not QoL
Funck RC, Blanc JJ, Mueller HH, et al. Biventricular stimulation to prevent cardiac desynchronization: rationale, design, and endpoints of the 'Biventricular Pacing for Atrioventricular Block to Prevent Cardiac Desynchronization (BioPace)' study. Europace. 2006;8:629-635.	Not QoL
Magovern GJ, Sr., Simpson KA, Magovern GJS, et al. Clinical cardiomyoplasty: review of the ten-year United States experience. Annals of Thoracic Surgery. 1996;61:413-419.	Not QoL
Mitsuoka T, Kenny RA, Yeung TA, et al. Benefits of dual chamber pacing in sick	Not QoL

sinus syndrome. British Heart Journal. 1988;60:338-347.	
Occhetta E.Bortnik. Permanent parahisian pacing. Indian Pacing and Electrophysiology Journal. 2007;7:110-125.	Review paper
Pachon EIA. Ventricular endocardial right bifocal stimulation in the treatment of severe dilated cardiomyopathy heart failure with wide QRS. PACE - Pacing and Clinical Electrophysiology. 2001;24:1369-1376.	Heart failure
Parsonnet V, Roelke M, Parsonnet V, et al. Single-chamber versus dual-chamber pacemakers. New England Journal of Medicine. 1998;339:630-631.	Not QoL
Prech M, Grygier M, Mitkowski P, et al. Effect of restoration of AV synchrony on stroke volume, exercise capacity, and quality-of-life: can we predict the beneficial effect of a pacemaker upgrade? Pacing & Clinical Electrophysiology. 2001;24:302-307.	Not QoL
Vassolo ML. Dual-chamber vs ventricular pacing in the elderly: Quality of life and clinical outcomes. European Heart Journal. 1999;20:1607-1608.	Review
Wilkoff BL, Dual Chamber and VVI Implantable Defibrillator trial investigators., Wilkoff BL, et al. The Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial: rationale, design, results, clinical implications and lessons for future trials. Cardiac Electrophysiology Review. 2003;7:468-472.	Not QoL
Wilkoff BL, Kudenchuk PJ, Buxton AE, et al. The DAVID (Dual Chamber and VVI Implantable Defibrillator) II trial. Journal of the American College of Cardiology. 2009;53:872-880.	Not pacing
Abbreviations used in table: QoL, quality of life	

Appendix 5 One way sensitivity analysis

Parameter	**Difference from ICER when using lower 95% CI**	**Difference from ICER when using upper 95% CI**
Baseline age	£1,316.51	-£879.03
Prob of paroxysmal AF - DC	£3,217.40	-£4,306.96
Prob of chronic AF - DC	£118.11	-£226.83
Prob of heart failure - DC	-£1,120.31	£1,924.35
Prob of stroke - DC	£729.48	-£1,314.53
Prob of paroxysmal AF - SC	£14,889.37	-£6,020.61
Prob of chronic AF - SC	£5,251.39	-£4,175.77
Prob of heart failure - SC	Dominated	-£5,453.46
Prob of stroke - SC	£10,355.33	-£5,979.09

Proportion of new heart failure events leading to hospitalisation - DC	-£79.77	£151.52
Proportion of new heart failure events leading to hospitalisation - SC	£313.79	-£597.08
Prob of AV block	£572.27	-£1,104.21
HR death AF (versus general population)	£155.84	-£169.64
HR death Stroke - males (versus general population)	£94.13	-£124.56
HR death Stroke - females (versus general population)	£86.60	-£108.29
HR death Heart failure (versus general population)	£161.73	-£167.05
HR death AF & stroke (versus stroke population)	£11.69	-£13.19
HR death AF & HF (versus HF population)	£29.08	-£30.81
Implant SC Cost	£21,352.97	Dominant
Implant DC Cost	Dominant	£16,954.46
HF hospitalisation cost	-£1,042.55	£1,136.94
Stroke episode costs	£355.89	-£153.07
Monitoring cost	-£332.83	£154.17
Total UK direct health care cost of CVD	£0.00	£0.00
Average annual post-stroke hospitalisation cost	£96.99	-£190.57
Total annual UK Stroke medication costs	£6.66	-£13.08
Total UK Stroke primary care costs	£3.09	-£6.08
Episode cost of stroke in people with AF	£308.52	-£1,304.69
Average annual post-stroke hospitalisation cost in people with AF	£0.00	£0.00
Cost of GP referrals for AF	£120.31	-£236.40

Cost of hospital outpatient referrals for AF	£87.94	-£172.79
Cost of hospital admissions with principal diagnosis of AF	£656.14	-£1,289.26
Cost of post-discharge outpatient visits	£76.58	-£150.48
Utility Change from implant to heart failure	£519.79	-£902.75
Utility Heart failure	-£1,532.03	£3,254.86
Utility Stroke (month 1)	-£0.76	£0.56
Utilitiy Stroke (> month 1)	-£886.91	£736.55
Utility Change from with pacemaker to AF	£180.17	-£335.43
Utility AF & stroke (month 1)	-£354.98	£276.31
Utility AF & stroke (> month 1)	£0.00	£0.00
Utility AF & HF	-£725.92	£1,197.70

Appendix 6 Calculation of long-term care costs associated with heart failure

In 2011, the UK prevalence of heart failure was 0.90% in men and 0.70% in women.[94] No UK CVD prevalence data were identified for 2011; however data are reported for 1988-2010 (Figure 17). By extrapolation of the 4 most recent data points, it is possible to estimate the UK CVD prevalence for 2011 (Figure 18). These extrapolations provide UK CVD prevalence estimates for 2011 of 11.95% for men and 10.95% for women, which give a relative prevalence of HF as a percentage of CVD of 7.53% for men and 6.39% for women; average 6.96%.

Figure 17. Time trends in UK prevalence data, Townsend et al[94]

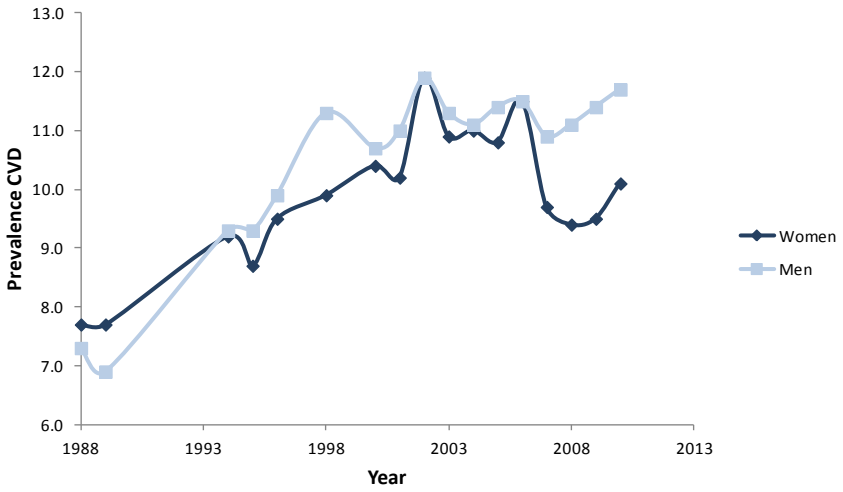
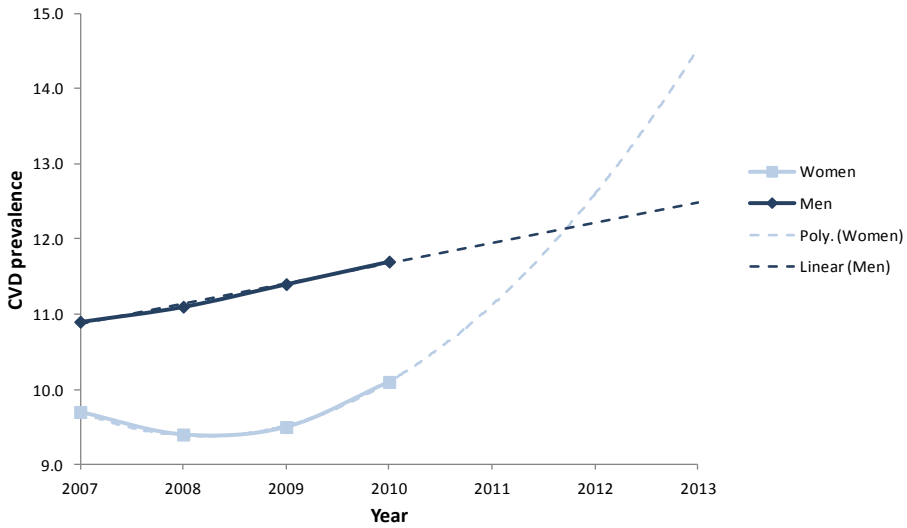


Figure 18. Extrapolation of previous 4 years of CVD prevalence data.



The total UK direct health care cost of CVD was £8,680,892,000 in 2009 and UK CVD prevalence increased by 1% between 2009 and 2011. Assuming that costs are directly proportional to prevalence, in 2009 prices, the 2011 total UK direct health care cost of CVD can be estimated as £8,767,700,920 (£8,680,892,000*1.01), which uplifted to 2011 prices is £9,086,227,882 (Table 2).

Table 2. Hospital and community health services (HCHS) inflation indices[109]

Year	Pay & prices index (1987/8=100)	% increase
2008/09	267	-
2009/10	268.6	0.60%
2010/11	276.7	3.02%
2011/12	282.5	2.10%
2012/13	289.1	2.34%

Based on the 2011 total direct health care cost of CVD and the relative prevalence of heart failure as a percentage of CVD, the 2011 total direct health care cost of heart failure can be estimated as £632,586,584 (£9,086,227,882*0.0696). There were 160,719 prevalent heart failure cases in the UK in 2011, which combined with the estimated total direct health care cost of heart failure results in an estimated per person cost of heart failure of £3,936 per annum; £4,112 per annum at 2013 prices.

Monthly probability of re-operation by treatment arm

Appendix 7 Monthly probability of re-operation by treatment arm

Time (months)	Single-chamber atrial pacemaker	Dual-chamber pacemaker
0.00	0.00%	0.00%
1.00	2.82%	2.51%
2.00	1.29%	0.32%
3.00	0.98%	0.32%
4.00	0.00%	0.65%
5.00	0.66%	0.00%
6.00	0.66%	0.00%
7.00	0.33%	0.00%
8.00	0.34%	0.33%
9.00	0.67%	0.00%
10.00	0.00%	0.33%
11.00	0.00%	0.00%
12.00	0.68%	0.00%
13.00	0.34%	0.33%
14.00	0.00%	0.00%

15.00	0.00%	0.00%
16.00	0.34%	0.00%
17.00	0.34%	0.00%
18.00	0.00%	0.00%
19.00	0.00%	0.00%
20.00	0.00%	0.00%
21.00	0.34%	0.33%
22.00	0.69%	0.00%
23.00	0.00%	0.33%
24.00	0.70%	0.00%
25.00	0.35%	0.00%
26.00	0.00%	0.00%
27.00	0.35%	0.00%
28.00	0.71%	0.00%
29.00	0.00%	0.00%
30.00	0.36%	0.33%
31.00	0.00%	0.00%
32.00	0.00%	0.33%
33.00	0.36%	0.33%
34.00	0.00%	0.00%
35.00	0.00%	0.00%
36.00	0.36%	0.33%
37.00	0.00%	0.00%
38.00	0.72%	0.00%
39.00	0.36%	0.00%
40.00	0.36%	0.00%
41.00	0.00%	0.34%
42.00	0.00%	0.00%
43.00	0.00%	0.00%
44.00	0.73%	0.00%
45.00	0.00%	0.00%
46.00	0.00%	0.00%
47.00	0.37%	0.00%
48.00	0.00%	0.00%

49.00	0.00%	0.34%
50.00	0.00%	0.00%
51.00	0.00%	0.00%
52.00	0.37%	0.00%
53.00	0.00%	0.00%
54.00	0.00%	0.00%
55.00	0.00%	0.00%
56.00	1.11%	0.34%
57.00	0.00%	0.00%
58.00	0.00%	0.00%
59.00	1.12%	0.00%
60.00	0.00%	0.00%
61.00	0.38%	0.00%
62.00	0.00%	0.00%
63.00	0.00%	1.02%
64.00	0.00%	0.00%
65.00	0.00%	0.00%
66.00	0.00%	0.00%
67.00	0.76%	0.34%
68.00	0.38%	0.34%
69.00	0.00%	0.34%
70.00	0.00%	0.00%
71.00	0.00%	0.00%
72.00	0.77%	1.38%
73.00	0.78%	0.70%
74.00	2.34%	0.35%
75.00	2.00%	1.06%
76.00	2.86%	1.43%
77.00	1.68%	1.09%
78.00	1.71%	0.37%
79.00	1.30%	0.37%
80.00	1.32%	0.74%
81.00	1.79%	1.12%
82.00	0.91%	0.38%

83.00	1.83%	2.27%
84.00	1.87%	0.78%
85.00	1.90%	0.00%
86.00	1.94%	1.56%
87.00	3.47%	3.57%
88.00	6.15%	2.47%
89.00	5.46%	2.11%
90.00	6.94%	3.02%
91.00	1.24%	3.11%
92.00	0.00%	0.46%
93.00	2.52%	0.46%
94.00	0.00%	1.39%
95.00	0.00%	1.41%
96.00	1.94%	0.48%